

MULTIFUNCTIONAL IMMUNE CELL THERAPIES

BACKGROUND

[0001] The adoptive transfer of genetically modified T cells is a rapidly evolving innovative treatment for cancer. Chimeric antigen receptor (CAR) engineered T cells are renewable drugs with the capacity to provide sustained functional immunity. Clinical efficacy has been demonstrated with CD19 CAR T in a range of hematological cancers and encouraging early clinical data has been reported for other genetically modified CAR T in solid tumors. However, significant challenges must be met before CAR technology can more fully realize its substantial potential.

[0002] Current clinical trials with CAR T cells observe a high incidence of relapse in one year or less due to the inability of CAR T cells to address antigen escape and the inherent heterogeneity in the cancer or tumor phenotype. Moreover, current CAR technologies are not adaptive to such changes in cancer or tumor phenotype. In solid tumors, for example, current CAR technologies exhibit limited efficacy due to tumor target heterogeneity and the inability to reprogram CAR T cells to recognize an expanded set of antigenic targets expressed over time. In addition to improving the durability and sustainability of clinical responses, other key impediments to the use of current CAR cell-based technologies include the time required to generate CAR T cells, and the suboptimal specificity, efficacy, and safety of CAR cells for use in cancers beyond leukemia. Accordingly, there is a need for CAR cell-based technology that provides simultaneous and/or sequential target multispecificity and the ability to modulate, alter, or redirect CAR cell-mediated immune responses *in vivo*.

[0003] Bone marrow transplantation (BMT) and hematopoietic stem cell transplantation (HSCT) hold the promise of correcting any blood or immune disease. Czechowicz *et al.*, Blood 128 (22): 493 (2016). Despite their tremendous potential, the clinical use of BMT and HSCT remain fairly limited in part due to the severe safety and toxicity risks associated with current high dose chemotherapy/ irradiation conditioning regimens to prepare patients for transplant and subsequent donor HSC engraftment. The most common toxicities experienced by patients include neutropenia, infections, anemia, mucositis, infertility, organ damage particularly in the bone marrow compartment and secondary malignancies. Complete elimination of these toxic conditioning regimens would dramatically improve the safety profile of BMT and HSCT and expand the potential applications to include many more non-malignant hematologic disorders, a wide variety of autoimmune disorders, as well as facilitate solid organ transplant. Accordingly, there is a need for the development of improved conditioning regimens that limit or eliminate toxicities associated with current high dose chemotherapy/ irradiation while also effectively treating the underlying disease state.

BRIEF SUMMARY

[0004] Provided herein are multi-functional chimeric antigen receptor (CAR)-based compositions and their use in directing immune responses to target cells. The compositions have uses that include treating hyperproliferative disorders such as cancer. The provided methods generally include the use of a CAR cell in combination with an Adapter. The Adapter confers the ability to modulate, alter, and/or redirect CAR cell-mediated immune response *in vitro* and *in vivo*.

[0005] The present disclosure relates to compositions comprising: (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises an antigenic determinant binding domain (ADBD), and (b) a soluble protein (an "Adapter") which comprises (i) an antigenic determinant (AD) and (ii) an ADBD. The present disclosure also provides methods of killing a target cell with the compositions provided herein, including therapeutic applications of the compositions provided herein.

[0006] In some embodiments, the disclosure provides a composition comprising: (a) a cell expressing a CAR, wherein the CAR comprises an (i) an ADBD that binds to a first AD on a target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0007] In some embodiments, the disclosure provides a composition comprising: (a) a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on a target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0008] In some embodiments, the disclosure provides a composition comprising: (a) a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that is an alternative scaffold binding domain (ASBD) that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell.

[0009] In some embodiments, the disclosure provides a composition comprising: (a) a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD comprising an ASBD that binds to a second AD on a target cell.

[0010] In some embodiments, the disclosure provides a composition comprising: (a) a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) a D domain that binds to a second AD on a target cell.

[0011] In some embodiments, the disclosure provides a composition comprising: (a) a cell expressing a CAR, wherein the CAR comprises (i) a D domain that binds to a first AD, (ii) a transmembrane domain, and

(iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell.

[0012] In some embodiments, the disclosure provides a composition comprising: (a) a cell expressing a CAR, wherein the CAR comprises (i) a first D domain that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) a second D domain that binds to a second AD on a target cell.

[0013] In some embodiments, the disclosure provides a method of killing a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0014] In some embodiments, the disclosure provides a method of killing one or more target cells comprising contacting a composition comprising a first target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on said first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0015] In some embodiments, the disclosure provides a method of killing a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0016] In some embodiments, the disclosure provides a method of killing a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell.

[0017] In some embodiments, the disclosure provides a method of killing a target cell comprising contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the first target cell further comprises an Adapter comprising (i) said first AD and (ii) an ADBD that binds to a second AD on the target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0018] In some embodiments, the disclosure provides a method of killing one or more target cells comprising contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the first target cell; (b) the composition comprising the first target cell further comprises a second target cell and an Adapter comprising (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the first target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0019] In some embodiments, the disclosure provides a method of killing a target cell comprising contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an ADBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0020] In some embodiments, the disclosure provides a method of killing a target cell comprising contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an ADBD that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0021] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0022] In some embodiments, the disclosure provides a method of delivering an immune response to one or more target cells comprising contacting a composition comprising a first target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on said first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0023] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an

intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0024] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell.

[0025] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the first target cell further comprises an Adapter comprising (i) said first AD and (ii) an ADBD that binds to a second AD on the target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0026] In some embodiments, the disclosure provides a method of delivering an immune response to one or more target cells comprising contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the first target cell; (b) the composition comprising the first target cell further comprises a second target cell and an Adapter comprising (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the first target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0027] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an ADBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0028] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with a CAR, wherein (a) a first antigenic determinant (AD) is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an ADBD that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0029] In some embodiments, the disclosure provides a method of killing a target cell in a patient comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR,

wherein the CAR comprises (i) an ADBD that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0030] In some embodiments, the disclosure provides a method of redirecting target cell killing in a patient comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0031] In some embodiments, the disclosure provides a method of killing a target cell in a patient comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0032] In some embodiments, the disclosure provides a method of killing a target cell in a patient comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell.

[0033] In some embodiments, the disclosure provides a method of killing a target cell in a patient comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD and a second AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an ADBD that binds to said second AD on said target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0034] In some embodiments, the disclosure provides a method of directing target cell killing in a patient comprising administering a cell expressing a CAR to the patient, wherein (a) the patient has been treated with an Adapter comprising (i) a first AD and (ii) an ADBD that binds to a second AD on the target cell; and (b) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0035] In some embodiments, the disclosure provides a method of killing a target cell in a patient comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) an ADBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0036] In some embodiments, the disclosure provides a method of killing a target cell in a patient comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) an ADBD that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0037] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell in a patient comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0038] In some embodiments, the disclosure provides a method of redirecting an immune response to a target cell in a patient comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0039] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell in a patient comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0040] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell in a patient comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell.

[0041] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell in a patient comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD and a second AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an ADBD that binds to said second AD on said target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0042] In some embodiments, the disclosure provides a method of directing an immune response to a target cell in a patient comprising administering a cell expressing a CAR to the patient, wherein (a) the patient has been treated with an Adapter comprising (i) a first AD and (ii) an ADBD that binds to a second AD on the

target cell; and (b) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0043] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell in a patient comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) an ADBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0044] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell in a patient comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD is present on the target cell; (b) the patient has been treated with a an Adapter comprising (i) an ADBD that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0045] In some embodiments, the disclosure provides a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an ADBD that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0046] In some embodiments, the disclosure provides a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0047] In some embodiments, the disclosure provides a method of redirecting treatment of a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0048] In some embodiments, the disclosure provides a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular

domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0049] In some embodiments, the disclosure provides a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell.

[0050] In some embodiments, the disclosure provides a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD and a second AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an ADBD that binds to said second AD on said target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0051] In some embodiments, the disclosure provides a method of directing treatment of a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering a cell expressing a CAR to the patient, wherein (a) the patient has been treated with an Adapter comprising (i) a first AD and (ii) an ADBD that binds to a second AD on the target cell; and (b) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0052] In some embodiments, the disclosure provides a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) an ADBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0053] In some embodiments, the disclosure provides a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) an ADBD that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0054] In some embodiments, the disclosure provides a method of treating hematological cancer comprising contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter

comprising (i) an ADBD that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0055] In some embodiments, the disclosure provides a method of treating hematological cancer comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0056] In some embodiments, the disclosure provides a method of redirecting treatment of a hematological cancer comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0057] In some embodiments, the disclosure provides a method of treating hematological cancer comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0058] In some embodiments, the disclosure provides a method of treating hematological cancer comprising administering an Adapter to the patient, wherein (a) the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an ADBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell.

[0059] In some embodiments, the disclosure provides a method of treating hematological cancer comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD and a second AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an ADBD that binds to said second AD on said target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0060] In some embodiments, the disclosure provides a method of directing treatment of a hematological cancer comprising administering a cell expressing a CAR to the patient, wherein (a) the patient has been treated with an Adapter comprising (i) a first AD and (ii) an ADBD that binds to a second AD on the target cell; and (b) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0061] In some embodiments, the disclosure provides a method of treating hematological cancer comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD is present on the target cell; (b) the patient has been treated with an Adapter comprising (i) an ADBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0062] In some embodiments, the disclosure provides method of treating hematological cancer comprising administering a cell expressing a CAR to the patient, wherein (a) a first AD is present on the target cell; (b) the patient has been treated with a an Adapter comprising (i) an ADBD that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0063] In some embodiments, the disclosure provides an engineered human immune effector cell comprising (a) a chimeric antigen receptor (CAR) comprising (1) an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (b) a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell, wherein the engineered cell is capable of directing an immune response to a CD45 AD expressing cell in an in vitro assay, and wherein the engineered cell does not express the CD45 AD.

[0064] In some embodiments, the disclosure provides a method of killing a human CD45 expressing target cell comprising contacting the target cell with an engineered human immune effector cell, wherein the engineered human immune effector cell comprises (a) a chimeric antigen receptor (CAR) comprising (1) an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (b) a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell.

[0065] In some embodiments, the disclosure provides a method of delivering an immune response to a human CD45 expressing target cell comprising contacting the target cell with an engineered human immune effector cell, wherein the engineered human immune effector cell comprises (a) a chimeric antigen receptor (CAR) comprising (1) an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (b) a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell.

[0066] In some embodiments, the disclosure provides a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell, wherein the engineered human immune effector cell comprises (a) a chimeric antigen receptor (CAR) comprising (1) an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 antigenic

determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (b) a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell.

[0067] In some embodiments, the disclosure provides an engineered human immune effector cell comprising (a) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBDB) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (b) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell, wherein the first AD is not the at least one human CD45 AD, wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a CD45 expressing cell in an in vitro assay, wherein the Adapter comprises the first AD and a second ADBDB that specifically binds to the at least one human CD45 AD, and wherein the engineered cell does not express the at least one human CD45 AD.

[0068] In some embodiments, the disclosure provides a method of killing a target cell comprising contacting the target cell with an engineered human immune effector cell and an Adapter, wherein the target cell expresses CD45, wherein the engineered human immune effector cell comprises (a) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBDB) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (b) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell, and wherein the Adapter comprises the first AD and a second ADBDB that specifically binds to a human CD45 AD.

[0069] In some embodiments, the disclosure provides a method of delivering an immune response to a target cell comprising contacting the target cell with an engineered human immune effector cell and an Adapter, wherein the target cell expresses CD45, wherein the engineered human immune effector cell comprises (a) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBDB) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (b) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell, and wherein the Adapter comprises the first AD and a second ADBDB that specifically binds to a human CD45 AD.

[0070] In some embodiments, the disclosure provides a method of directing an immune response to a CD45 expressing target cell in a subject comprising (a) administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBDB) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell; and (b)

administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD.

[0071] In some embodiments, the disclosure provides a method of directing an immune response to a CD45 expressing target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell, wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD.

[0072] In some embodiments, the disclosure provides a method of directing an immune response to a CD45 expressing target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell.

[0073] In some embodiments, the disclosure provides a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising (a) administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell; and (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD.

[0074] In some embodiments, the disclosure provides a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell, wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD.

[0075] In some embodiments, the disclosure provides a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell.

[0076] In some embodiments, the disclosure provides an engineered human immune effector cell comprising (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that bind to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) a genetic modification that eliminates the expression of the first AD on the engineered cell, wherein the engineered cell does not express the first AD.

[0077] In some embodiments, the disclosure provides a method of killing a target cell comprising contacting the target cell with an engineered cell engineered human immune effector cell comprising (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that bind to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) a genetic modification that eliminates the expression of the first AD on the engineered cell.

[0078] In some embodiments, the disclosure provides a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of an engineered cell engineered human immune effector cell comprising (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that bind to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) a genetic modification that eliminates the expression of the first AD on the engineered cell.

[0079] In some embodiments, the disclosure provides a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell comprising (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that bind to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) a genetic modification that eliminates the expression of the first AD on the engineered cell.

[0080] In some embodiments, the disclosure provides a method of directing an immune response to a target cell in a subject comprising (a) administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR), wherein the CAR comprises (1) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that bind to a first antigenic determinants (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of the first AD on the engineered cell; and (b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell.

[0081] In some embodiments, the disclosure provides a engineered human immune effector cell comprising (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) a genetic modification that eliminates the expression of a second AD on the engineered cell, wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a cell expressing the second AD in an in vitro assay, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the engineered cell does not express the second AD.

[0082] In some embodiments, the disclosure provides a method of directing an immune response to a target cell in a subject comprising (a) administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR), wherein the CAR comprises (1) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of a second AD on the engineered cell; and (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD recognized by the CAR and a second ADBD that is capable of binding the second AD, wherein the second AD is expressed on the target cell.

[0083] In some embodiments, the disclosure provides an engineered human immune effector cell comprising (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that specifically binds to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) a genetic modification that eliminates the expression of a second AD on the engineered cell, wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a cell expressing the second AD in an in vitro assay, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the engineered cell does not express the second AD.

[0084] In some embodiments, the disclosure provides a method of directing an immune response to a target cell in a subject comprising (a) administering to the subject in need thereof a therapeutically effective amount of an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR), wherein the CAR comprises (1) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that specifically binds to a first antigenic determinants (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of a second AD on the engineered cell; and (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD recognized by the CAR and a second ADBD that is capable of binding the second AD, wherein the second AD is expressed on the target cell.

[0085] In some embodiments, the disclosure provides:

[1.] A composition comprising:

- (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;

[2.] a composition comprising:

- (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;

[3.] a composition comprising:

- (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an alternative scaffold binding domain (ASBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell;

[4.] a composition comprising:

- (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) an Adapter which comprises (i) said first AD and (ii) an ADBD comprising an ASBD that binds to a second AD on a target cell;
- [5.] a composition comprising:
- (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) an Adapter which comprises (i) said first AD and (ii) a D domain that binds to a second AD on a target cell;
- [6.] a composition comprising:
- (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a D domain that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell;
- [7.] a composition comprising:
- (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a first D domain that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) an Adapter which comprises (i) said first AD and (ii) a second D domain that binds to a second AD on a target cell;
- [8.] the composition of any of [1]-[7], wherein CAR comprises a single-chain variable fragment (scFv) ADBD;
- [9.] the composition of any of [1]-[7], wherein the CAR comprises an alternative scaffold binding domain (ASBD) ADBD;

- [10.] the composition of [9], wherein the CAR comprises a D domain, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 17-26, and 27 or SEQ ID NO: 44-1078, and 1079;
- [11.] the composition of any one of [1]-[10], wherein the CAR comprises 2 ADBDs;
- [12.] the composition of [11], wherein the CAR comprises an ASBD and a scFv;
- [13.] the composition of [11], wherein the CAR comprises a D domain and a scFv;
- [14.] the composition of [11], wherein the CAR comprises 2 ASBDs;
- [15.] the composition of [11], wherein the CAR comprises 2 D domains;
- [16.] the composition of any of [1]-[15], wherein the CAR intracellular domain is a signaling domain;
- [17.] the composition of [16], wherein the CAR intracellular domain comprises a primary signaling domain;
- [18.] the composition of [16], wherein the CAR intracellular domain comprises a CD3 ζ primary signaling domain;
- [19.] the composition of [17] or [18], wherein the CAR intracellular domain further comprises a costimulatory signaling domain;
- [20.] the composition of [19], wherein the CAR intracellular domain comprises a costimulatory signaling domain selected from: CD28, 41BB, CD27, and CD134;
- [21.] the composition of [20], wherein the CAR intracellular domain comprises a 41BB costimulatory signaling domain;
- [22.] the composition of any of [1]-[21], wherein the CAR binds to an antigen selected from: CD19, CD22, CD123, BCMA, CS1, HER2, TACI, BAFFR, and PDL1;
- [23.] the composition of [22], wherein the CAR binds to BCMA, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 44-338, and 339;
- [24.] the composition of [22], wherein the CAR binds to CD123, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 340-77 and 773;
- [25.] the composition of [22], wherein the CAR binds to CD19, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1030-1058, and 1059;

- [26.] the composition of [22], wherein the CAR binds to CD22, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1060-1068, and 1069;
- [27.] the composition of [22], wherein the CAR binds to CS1, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 780-794, and 795;
- [28.] the composition of [22], wherein the CAR binds to HER2, optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 800-839, and 840;
- [29.] the composition of [22], wherein the CAR binds to PDL1, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079;
- [30.] the composition of any of [1]-[21], wherein the CAR binds to AFP p26, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 841-983, and 984;
- [31.] the composition of any of [1]-[30], wherein the CAR comprises 2 ADBDs that bind to separate targets;
- [32.] the composition of [31], wherein the CAR binds to CD19 and CD123;
- [33.] the composition of [31], wherein the CAR binds to BCMA and CS1;
- [34.] the composition of [31], wherein the CAR binds to CD22 and CD123;
- [35.] the composition of [31], wherein the CAR binds to PDL1 and CD123;
- [36.] the composition of [32], wherein the CAR comprises a first ASBD that binds to CD19 and a second ASBD that binds to CD123;
- [37.] the composition of [36] wherein the CAR comprises a first D domain that binds to CD19 and a second D domain that binds to CD123;
- [38.] the composition of [32], wherein the CAR comprises a D domain that binds to CD19 and a scFv that binds to CD123;
- [39.] the composition of [33], wherein the CAR comprises a first ASBD that binds to BCMA and a second ASBD that binds to CS1;
- [40.] the composition of [39] wherein the CAR comprises a first D domain that binds to BCMA and a second D domain that binds to CS1;
- [41.] the composition of [33], wherein the CAR comprises a D domain that binds to CS1 and a scFv that binds to BCMA;

- [42.] the composition of [39], wherein the CAR comprises a D domain that binds to BCMA and a scFv that binds to CS1;
- [43.] the composition of [34], wherein the CAR comprises a first ASBD that binds to CD22 and a second ASBD that binds to CD123;
- [44.] the composition of [43], wherein the CAR comprises a first D domain that binds to CD22 and a second D domain that binds to CD123;
- [45.] the composition of [34], wherein the CAR comprises a D domain that binds to CD22 and a scFv that binds to CD123;
- [46.] the composition of [35], wherein the CAR comprises a first ASBD that binds to PDL1 and a second ASBD that binds to CD123;
- [47.] the composition of [46], wherein the CAR comprises a first D domain that binds to PDL1 and a second D domain that binds to CD123;
- [48.] the composition of [35], wherein the CAR comprises a D domain that binds to PDL1 and a scFv that binds to CD123;
- [49.] the composition of [32], wherein the CAR comprises an ASBD that binds to CD19 and a scFv that binds to CD123;
- [50.] the composition of any of [1]-[49], wherein the Adapter comprises an AD of a tumor antigen, optionally wherein the tumor antigen is selected from the group: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1;
- [51.] the composition of [1]-[50], wherein the Adapter comprises an AD that is an epitope of AFP p26 or AFP, and optionally comprises the amino acid residues of SEQ ID NO: 16 or 1117-1123-;
- [52.] the composition of any of [1]-[51] wherein the Adapter comprises an ADBD that is a scFv;
- [53.] the composition of any of [1]-[51], wherein the Adapter comprises an ADBD that is an ASBD;
- [54.] the composition of [53], wherein the Adapter comprises a D domain, and optionally wherein the Adapter comprises a sequence selected from the group: SEQ ID NO: 17-26, and 27, or SEQ ID NO: 44-1078, and 1079;
- [55.] the composition of any one of [1]-[54], wherein the Adapter comprises two ADBDs;

- [56.] the composition of [55], wherein the two ADBDs (a) are the same, (b) bind to the same antigenic determinant, (c) bind to different ADs of the same antigen, or (d) bind to different antigens on the same cell, or (e) bind to different antigens on different cells;
- [57.] the composition of [55] or [56], wherein the Adapter comprises two ASBDs;
- [58.] the composition of any one of [55]-[57], wherein the Adapter comprises two D domains, and optionally wherein the Adapter comprises an amino acid sequence selected from the group: SEQ ID NO: 44-1079;
- [59.] the composition of any one of [55] or [56], wherein the Adapter comprises an ADBD that is a scFv and an ADBD that is an ASBD;
- [60.] the composition of [59], wherein the Adapter comprises an ADBD that is a scFv and an ADBD that is a D domain;
- [61.] the composition of any of [1]-[60], wherein the Adapter comprises an ADBD that binds to a member selected from: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1;
- [62.] the composition of [61], wherein the Adapter comprises an ADBD that binds to BCMA, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 44-338, and 339;
- [63.] the composition of [61], wherein the Adapter comprises an ADBD that binds to CS1, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 780-794, and 795;
- [64.] the composition of [61], wherein the Adapter comprises an ADBD that binds to CD123, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 340-772 and 773;
- [65.] the composition of [61], wherein the Adapter comprises an ADBD that binds to CD19, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1030-1058, and 1059;
- [66.] the composition of [61], wherein the Adapter comprises an ADBD that binds to binds to CD22, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1060-1068, and 1069;

- [67.] the composition of [61], wherein the Adapter comprises an ADBD that binds to binds to binds to HER2, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 800-839, and 840;
- [68.] the composition of [61], wherein the Adapter comprises an ADBD that binds to TACI or BAFFR;
- [69.] the composition of [61], wherein the Adapter comprises an ADBD that binds to PDL1, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079;
- [70.] the composition of any of [1]-[69], wherein the Adapter is bispecific;
- [71.] the composition of [70], wherein the Adapter comprises an ADBD that binds to CD19 and an ADBD that binds to CD123;
- [72.] the composition of [70], wherein the Adapter comprises an ADBD that binds to BCMA and an ADBD that binds to CS1;
- [73.] the composition of [70], wherein the Adapter comprises an ADBD that binds to CD22 and an ADBD that binds to CD123;
- [74.] the composition of [70], wherein the Adapter comprises an ADBD that binds to PDL1 and an ADBD that binds to CD123;
- [75.] the composition of any of [1]-[74], wherein the target cell is a tumor cell;
- [76.] the composition of [75], wherein the tumor cell is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, myelodysplasia, breast cancer, and ovarian cancer;
- [77.] the composition of [75], wherein the tumor cell is multiple myeloma;
- [78.] the composition of [75], wherein at least one target cell is a tumor cell;
- [79.] the composition of [75], wherein the first and second target cells are tumor cells;
- [80.] the composition of [79], wherein the first and second tumor cells are of the same type;
- [81.] the composition of [79], wherein the first and second tumor cells are of a different type;
- [82.] the composition of [80] or [81], wherein the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple

myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, myelodysplasia, breast cancer, and ovarian cancer;

- [83.] the composition of [82], wherein the tumor cells are multiple myeloma;
- [84.] the composition of any of [1]-[83], wherein the cell expressing the CAR is an immune effector cell;
- [85.] the composition of [84], wherein the immune effector cell is a T cell;
- [86.] the composition of [84], wherein the immune effector cell is an NK cell;
- [87.] the composition of any of [1]-[86], wherein the cell expressing the CAR kills the target cell;
- [88.] the composition of any of [1]-[87], wherein binding of the Adapter to an antigenic determinant blocks the activity of the antigen comprising the AD;
- [89.] a method of killing a target cell comprising contacting the target cell with the composition of any one of [1]-[88];
- [90.] a method of killing a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein
 - (a) the composition comprising the target cell further comprises a cell expressing a CAR], wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- [91.] a method of killing one or more target cells comprising contacting a composition comprising a first target cell with an Adapter, wherein
 - (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
- [92.] a method of killing a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein

- (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- [93.] a method of killing a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein
- (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;
- [94.] a method of killing a target cell comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the composition comprising the first target cell further comprises an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on the target cell; and
 - (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [95.] a method of killing one or more target cells comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first AD is present on the first target cell;
 - (b) the composition comprising the first target cell further comprises a second target cell and an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on a second target cell; and
 - (c) the CAR comprises (i) an ADBD that binds to said first AD on the first target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;

- [96.] a method of killing a target cell comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [97.] a method of killing a target cell comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [98.] a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein
- (a) the composition comprising the target cell further comprises a cell expressing a CAR], wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- [99.] a method of delivering an immune response to one or more target cells comprising contacting a composition comprising a first target cell with an Adapter, wherein
- (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and

- (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
- [100.] a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein
- (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- [101.] a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with an Adapter, wherein
- (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;
- [102.] a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
- (b) the composition comprising the first target cell further comprises an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on the target cell; and
- (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.
- [103.] a method of delivering an immune response to one or more target cells comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first AD is present on the first target cell;

- (b) the composition comprising the first target cell further comprises a second target cell and an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on a second target cell; and
 - (c) the CAR comprises (i) an ADBD that binds to said first AD on the first target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [104.] a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [105.] a method of delivering an immune response to a target cell comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [106.] a method of killing a target cell in a patient comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;

- [107.] a method of redirecting target cell killing in a patient comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
- [108.] a method of killing a target cell in a patient comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- [109.] a method of killing a target cell in a patient comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;
- [110.] a method of killing a target cell in a patient comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) a first antigenic determinant (AD) and a second AD is present on the target cell;
 - (b) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to said second AD on said target cell; and

- (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [111.] a method of directing target cell killing in a patient comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) the patient has been treated with an Adapter comprising (i) a first antigenic determinant (AD) and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on the target cell; and
 - (b) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [112.] a method of killing a target cell in a patient comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the patient has been treated with an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [113.] a method of killing a target cell in a patient comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the patient has been treated with a an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [114.] a method of delivering an immune response to a target cell in a patient comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first

antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and

(b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;

[115.] a method of redirecting an immune response to a target cell in a patient comprising administering an Adapter to the patient, wherein

(a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and

(b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;

[116.] a method of delivering an immune response to a target cell in a patient comprising administering an Adapter to the patient, wherein

(a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and

(b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;

[117.] a method of delivering an immune response to a target cell in a patient comprising administering an Adapter to the patient, wherein

(a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and

(b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;

[118.] a method of delivering an immune response to a target cell in a patient comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein

- (a) a first antigenic determinant (AD) and a second AD is present on the target cell;
- (b) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBBD) that binds to said second AD on said target cell; and
- (c) the CAR comprises (i) an ADBBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;

[119.] a method of directing an immune response to a target cell in a patient comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein

- (a) the patient has been treated with an Adapter comprising (i) a first antigenic determinant (AD) and (ii) an antigenic determinant binding domain (ADBBD) that binds to a second AD on the target cell; and
- (b) the CAR comprises (i) an ADBBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;

[120.] a method of delivering an immune response to a target cell in a patient comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein

- (a) a first antigenic determinant (AD) is present on the target cell;
- (b) the patient has been treated with an Adapter comprising (i) an antigenic determinant binding domain (ADBBD) that binds to said first AD on said target cell and (ii) a second AD; and
- (c) the CAR comprises (i) an ADBBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;

[121.] a method of delivering an immune response to a target cell in a patient comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein

- (a) a first antigenic determinant (AD) is present on the target cell;
- (b) the patient has been treated with a an Adapter comprising (i) an antigenic determinant binding domain (ADBBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
- (c) the CAR comprises (i) an ADBBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;

- [122.] a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [123.] a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- [124.] a method of redirecting treatment of a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
- [125.] a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD

that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and

(b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;

[126.] a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter to the patient, wherein

(a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and

(b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;

[127.] a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein

(a) a first antigenic determinant (AD) and a second AD is present on the target cell;

(b) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to said second AD on said target cell; and

(c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;

[128.] a method of directing treatment of a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein

(a) the patient has been treated with an Adapter comprising (i) a first antigenic determinant (AD) and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on the target cell; and

(b) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;

- [129.] a method of treating proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the patient has been treated with an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [130.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the patient has been treated with a an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [131.] the method of any one of [122]-[130], wherein the proliferative disorder or cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, myelodysplasia, breast cancer, and ovarian cancer ;
- [132.] the method of any one of [122]-[130], wherein the proliferative disorder or cancer is multiple myeloma;
- [133.] a method of treating hematological cancer comprising contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and

- (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [134.] a method of treating hematological cancer comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- [135.] a method of redirecting treatment of a hematological cancer comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
- [136.] a method of treating hematological cancer comprising administering an Adapter to the patient, wherein
- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- [137.] a method of treating hematological cancer comprising administering an Adapter to the patient, wherein

- (a) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;
- [138.] a method of treating hematological cancer comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) a first antigenic determinant (AD) and a second AD is present on the target cell;
 - (b) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to said second AD on said target cell; and
 - (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [139.] a method of directing treatment of a hematological cancer comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) the patient has been treated with an Adapter comprising (i) a first antigenic determinant (AD) and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on the target cell; and
 - (b) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [140.] a method of treating hematological cancer comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the patient has been treated with an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [141.] a method of treating hematological cancer comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein

- (a) a first antigenic determinant (AD) is present on the target cell;
 - (b) the patient has been treated with a an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
 - (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- [142.] the method of any one of [133]-[141], wherein the hematological cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
- [143.] the method of any one of [133]-[141], wherein the hematological cancer is multiple myeloma;
- [144.] the method of any of [90]-[131], wherein CAR comprises a single-chain variable fragment (scFv) ADBD;
- [145.] the method of any of [90]-[143], wherein the CAR comprises an alternative scaffold binding domain (ASBD) ADBD;
- [146.] the method of [145], wherein the CAR comprises a D domain, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 17-26, and 27 or SEQ ID NO: 44-1078, and 1079;
- [147.] the method of any one of [90]-[146], wherein the CAR comprises 2 ADBDs;
- [148.] the method of [147], wherein the CAR comprises an ASBD and a scFv;
- [149.] the method of [147], wherein the CAR comprises a D domain and a scFv;
- [150.] the method of [147], wherein the CAR comprises 2 ASBDs;
- [151.] the method of [147], wherein the CAR comprises 2 D domains;
- [152.] the method of any one of [90]-[151], wherein the CAR intracellular domain is a signaling domain;
- [153.] the method of [152], wherein the CAR intracellular domain comprises a primary signaling domain;
- [154.] the method of [152], wherein the CAR intracellular domain comprises a CD3 ζ primary signaling domain;

- [155.] the method of [153] or [154], wherein the CAR intracellular domain further comprises a costimulatory signaling domain;
- [156.] the method of [155], wherein the CAR intracellular domain comprises a costimulatory signaling domain selected from: CD28, 41BB, CD27, and CD134;
- [157.] the method of [156], wherein the CAR intracellular domain comprises a 41BB costimulatory signaling domain;
- [158.] the method of any one of [90]-[157], wherein the CAR binds to an antigen selected from: CD19, CD22, CD123, BCMA, CS1, HER2, TACI, BAFFR, and PDL1;
- [159.] the method of [158], wherein the CAR binds to BCMA, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 44-338, and 339;
- [160.] the method of [158], wherein the CAR binds to CS1, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 780-794, and 795;
- [161.] the method of [158], wherein the CAR binds to CD123, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 340-772 and 773;
- [162.] the method of [158], wherein the CAR binds to CD19, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1030-1058, and 1059;
- [163.] the method of [158], wherein the CAR binds to CD22, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1060-1068, and 1069;
- [164.] the method of [158], wherein the CAR binds to binds to HER2, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 800-839, and 840;
- [165.] the method of [158], wherein the CAR binds to PDL1, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079;
- [166.] the method of any one of [90]-[157], wherein the CAR binds to AFP p26, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 841-983, and 984;
- [167.] the method of any one of [90]-[166], wherein the CAR comprises 2 ADBDs that bind to separate targets;
- [168.] the method of [167], wherein the CAR binds to CD19 and CD123;
- [169.] the method of [167], wherein the CAR binds to CD22 and CD123;

- [170.] the method of [167], wherein the CAR binds to PDL1 and CD123;
- [171.] the method of [167], wherein the CAR binds to CS1 and BCMA;
- [172.] the method of [168], wherein the CAR comprises a first ASBD that binds to CD19 and a second ASBD that binds to CD123;
- [173.] the method of [172], wherein the CAR comprises a first D domain that binds to CD19 and a second D domain that binds to CD123;
- [174.] the method of [168], wherein the CAR comprises a D domain that binds to CD19 and a scFv that binds to CD123;
- [175.] the method of [169], wherein the CAR comprises a first ASBD that binds to CD22 and a second ASBD that binds to CD123;
- [176.] the method of [175], wherein the CAR comprises a first D domain that binds to CD22 and a second D domain that binds to CD123;
- [177.] the method of [169], wherein the CAR comprises a D domain that binds to CD22 and a scFv that binds to CD123;
- [178.] the method of [170], wherein the CAR comprises a first ASBD that binds to PDL1 and a second ASBD that binds to CD123;
- [179.] the method of [178], wherein the CAR comprises a first D domain that binds to PDL1 and a second D domain that binds to CD123;
- [180.] the method of [170], wherein the CAR comprises a D domain that binds to PDL1 and a scFv that binds to CD123;
- [181.] the method of [168], wherein the CAR comprises an ASBD that binds to CD19 and a scFv that binds to CD123;
- [182.] the method of [171], wherein the CAR comprises a first ASBD that binds to BCMA and a second ASBD that binds to CS1;
- [183.] the method of [182], wherein the CAR comprises a first D domain that binds to BCMA and a second D domain that binds to CS1;
- [184.] the method of [171], wherein the CAR comprises a D domain that binds to BCMA and a scFv that binds to CS1;

- [185.] the method of [171], wherein the CAR comprises a D domain that binds to CS1 and a scFv that binds to BCMA;
- [186.] the method of any one of [90]-[185], wherein the Adapter comprises an AD of a tumor antigen, optionally wherein the tumor antigen is selected from the group: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1;
- [187.] the method of [90]-[186], wherein the Adapter comprises an AD that is an epitope of AFP p26 or AFP, and optionally comprises the amino acid residues of SEQ ID NO: 16 or 1117-1123;
- [188.] the method of any one of [90]-[187], wherein the Adapter comprises an ADBD that is a scFv;
- [189.] the method of any one of [90]-[187], wherein the Adapter comprises an ADBD that is an ASBD;
- [190.] the method of [189], wherein the Adapter comprises a D domain, and optionally wherein the Adapter comprises a sequence selected from the group: SEQ ID NO: 17-26, and 27, or SEQ ID NO: 44-1078, and 1079;
- [191.] the method of any one of [90]-[190], wherein the Adapter comprises two ADBDs;
- [192.] the method of [191], wherein the two ADBDs (a) are the same, (b) bind to the same antigenic determinant, (c) bind to different ADs of the same antigen, or (d) bind to different antigens on the same cell, or (e) bind to different antigens on different cells;
- [193.] the method of [191] or [192], wherein the Adapter comprises two ASBDs;
- [194.] the method of any one of [191], [192], or [193], wherein the Adapter comprises two D domains, and optionally wherein the Adapter comprises an amino acid sequence selected from the group: SEQ ID NO: 44-1079;
- [195.] the method of [191] or [192], wherein the Adapter comprises an ADBD that is a scFv and an ADBD that is an ASBD;
- [196.] the method of [195], wherein the Adapter comprises an ADBD that is a scFv and an ADBD that is a D domain;
- [197.] the method of any one of [90]-[196], wherein the Adapter comprises an ADBD that binds to a member selected from: BCMA, CS1, HER2, CD123, CD19, CD22, TACI, BAFFR, and PDL1;
- [198.] the method of [197], wherein the Adapter comprises an ADBD that binds to BCMA, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 44-338, and 339;

- [199.] the method of [197], wherein the Adapter comprises an ADBD that binds to CS1, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 780-794, and 795;
- [200.] the method of [197], wherein the Adapter comprises an ADBD that binds to CD123, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 340-772, and 773;
- [201.] the method of [197], wherein the Adapter comprises an ADBD that binds to CD19, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1030-1058, and 1059;
- [202.] the method of [197], wherein the Adapter comprises an ADBD that binds to binds to CD22, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1060-1068, and 1069;
- [203.] the method of [197], wherein the Adapter comprises an ADBD that binds to binds to HER2, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 800-839, and 840;
- [204.] the method of [197], wherein the Adapter comprises an ADBD that binds to TACI or BAFFR;
- [205.] the method of [197], wherein the Adapter comprises an ADBD that binds to PDL1, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079;
- [206.] the method of any one of [90]-[205], wherein the Adapter is bispecific;
- [207.] the method of [206], wherein the Adapter comprises an ADBD that binds to BCMA and an ADBD that binds to CS1;
- [208.] the method of [206], wherein the Adapter comprises an ADBD that binds to CD19 and an ADBD that binds to CD123;
- [209.] the method of [206], wherein the Adapter comprises an ADBD that binds to CD22 and an ADBD that binds to CD123;
- [210.] the method of [206], wherein the Adapter comprises an ADBD that binds to PDL1 and an ADBD that binds to CD123;
- [211.] the method of any one of [90]-[210], wherein the target cell is a tumor cell;
- [212.] the method of [211], wherein the tumor cell is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma,

Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, myelodysplasia, breast cancer, and ovarian cancer;

- [213.] the method of [211], wherein the tumor cell is multiple myeloma;
- [214.] the method of [211], wherein at least one target cell is a tumor cell;
- [215.] the method of [211], wherein the first and second target cells are tumor cells;
- [216.] the method of [215], wherein the first and second tumor cells are of the same type;
- [217.] the method of [215], wherein the first and second tumor cells are of a different type;
- [218.] the method of [214] or [215], wherein the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, myelodysplasia, breast cancer, and ovarian cancer;
- [219.] the method of [214] or [215], wherein the tumor cells are multiple myeloma;
- [220.] the method of any one of [90]-[219], wherein the cell expressing the CAR is an immune effector cell;
- [221.] the method of [220], wherein the immune effector cell is a T cell;
- [222.] the method of [220], wherein the immune effector cell is an NK cell;
- [223.] the method of any one of [90]-[222], wherein the cell expressing the CAR kills the target cell;
- [224.] An engineered human immune effector cell comprising
 - (a) a chimeric antigen receptor (CAR) comprising (1) an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and
 - (b) a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell,wherein the engineered cell is capable of directing an immune response to a CD45 AD expressing cell in an in vitro assay, and wherein the engineered cell does not express the CD45 AD;
- [225.] a method of killing a target cell comprising contacting the engineered cell according to [224] with the target cell], wherein the target cell expresses human CD45;

- [226.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to [224] with the target cell], wherein the target cell expresses human CD45;
- [227.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [224];
- [228.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [224];
- [229.] a method of depleting lymphocytes comprising administering to a subject in need thereof an effective amount of the engineered cell according to [224];
- [230.] a method of depleting memory T cell comprising administering to a subject in need thereof an effective amount of the engineered cell according to [224];
- [231.] a method of treating an autoimmune disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [224];
- [232.] a method of conditioning a subject for transplantation comprising administering to the subject in need thereof an effective amount of the engineered cell according to [224];
- [233.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [224];
- [234.] An engineered human immune effector cell comprising
- (a) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and
 - (b) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell,

wherein the first AD is not the at least one human CD45 AD], wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a CD45 AD expressing cell in an in vitro assay], wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the at least one human CD45 AD, and wherein the engineered cell does not express the at least one human CD45 AD;

- [235.] a method of killing a target cell comprising contacting the engineered cell according to [234] with an Adapter and the target cell], wherein the target cell expresses CD45, and wherein the Adapter comprises the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [236.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to [234] with an Adapter and the target cell], wherein the target cell expresses CD45, and wherein the Adapter comprises the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [237.] a method of treating hematological cancer comprising contacting the engineered cell according to [234] with an Adapter and a cancer cell], wherein the cancer cell expresses CD45, and wherein the Adapter comprises the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [238.] a method of directing an immune response to a target cell in a subject comprising
- (a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [234]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [239.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [234], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [240.] a method of directing an immune response to a target cell in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];
- [241.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising
- (a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [234]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;

- [242.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [234], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [243.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];
- [244.] a method of depleting lymphocytes comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [234]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [245.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [234], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [246.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];
- [247.] a method of depleting memory T cell comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [234]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [248.] a method of depleting memory T cell comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that

specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];

[249.] a method of depleting memory T cell comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];

[250.] a method of treating an autoimmune disease or disorder comprising

(a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [234]; and

(b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;

[251.] a method of treating an autoimmune disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];

[252.] a method of treating an autoimmune disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];

[253.] a method of conditioning a subject for transplantation comprising

(a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [234]; and

(b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;

[254.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [234], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;

- [255.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];
- [256.] a method of treating a hematological cancer comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [234]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [257.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [234], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [258.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD], wherein the subject has been administered the engineered cell according to [234];
- [259.] An engineered human immune effector cell comprising:
- (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that bind to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) a genetic modification that eliminates the expression of the first AD on the engineered cell, wherein the engineered cell does not express the first AD;
- [260.] a method of killing a target cell comprising contacting the engineered cell according to [259] with the target cell;
- [261.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to [259] with the target cell;
- [262.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [259];

- [263.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [259];
- [264.] a method of depleting lymphocytes comprising administering to a subject in need thereof an effective amount of the engineered cell according to [259];
- [265.] a method of conditioning a subject for transplantation comprising administering to the subject in need thereof an effective amount of the engineered cell according to [259];
- [266.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [259];
- [267.] a method of killing a target cell comprising contacting the engineered cell according to [259] with an Adapter and the target cell], wherein the Adapter comprises an AD recognized by the CAR and a second ADBD;
- [268.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to [259] with an Adapter and the target cell, and wherein the Adapter comprises an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell;
- [269.] a method of treating hematological cancer comprising contacting the engineered cell according to [259] with an Adapter and a cancer cell], wherein the Adapter comprises an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the cancer cell;
- [270.] a method of directing an immune response to a target cell in a subject comprising
- (a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [259]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell;
- [271.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [259], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell;

- [272.] a method of directing an immune response to a target cell in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell], wherein the subject has been administered the engineered cell according to [259];
- [273.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising
- (a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [259]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [274.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [259], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [275.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell], wherein the subject has been administered the engineered cell according to [259];
- [276.] a method of depleting lymphocytes comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [259]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [277.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [259], wherein the subject has

been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;

- [278.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell], wherein the subject has been administered the engineered cell according to [259];
- [279.] a method of conditioning a subject for transplantation comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [259]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [280.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [259], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [281.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell], wherein the subject has been administered the engineered cell according to [259];
- [282.] a method of treating a hematological cancer comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [259]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [283.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [259], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;

- [284.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell], wherein the subject has been administered the engineered cell according to [259];
- [285.] An engineered human immune effector cell comprising:
- (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) a genetic modification that eliminates the expression of a second AD on the engineered cell,
- wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a cell expressing the second AD in an in vitro assay], wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the engineered cell does not express the second AD;
- [286.] An engineered human immune effector cell comprising:
- (a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that specifically binds to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (b) a genetic modification that eliminates the expression of a second AD on the engineered cell,
- wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a cell expressing the second AD in an in vitro assay], wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the engineered cell does not express the second AD;
- [287.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286];
- [288.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286];

- [289.] a method of depleting lymphocytes comprising administering to a subject in need thereof an effective amount of the engineered cell according to [285] or [286];
- [290.] a method of conditioning a subject for transplantation comprising administering to the subject in need thereof an effective amount of the engineered cell according to [285] or [286];
- [291.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286];
- [292.] a method of killing a target cell comprising contacting the engineered cell according to [285] or [286] with an Adapter and the target cell], wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the target cell;
- [293.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to [285] or [286] with an Adapter and the target cell], wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the target cell;
- [294.] a method of treating hematological cancer comprising contacting the engineered cell according to [285] or [286] with an Adapter and a cancer cell], wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the cancer cell;
- [295.] a method of directing an immune response to a target cell in a subject comprising
- (a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the second AD is expressed on the target cell;
- [296.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the target cell;
- [297.] a method of directing an immune response to a target cell in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a

second ADBD that specifically binds to the second AD], wherein the subject has been administered the engineered cell according to [285] or [286], and wherein the second AD is expressed on the target cell;

- [298.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising
- (a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the second AD is expressed on a target cell associated with the proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection;
- [299.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on a target cell associated with the proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection;
- [300.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the subject has been administered the engineered cell according to [285] or [286], and wherein the second AD is expressed on a target cell associated with the proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection;
- [301.] a method of depleting lymphocytes comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the second AD is expressed on a lymphocyte target cell;

- [302.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on a lymphocyte target cell;
- [303.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the subject has been administered the engineered cell according to [285] or [286], and wherein the second AD is expressed on a lymphocyte target cell;
- [304.] a method of conditioning a subject for transplantation comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]; and
 - (b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the second AD is expressed on a target cell associated with the transplantation;
- [305.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on a target cell associated with the transplantation;
- [306.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the subject has been administered the engineered cell according to [285] or [286], and wherein the second AD is expressed on a target cell associated with the transplantation;
- [307.] a method of treating a hematological cancer comprising
- (a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]; and

(b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the second AD is expressed on a target cell associated with the hematological cancer;

[308.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to [285] or [286]], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on a target cell associated with the hematological cancer;

[309.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD], wherein the subject has been administered the engineered cell according to [285] or [286], and wherein the second AD is expressed on a target cell associated with the hematological cancer;

[310.] an isolated Adapter polypeptide comprising (1) an antigenic determinant (AD) and (b) one or more antigenic determinant binding domain (ADBD),

wherein at least one ADBD specifically binds to a human CD45 AD, and wherein contacting the Adaptor with a CD45 AD expressing target cell in the presence of an engineered cell according to [234] is capable of directing an immune response by the engineered cell to the target cell in an in vitro assay.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0086] FIG. 1A-1D: The cytolytic activity of CD123-specific (cg06) and BCMA-specific (bc-40) CARs were compared to a CAR with no known target-specificity (α 3D) on a panel of tumors using effector cell to target cell ratios ranging from 1: 4 to 1: 64. Briefly, 20,000 T cells expressing the bc40, cg06, or α 3D CAR were incubated with increasing numbers of a CD123⁺/BCMA⁻ tumor target (MOLM13)(**FIG. 1A**); a CD123⁻/BCMA⁺ tumor target (H929)(**FIG. 1B**); a CD123⁻ tumor target (RAJI)(**FIG. 1C**); or a CD123⁺/BCMA⁻ tumor target (MOLM13)(**FIG. 1D**). After 16 hours, cells were washed and luciferase activity was assessed.

[0087] FIGS. 2A -2B: Adapter binding associates with the Adapter and CAR binding specificity. Jurkat NFAT-Luciferase reporter cells were transduced with a negative control CAR (α 3D), an AFP (p26)-binding CAR (af03), or a BCMA-binding CAR (bc40). In **FIG. 2A**, CAR transduced Jurkat cells were incubated with

0.5µg of Adapter protein (4°C for 20 minutes), washed, and then stained with anti-HIS PE (clone J095G46, 4°C for 20 minutes). **FIG. 2B** shows CAR expression based on FLAG staining (clone L5) versus mock transduced Jurkat cells.

[0088] **FIGS. 3A-3C** show that the Adapter binding of matching CAR: Adapter and Target: Adapter specificity drives lysis of target cells. In **FIG. 3A**, 40,000 CD123⁺BCMA⁻ MOLM13-GFP/Luciferase cells were incubated with various Adapters in the presence or absence of 20,000 T cells (E: T ratio of 1: 2, donor D14-053017, Day 7) transduced with BCMA-binding CAR (bc40) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of MOLM13-GFP/Luciferase cultured in the absence of T cells or Adapter protein. A control of CD123-specific CAR T cells (cg06) cultured at the same ratio was used as a positive control for lysis. In **FIG. 3B**, 40,000 CD123⁺BCMA⁻ MOLM13-GFP/Luciferase cells were incubated with CD123 (cg06)-AFP (p26) Adapter in the presence or absence of 20,000 T cells (E: T ratio of 1: 2, donor D16-061317, Day 7) transduced with AFP-binding CARs (Af03 or Af05) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of MOLM13-GFP/Luciferase cultured in the absence of T cells or Adapter protein. A control of CD123-specific CAR T cells (cg06) cultured at the same ratio was used as a positive control for lysis. In **FIG. 3C**, 40,000 BCMA⁺ NCI H929-GFP/Luciferase cells were incubated with bc40-AFP (p26) Adapter in the presence or absence of 10,000 T cells (E: T ratio of 1: 4, donor D15-062017, Day 8) mock transduced or transduced with AFP-binding CARs (Af03 or Af05) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of NCI-H929-GFP/Luciferase cultured in the absence of T cells or Adapter protein.

[0089] **FIGS. 4A – 4D** show that Adapter binding of matching CAR: Adapter and Target: Adapter specificity drives cytokine production by CAR T cells. In **FIGS. 4A** and **4B**, donor D14-053017 T cells transduced with BCMA-binding CAR (bc40) were cultured overnight with various Adapters in the presence or absence of CD123⁺BCMA⁻ MOLM13 cells (25,000 T cells and target cells). Cultured supernatants were collected and assessed for the production of IL-2 (**FIG. 4A**) and IFN-γ (**FIG. 4B**). In **FIGS. 4C** and **4D**, donor D15-062017 T cells transduced with AFP-binding CARs (Af03 and Af05) were cultured overnight with cg06-AFP (p26) Adapter in the presence or absence of CD123⁺BCMA⁻ MOLM13 cells (25,000 T cells and target cells). Cultured supernatants were collected and assessed for the production of IL-2 (**FIG. 4C**) and IFN-γ (**FIG. 4D**).

[0090] **FIG. 5:** Adapter binding of matching CAR: Adapter and Target: Adapter specificity drives proliferation of CAR T cells. Donor D16-062717 cells transduced with AFP-binding CAR (Af03) were CFSE

labeled (10 minutes at 0.5 μ M), then cultured (25,000) in the presence of CD123-specific Adapter or BCMA-specific Adapter in the presence or absence of mitomycin-C treated CD123⁻ BCMA⁺ NCI-H929 cells (25,000) for 72 hours. At 72 hours, cells were stained for CD3, then analyzed for absolute numbers of CD3⁺ cells via flow cytometry.

[0091] FIGS. 6A and 6B show that Adapter binding of matching CAR: Adapter and Target: Adapter drives signaling by CAR-expressing Jurkat NFAT-Luciferase reporter cells. In FIG. 6A, 50,000 reporter cells previously transduced with a BCMA-binding CAR (bc40) were cultured for 5 hours in the presence of various Adapter proteins in the presence or absence of 50,000 CD123⁺BCMA⁻ MOLM14 cells, then assessed for luciferase activity. In FIG. 6B, 50,000 reporter cells previously transduced with an AFP (p26)-binding CAR (af03) were cultured for 5 hours in the presence of the aspecific α 3D-Adapter or the BCMA-specific Bc40-Adapter protein in the presence or absence of 50,000 BCMA⁺ NCI-H929 cells, then assessed for luciferase activity.

[0092] FIGS. 7A and 7B show that the CD123-specific Adapter with a BCMA antigenic determinant can function with either a BCMA-specific D domain CAR (bc40) or a BCMA-specific scFv CAR (c11D5-3). In FIG. 7A, 40,000 CD123⁺BCMA⁻ MOLM13-GFP/Luciferase cells were incubated with the Cg06-BCMA Adapter in the presence or absence of 20,000 T cells (E: T ratio of 1: 2, donor D14-062717, Day 9) transduced with a non-specific CAR (α 3D), the BCMA-binding D domain CAR (bc40), or the BCMA-binding scFv CAR (c11D5-3) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of MOLM13-GFP/Luciferase cultured in the absence of T cells or Adapter protein. Solid lines indicate calculated 3-parameter non-linear curves, while the dashed line for c11D5-3 is present for illustrative purposes only. In FIG. 7B, CD123⁺BCMA⁻ MOLM13-GFP/Luciferase cells were cultured in the same experiment as in FIG. 7A with transduced T cells in the absence of Adapter protein.

[0093] FIGS. 8A and 8B show that AFP-specific CARs can simultaneously have CD123 and BCMA-binding capacity via incubation with multiple Adapter proteins. 10⁵ Jurkat NFAT-Luciferase transduced with an AFP (p26)-binding CAR (af03) were incubated with a total of 0.5 μ g of Adapter proteins at various ratios of the BCMA- to CD123-specific Adapters (4°C for 20 minutes), washed, and then incubated with CD123-Fc and biotinylated BCMA (0.5 μ g of each) (4°C for 20 minutes), washed, then binding detected with Anti-Fc A488 and Streptavidin-PE. FIG. 8A presents a flow cytometric analysis of CD123-binding and BCMA-binding to their respective target proteins, FIG. 8B provides a comparison of mean fluorescence intensity (MFI) of A488 MFI (CD123-binding, left axis) and PE MFI (BCMA-binding, right axis) flow cytometric data presented in FIG. 8A.

[0094] FIGS. 9A and 9B show that dual-binding domain adaptor proteins drive enhanced signaling by CAR-expressing Jurkat NFAT-Luciferase reporter cells over single-binding domain adaptor proteins. In FIG. 9A, 50,000 reporter cells previously transduced with an AFP (p26 domain)-binding CAR (af03) were cultured for 5 hours in the presence of the CD123-specific Cg06-adaptor (Cg06-p26) or the Cg06-dual adaptor protein (Cg06-p26-Cg06) in the presence of 50,000 CD123⁺ MOLM13 or CD123-deficient MOLM13 cells, then assessed for luciferase activity. CD123 deficient cells were generated using CRISPR/Cas9 genetic engineering technology. In FIG. 9B, 50,000 reporter cells previously transduced with an AFP (p26 domain)-binding CAR (af03) were cultured for 5 hours in the presence of the BCMA-specific Bc40-adaptor (Bc40-p26) or the Bc40-dual adaptor protein (Bc40-p26-Bc40) in the presence or absence of 50,000 BCMA⁺ U266 cells, then assessed for luciferase activity.

[0095] FIG. 10 shows that binding of truncated and full length p26 to human FcRn is pH dependent.

[0096] FIGS. 11A-11D show that adapters comprising CS1 (SLAMF7, CRACC, CD319) specific ADBD modulate intracellular signaling and killing of CS1 positive tumors. In FIG. 11A, the cc02 and cc08 ADBD displayed the most potent NFAT signaling when cultured in the presence of af59-CAR expressing JNL10 cells (FIG. 11A) and the CS1 positive tumor cell line, MM.1S. FIG. 11B shows that the bispecific bc98-p26-cc02 adapter capable of binding both CS1 and BCMA was more potent in its ability to signal than were the monospecific BCMA-binding bc98-p26- α 3DQ19E adapter and the monospecific CS1-binding α 3DQ19E-p26-cc02 adapter. FIGS 11C and 11D indicate the bispecific bc98-p26-cc02 is an effective adapter in killing HT929 (high expression of both BCMA and CS1; FIG. 11C) and MM.1S (high BCMA, low CS1; FIG. 11D).

[0097] FIGS. 12A-12C show that adapters comprising HER2 binding ADBD induce signaling in Af59-CAR expressing JNL10-cells cultured with HER2-positive SKBR3 tumor. FIG. 12A shows that the adapter comprising eb08 HER2-binding ADBD was the most potent stimulator in this assay. FIG 12B shows that the NFAT signaling in JNL10 cells mediated by the adapter comprising eb08 is greater than that of mediated by the adapter comprising zHERs:4, comparable to that of mediated by the adapter comprising 9.29, and less than that of G3 and zHER2:342. FIG. 12C demonstrates that adapters comprising the HER2-binding eb08 or eb04 modulate tumor lysis in a dose-dependent manner.

DETAILED DESCRIPTION

I. Definitions

[0098] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosure pertains.

[0099] It is understood that wherever embodiments are described herein with the language "comprising" otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are

also provided. However, when used in the claims as transitional phrases, each should be interpreted separately and in the appropriate legal and factual context (*e.g.*, "comprising" is considered more of an open-ended phrase while "consisting of" is more exclusive and "consisting essentially of" achieves a middle ground).

[0100] As used herein, the singular form "a", "an", and "the" includes plural references unless indicated otherwise.

[0101] The term "and/or" as used in a phrase such as "A and/or B" herein is intended to include both A and B; A or B; A (alone); and B (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0102] "About" as the term is used herein, when referring to a measurable value such as an amount, a temporal duration, and other measurable values known in the art, is meant to encompass variations of $\pm 20\%$ or in some embodiments $\pm 10\%$, or in some embodiments $\pm 5\%$, or in some embodiments $\pm 1\%$, or in some embodiments $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

[0103] The terms "protein" and "polypeptide" are used interchangeably herein to refer to a biological polymer comprising units derived from amino acids linked via peptide bonds; a protein can be composed of two or more polypeptide chains.

[0104] "Cell surface receptor" refers to molecules and complexes of molecules capable of receiving a signal and the transmission of such a signal across the plasma membrane of a cell. An example of a cell surface receptor provided herein is an activated integrin receptor, for example, an activated $\alpha\beta 3$ integrin receptor on a metastatic cell. As used herein, "cell surface receptor" also includes a molecule expressed on a cell surface that contains a CAR capable of binding an antigenic determinant target of interest. The term "receptor" denotes a cell-associated protein that binds to, or otherwise interacts with, a molecule (*e.g.*, a ligand) and mediates the effect of the ligand on the cell. In several embodiments, the molecule that interacts with a receptor is a bioactive molecule. Membrane-bound cell-surface receptors are characterized by a multi-domain structure comprising an extracellular ligand-binding domain, a membrane spanning domain, and an intracellular effector domain that is typically involved in signal transduction.

[0105] The term "Chimeric antigen receptor" or "CAR" or "CARs" as used herein refers to an engineered chimeric polypeptide that grafts an antigen or target specificity onto a cell such as an immune cell (*e.g.*, a T cell such as a naive T cell, central memory T cell, effector memory T cell, NK cell, NKT cell, or a plurality or combination thereof). CARs may also be referred to herein as artificial T cell receptors, chimeric T cell receptors or chimeric immunoreceptors. The CARs share structural or functional properties with a cell immune-function receptor or Adapter molecule. Upon binding to cognate antigen, a CAR can activate or inactivate the cytotoxic cell in which it is disposed, or modulate the cell's antitumor activity or otherwise

modulate the cells immune response. In some embodiments, CARs comprise one or more element (*e.g.*, domain) from a T cell receptor (TCR, *e.g.*, the zeta chain associated with the T cell receptor complex) or a natural killer cell receptor (NKR). In some embodiments, CARs comprise (1) an antigenic determinant binding domain (ADBD) that specifically binds to antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain. In some embodiments, CARs comprise more than one antigenic determinant binding domains. In some embodiments, CARs comprise more than one antigenic determinant binding domains that bind to different antigenic determinants of the same antigen, different antigenic determinants on different antigens, or antigenic determinants expressed by different target cells.

[0106] The term "immune cell" as used herein refers to the cells of the mammalian immune system including but not limited to antigen presenting cells, B-cells, basophils, cytotoxic T cells, dendritic cells, eosinophils, granulocytes, helper T cells, leukocytes, lymphocytes, macrophages, mast cells, memory cells, monocytes, natural killer cells, neutrophils, phagocytes, plasma cells and T cells.

[0107] The terms "T cell" and "T-lymphocyte" are interchangeable and used synonymously herein. Examples include but are not limited to naive T cells, central memory T cells, effector memory T cells or combinations thereof.

[0108] "Autologous" as the term is used herein refers to any material derived from the same individual to whom it is later to be re-introduced.

[0109] "Allogeneic" as the term is used herein refers to any material derived from a different animal of the same species as the individual to whom the material is introduced. Two or more individuals are said to be allogeneic to one another when the genes at one or more loci are not identical. In some aspects, allogeneic material from individuals of the same species may be sufficiently unlike genetically to interact antigenically.

[0110] The term "effector cells" are leukocytes which express one or more FcRs and perform effector functions. Preferably, the cells express at least FcRIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred in certain embodiments. The effector cells can be isolated from native source thereof, *e.g.*, from blood or PBMCs as described herein or otherwise known in the art. In a specific embodiment, the effector cells are human effector cells.

[0111] The term "effector function" refers to the specialized immune function of a differentiated cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

[0112] The term "immune response" as used herein refers to immunities including but not limited to innate immunity, humoral immunity, cellular immunity, immunity, inflammatory response, acquired (adaptive) immunity, autoimmunity and/or overactive immunity. Indicators of an immune response may include

secretion of cytokines by immune cells, expansion of immune cell populations, production of antibodies, degranulation of cytotoxic cells, and killing of target cells. Such indicators may routinely be measured using readily available assays, *e.g.*, ELISA or ELISpot, known in the art.

[0113] The term "Adapter" as used herein refers to a multi-domain soluble protein that comprises an antigenic determinant (AD) and an antigenic determinant binding domain (ADBD), wherein the ADBD binds to a second AD. In addition to the AD and the ADBD, an Adapter can comprise additional AD, additional ADBD, and/or other additional domains.

[0114] The terms "antibody" or "immunoglobulin," as used interchangeably herein, includes whole antibodies. A whole antibody comprises at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2, and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, Cl. The VH and VL regions can be further subdivided into regions of hypervariability, termed Complementarity Determining Regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FW). Each VH and VL is composed of three CDRs and four FWs, arranged from amino-terminus to carboxy-terminus in the following order: FW1, CDR1, FW2, CDR2, FW3, CDR3, FW4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

[0115] The terms "antibody fragments" and the like as used herein, include any functional domain of an antibody such as an antigen-binding fragment or single chains thereof, an effector domain, salvage receptor binding epitope, or portion thereof. The antibody fragments described herein may exist in a variety of forms. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')₂, and Fv fragments, an disulfide-linked Fv (sdFv), a Fd fragment consisting of VH and CH1 domains, an scFv, a minibody, a BiTE, a Tandab, a diabody ((VL-VH)₂ or (VH-VL)₂), a single domain antibody (*e.g.*, an sdAb such as a nanobody (either VL or VH)), and a camelid VHH domain), and multi-specific antibodies formed from antibody fragments. In some embodiments, an "antibody fragment" corresponds to an antigen-binding site or epitope binding site of an antibody. In other embodiments, an "antibody fragment" corresponds to other functional regions of an antibody such as, an effector domain or portion thereof, or a salvage receptor binding epitope, or portion thereof.

[0116] The terms "single chain variable fragment(s)," or "scFv" antibodies as used herein refer to forms of antibodies (*e.g.*, antibody fragments) comprising the variable regions of only the heavy and light chains,

connected by a linker peptide. The scFv may comprise VL-linker-VH or may comprise VH-linker-VL. ScFv antibodies are generally 220-250 amino acids in length and contain linkers 10-25 amino acids in length.

[0117] As used herein, the term, "Fc region" or simply "Fc" is understood to mean the carboxyl-terminal portion of an immunoglobulin chain constant region, preferably an immunoglobulin heavy chain constant region, or a portion thereof. For example, an immunoglobulin Fc region may comprise (1) a CH1 domain, a CH2 domain, and a CH3 domain, (2) a CH1 domain and a CH2 domain, (3) a CH1 domain and a CH3 domain, (4) a CH2 domain and a CH3 domain, or (5) a combination of two or more domains and an immunoglobulin hinge region. In a preferred embodiment the immunoglobulin Fc region comprises at least an immunoglobulin hinge region a CH2 domain and a CH3 domain, and preferably lacks the CH1 domain. In one embodiment, the class of immunoglobulin from which the heavy chain constant region is derived is IgG (Ig γ)(γ subclasses 1, 2, 3, or 4). Other classes of immunoglobulin, IgA (Ig α), IgD (Ig δ), IgE (Ig ϵ) and IgM (Ig μ), may be used. The choice of appropriate immunoglobulin heavy chain constant region is discussed in detail in U.S. Pat. Nos. 5,541,087, and 5,726,044, each of which is incorporated by reference herein, in their entirety. The choice of particular immunoglobulin heavy chain constant region sequences from certain immunoglobulin classes and subclasses to achieve a particular result is considered to be within the level of skill in the art. The portion of the DNA construct encoding the immunoglobulin Fc region preferably comprises at least a portion of a hinge domain, and preferably at least a portion of a CH3 domain of Fc gamma or the homologous domains in any of IgA, IgD, IgE, or IgM. Furthermore, it is contemplated that substitution or deletion of amino acids within the immunoglobulin heavy chain constant regions may be useful in the practice of the methods and compositions disclosed herein. One example would be to introduce amino acid substitutions in the upper CH2 region to create an Fc variant with reduced affinity for Fc receptors (Cole, J. Immunol. 159: 3613 (1997)).

[0118] "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refer to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs)(*e.g.*, Natural Killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and subsequently cause lysis (or other cytotoxic effects) of the target cell. To assess ADCC activity of a molecule of interest, any *in vitro* ADCC assay known in the art can be used, such as that described in U.S. Pat. Nos. 5,500,362 or 5,821,337. Useful effector cells for such assays include, but are not limited to, peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest can be assessed *in vivo*, *e.g.*, in an animal model such as that disclosed in Clynes *et al.*, PNAS 95: 652-656 (1998).

[0119] The term "antigenic determinant binding domain" or "ADBD" as the term is used herein, refers to a sequence of a polypeptide (*e.g.*, an Adapter or CAR) that is sufficient to confer recognition and specific binding to a target antigenic determinant (AD). In some embodiments, the ADBD is an antigen-binding antibody fragment, a scFv, or an antigen-binding peptide that is not based on an antibody or antibody

fragment sequence (*e.g.*, a D domain or an affibody). In some embodiments, the ADBD comprises a non antibody-based binding scaffold (*e.g.*, a D domain, affibody, fibronectin domain, nanobody, lipocalin domain, ankyrin domain, maxybody, Protein A domain, or affilin domain). In some embodiments the ADBD is a D domain. In some embodiments, the ADBD is an antibody-based binding sequence. In some embodiments the ADBD is a scFv or a domain antibody (dAb). In some embodiments, the ADBD has the ability to bind to a target antigen on the surface of a cell. In some embodiments, the ADBD has the ability to bind to a target antigen on the surface of an immune effector cell. In some embodiments, the ADBD has the ability to bind a growth factor receptor or a hormone receptor.

[0120] In particular embodiments, the ADBD is a non antibody-scaffold based polypeptide sequence that is sufficient to confer recognition and specific binding to a target antigenic determinant. In some embodiments, non-antibody based ADBD is a polypeptide that has the ability to bind to target antigen on the surface of a cell. In some embodiments, the non-antibody based ADBD has the ability to bind a growth factor receptor or a hormone receptor. In some embodiments, the ADBD is a D domain-based polypeptide. In particular embodiments, the ADBD is a D domain-based polypeptide that is sufficient to confer recognition and specific binding to a target antigenic determinant. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to target antigen on the surface of a cell. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind a growth factor receptor or a hormone receptor. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind a target antigen on a serum protein.

[0121] The terms "specifically binds" or "having selective affinity for" mean that a binding agent such as an Adapter or CAR, reacts or associates more frequently, more rapidly, with greater duration, with greater affinity, or with some combination of the above to the epitope, protein, or target molecule than with alternative substances, including proteins unrelated to the target epitope. Because of the sequence identity between homologous proteins in different species, specific binding can, in several embodiments, include a binding agent that recognizes a protein or target in more than one species. Likewise, because of homology within certain regions of polypeptide sequences of different proteins, specific binding can include a binding agent that recognizes more than one protein or target. It is understood that, in certain embodiments, a binding agent that specifically binds a first target may or may not specifically bind a second target. As such, "specific binding" does not necessarily require (although it can include) exclusive binding, *e.g.*, binding to a single target. Thus, a binding agent may, in certain embodiments, specifically bind more than one target. In certain embodiments, multiple targets may be bound by the same antigen-binding site on the binding agent.

[0122] The terms "linker," "spacer," and "hinge" are used interchangeably herein to refer to a peptide or other chemical linkage located between two or more otherwise independent functional domains of an Adapter or CAR. For example, a linker may be located between an antigenic determinant domain and an antigenic

determinant binding domain of an Adapter. Similarly, a linker may be located between two antigenic determinant binding domains or an antigenic binding domain and a transmembrane domain of a CAR. Suitable linkers for coupling the two or more domains of an Adapter are described herein and/or will otherwise be clear to a person skilled in the art.

[0123] The term "operably linked," as used herein, indicates that two molecules are attached so as to each retain at least some level of functional activity that each molecule had alone (assuming that each molecule had a function activity). In embodiments when one molecule was without functional activity, it is operably linked with another molecule if the other molecule retains at least some level of its functional activity. Operably linked can also refer to linkage of two non-function molecules. Two molecules can be "operably linked" whether they are attached directly or indirectly (*e.g.*, via a linker).

[0124] "Target" refers to any molecule or combination of molecules that can be bound by an Adapter or CAR, or a component of the Adapter or CAR such as antigenic determinant binding domain.

[0125] The term "target cell" as used herein refers to cells which are involved in a disease and can be targeted by a CAR, an Adapter, and/or CAR/Adapter composition provided herein. Target cells include any cell in a subject (*e.g.*, a human or animal) that can be targeted by a CAR, an Adapter, and/or CAR/Adapter composition. The target cell can be a cell expressing or overexpressing a target specifically bound by a CAR, Adapter, and/or CAR/Adapter composition.

[0126] Expressions like "binding affinity for a target", "binding to a target" and analogous expressions known in the art refer to a property of a polypeptide which may be directly measured through the determination of the affinity constants, *e.g.*, the amount of Adapter that associates and dissociates at a given antigen concentration. Different methods can be used to characterize the molecular interaction, such as, but not limited to, competition analysis, equilibrium analysis and microcalorimetric analysis, and real-time interaction analysis based on surface plasmon resonance interaction (for example using a Biacore® instrument). These methods are well-known to the skilled person and are described, for example, in Neri *et al.*, *Tibtech* 14: 465-470 (1996), and Jansson *et al.*, *J. Biol. Chem.* 272: 8189-8197 (1997).

[0127] "The terms "antigenic determinant" and "epitope" are used interchangeably herein and refer to that portion of any molecule (*e.g.*, a target of interest, or an Adapter) capable of being recognized and specifically bound by a particular binding agent (*e.g.*, an Adapter or CAR). When the recognized molecule is a polypeptide, epitopes can be formed from contiguous amino acids and noncontiguous amino acids and/or other chemically active surface groups of molecules (such as carbohydrates) juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained upon protein denaturing, whereas epitopes formed by tertiary folding are typically lost upon protein denaturing. An epitope typically includes at least 3 amino acids, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

[0128] "Derived from" as that term is used herein, indicates a relationship between a first and a second molecule. It generally refers to structural similarity between the first molecule and a second molecule and does not connote or include a process or source limitation on a first molecule that is derived from a second molecule. For example, in the case of an intracellular signaling domain that is derived from a CD3zeta molecule, the intracellular signaling domain retains sufficient CD3zeta structure such that it has the required function, namely, the ability to generate a signal under the appropriate conditions. It does not connote or include a limitation to a particular process of producing the intracellular signaling domain, *e.g.*, it does not mean that, to provide the intracellular signaling domain, one must start with a CD3zeta sequence and delete unwanted sequence, or impose mutations, to arrive at the intracellular signaling domain.

[0129] The term "naturally occurring" when used in connection with biological materials such as a nucleic acid molecules, polypeptides, antigenic determinants, and host cells, refers to those which are found in nature and not modified by a human being. Conversely, "non-natural" or "synthetic" when used in connection with biological materials refers to those which are not found in nature and have been modified by a human being.

[0130] As used herein "modifications" with respect to a sequence of reference includes substitutions, deletions insertions and/or additions of a sequence when compared to the corresponding amino acid position(s) of the reference sequence.

[0131] A "substitution" with respect to a sequence of reference refers to a replacement of a particular amino acid residue with a different amino acid residue at a corresponding amino acid position of the reference sequence.

[0132] A "conservative" amino acid substitution is one in which one amino acid residue is replaced with another amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (*e.g.*, lysine (K), arginine (R), histidine (H)), acidic side chains (*e.g.*, aspartic acid (D), glutamic acid (E)), uncharged polar side chains (*e.g.*, glycine (G), asparagine (N), glutamine (Q), serine (S), threonine (T), tyrosine (Y), cysteine (C)), nonpolar side chains (*e.g.*, alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), methionine (M), tryptophan (W)), beta-branched side chains (*e.g.*, threonine (T), valine (V), isoleucine (I)) and aromatic side chains (*e.g.*, tyrosine (Y), phenylalanine (F), tryptophan (W), histidine (H)). For example, substitution of a phenylalanine for a tyrosine is a conservative substitution. In one embodiment, conservative substitutions in the sequences of the Adapter or CAR results in a retained specific binding of the Adapter or CAR containing the substitution to the target of interest to which it binds. Methods of identifying nucleotide and amino acid conservative substitutions and non-conservative substitutions which confer, alter or maintain selective binding affinity are known in the art (*see, e.g.*, Brummell, *Biochem.* 32: 1180-1187 (1993); Kobayashi, *Protein Eng.* 12(10): 879-884 (1999); and Burks, *PNAS* 94: 412-417 (1997)).

[0133] A "non-conservative" amino acid substitution is one in which one amino acid residue is replaced with another amino acid residue having a dissimilar side chain. In one embodiment, non-conservative substitutions in the sequences of the Adapter or CAR result in a retained specific binding of the Adapter or CAR containing the substitution to the target of interest to which it binds.

[0134] "Non natural amino acids," "amino acid analogs" and "non-standard amino acid residues" are used interchangeably herein. Non-natural amino acids that can be substituted in an Adapter as provided herein are known in the art. In one embodiment the non-natural amino acid is 4-hydroxyproline which can be substituted for proline; 5-hydroxylysine which can be substituted for lysine; 3-methylhistidine which can be substituted for histidine; homoserine which can be substituted for serine; and ornithine which can be substituted for lysine. Additional examples of non-natural amino acids that can be substituted in an Adapter include, but are not limited to molecules such as: D-isomers of the common amino acids, 2,4-diaminobutyric acid, alpha-amino isobutyric acid, A-aminobutyric acid, Abu, 2-amino butyric acid, gamma-Abu, epsilon-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, beta-alanine, lanthionine, dehydroalanine, γ -aminobutyric acid, selenocysteine and pyrrolysine fluoro-amino acids, designer amino acids such as beta-methyl amino acids, C alpha-methyl amino acids, and N alpha-methyl amino acids, or combinations of non-natural amino acids. Still additional non-natural amino acids can include 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine, and/or D-isomers of amino acids. As discussed herein, in several embodiments non-natural amino acids or amino acid analogs can include deletion of one or more amino acids from a sequence.

[0135] The terms "polynucleotide" and "nucleic acid," used interchangeably herein, refer to a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. These terms include, but are not limited to, DNA, RNA, cDNA (complementary DNA), mRNA (messenger RNA), rRNA (ribosomal RNA), shRNA (small hairpin RNA), snRNA (small nuclear RNA), snoRNA (short nucleolar RNA), miRNA (microRNA), genomic DNA, synthetic DNA, synthetic RNA, and/or tRNA. In some embodiments, an isolated polynucleotide is a modified mRNA comprising non-naturally occurring nucleosides or nucleotides. In some embodiments, a modified mRNA comprises 2-thiouridine, pseudouridine, or 1-methylpseudouridine.

[0136] The term "naked DNA" as used herein refers to DNA (*e.g.*, histone free DNA) encoding a protein, such as an Adapter or a CAR, that is cloned in a suitable expression vector in proper orientation for expression (*e.g.*, a plasmid). Viral vectors which may be used include but are not limited to SIN lentiviral vectors, retroviral vectors, foamy virus vectors, adenovirus vectors, adeno-associated virus (AAV) vectors, hybrid vectors and/or plasmid transposons (for example sleeping beauty transposon system) or integrase

based vector systems. Other vectors that can be used in connection with making and using Adapters and CARs are described herein or otherwise known in the art.

[0137] The terms "vector", "cloning vector" and "expression vector" as used herein refer to the vehicle by which a nucleic acid sequence (*e.g.*, an Adapter or CAR coding sequence) can be maintained or amplified in a host cell (*e.g.*, cloning vector) or introduced into a host cell, so as to transform the host and promote expression (*e.g.*, transcription and translation) of the introduced sequence. Vectors include plasmids, phages, viruses, etc.

[0138] A "host cell" includes an individual cell or cell culture which can be or has been a recipient of nucleic acids encoding an Adapter or CAR. Host cells include but are not limited to viral particles, phagemids, bacteria, yeast, plant, animal, and mammalian cells. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in total DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation and/or change. A host cell includes cells transfected or infected *in vivo*, *in vitro*, or *ex vivo* with nucleic acids encoding an Adapter or CAR. In some examples, the host cell is capable of expressing an Adapter. In some examples, the host cell is capable of expressing and secreting an Adapter. In some examples, the host cell is capable of expressing a CAR. In some examples, the host cell is capable of expressing and displaying a CAR on its surface. "Expression" includes transcription and/or translation.

[0139] As used herein, the terms "pharmaceutically acceptable," or "physiologically tolerable" and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used interchangeably and represent that the materials are capable of administration to or upon a human without the production of therapeutically prohibitive undesirable physiological effects such as nausea, dizziness, gastric upset and other therapeutically prohibitive undesirable physiological effects known in the art.

[0140] "Parenteral" administration of an immunogenic composition includes, *e.g.*, subcutaneous (*s.c.*), intravenous (*i.v.*), intramuscular (*i.m.*), or intrasternal injection, or infusion techniques.

[0141] The term "stimulate" or "stimulation" refers to a primary response induced by binding of a stimulatory molecule with its cognate ligand thereby mediating a signal transduction event, such as, but not limited to, signal transduction via the appropriate receptor, *e.g.*, T or NK receptor.

[0142] "Modulate" or "modulation" means adjustment or regulation of amplitude, frequency, degree, or activity. In another related aspect, such modulation may be positively modulated (*e.g.*, an increase in frequency, degree, or activity) or negatively modulated (*e.g.*, a decrease in frequency, degree, or activity). In several embodiments, modulation in a positive or negative direction is referenced as compared to the cell, tissue, or organ function prior to administration of a therapeutic. In additional embodiments, modulation in a positive or negative direction is referenced with respect to a normal, healthy cell, tissue or organ.

[0143] An "effective amount" of a CAR cell, Adapter, and/or CAR cell/Adapter composition as provided herein is an amount sufficient to carry out a specifically stated purpose such as to bring about an observable change in the level of one or more biological activities related to the target to which the CAR cell and/or Adapter binds. In certain embodiments, the change increases the level of target activity. In other embodiments, the change decreases the level of target activity. An "effective amount" can be determined empirically and in a routine manner, in relation to the stated purpose. The term "therapeutically effective amount" refers to an amount of a CAR cell and/or Adapter, or other therapeutic agent effective to "treat" (*e.g.*, reduce symptoms of) a disease or disorder in a subject (mammal). A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result.

[0144] "Patient," "subject," "animal" and "mammal" are used interchangeably and refer to mammals such as human patients and non-human primates, as well as experimental animals such as rabbits, rats, and mice, and other animals. Animals include all vertebrates, *e.g.*, mammals and non-mammals, such as chickens, amphibians, and reptiles. "Mammal" as used herein refers to any member of the class Mammalia, including, without limitation, humans and nonhuman primates such as chimpanzees and other apes and monkey species; farm animals such as cattle, sheep, pigs, goats and horses; domestic mammals such as dogs and cats; laboratory animals including rodents such as mice, rats and guinea pigs, and other members of the class Mammalia known in the art. In a particular embodiment, the patient is a human. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as embryos and fetuses, whether male or female, are intended to be included within the scope of this term.

[0145] The terms "treat," "treatment," and "treating," as used herein refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen or delay) the symptoms, complications, or biochemical indicia of a disease, condition, or disorder, alleviating the symptoms or arresting or inhibiting further development of the disease, condition, or disorder. Treatment can be prophylactic (to prevent or delay the onset of the disease, or to prevent the manifestation of clinical or subclinical symptoms thereof) or therapeutic suppression or alleviation of symptoms after the manifestation of the disease, condition, or disorder targeted pathologic condition, prevent the pathologic condition, pursue or obtain beneficial results, or lower the chances of the individual developing the condition even if the treatment is ultimately unsuccessful. Those in need of treatment include those already with the condition as well as those prone to have the condition or those in whom the condition is to be prevented. Treatment can be with a CAR cell, Adapter, and/or CAR cell/Adapter composition, alone or in combination with an additional therapeutic agent. In some embodiments, the terms "treat," "treatment," and "treating," are used herein to refer to therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen or delay) the symptoms, complications, or biochemical indicia of a proliferative disorder, or the

amelioration of one or more symptoms (preferably, one or more discernible symptoms) of a proliferative disorder. In specific embodiments, the terms "treat", "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" refer to the inhibition of the progression of a proliferative disorder, either physically by, *e.g.*, stabilization of a discernible symptom, physiologically by, *e.g.*, stabilization of a physical parameter, or both. In other embodiments the terms "treat", "treatment" and "treating" refer to the reduction or stabilization of tumor size, tumor cell proliferation or survival, or cancerous cell count.

[0146] "Cancer," "tumor," or "malignancy" are used as synonymous terms and refer to any of a number of diseases that are characterized by uncontrolled, abnormal proliferation of cells, the ability of affected cells to spread locally or through the bloodstream and lymphatic system to other parts of the body (metastasize) as well as any of a number of characteristic structural and/or molecular features. "Tumor," as used herein refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. A "cancerous tumor," or "malignant cell" is understood as a cell having specific structural properties, lacking differentiation and being capable of invasion and metastasis. Cancers that can be treated using a CAR cell, Adapter, and/or CAR cell/Adapter composition provided herein include without limitation, breast, lung, brain, cervical, skin, bone, liver, pancreatic, colorectal, renal, head and neck, ovarian, hematopoietic (*e.g.*, leukemia), and prostate cancer, and lymphoma. Other types of cancer and tumors that may be treated using a CAR cell, Adapter, and/or CAR cell/Adapter composition are described herein or otherwise known in the art. A reference to cancers, tumors, or tumor cells of a particular "type" is understood to mean cancer, tumors, or tumor cells characterized by a specific disease. For example, in some embodiments a first and second cancer of the same type is mixed cellularity Hodgkin's lymphoma and lymphocyte rich Hodgkin's lymphoma. In other embodiments a first and second cancer of the same type is precursor B cell acute lymphoblastic leukemia (ALL) and mature B cell ALL. Examples of a first and second cancer of a different type include, for example, Hodgkin's lymphoma and ALL.

[0147] The term "tumor antigen" refers to an antigen that is common to a specific hyperproliferative disorder such as cancer. The terms "tumor antigen" or "cancer antigen" are used interchangeably herein. In certain aspects, antigens are derived from cancers including but not limited to primary or metastatic melanoma, thymoma, lymphoma, sarcoma, lung cancer (*e.g.*, NSCLC or SCLC), liver cancer, non-Hodgkin's lymphoma, Hodgkin's lymphoma, leukemias, multiple myeloma, glioblastoma, neuroblastoma, uterine cancer, cervical cancer, renal cancer, thyroid cancer, bladder cancer, kidney cancer, mesothelioma, and adenocarcinomas such as breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, colon cancer and other cancers known in the art. In some embodiments, the cancer is B-cell acute lymphoid leukemia ("BALL"), T cell acute lymphoid leukemia ("TALL"), acute lymphoid leukemia (ALL), acute myelogenous leukemia (AML); one or more

chronic leukemias including but not limited to chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL); additional hematologic cancers or hematologic conditions including, but not limited to B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia.

[0148] Tumor and cancer antigens may be further defined as "tumor-specific antigens (TSA)", "cancer-specific antigens (CSA)", "tumor-associated antigens (TAA)", or "cancer-associated antigens (CAA)". A TSA is an antigen that is unique to tumor cells and does not occur on other cells in the body. A TAA is an antigen that is found on both tumor and some normal cells. A TAA may be expressed on normal cells under conditions that fail to induce a state of immunologic tolerance to the antigen. The expression of the TAAs on the tumor may occur under conditions that enable the immune system to respond to the antigen. TAAs may be expressed on normal cells during fetal development when the immune system is immature and unable to respond or may be normally present at extremely low levels on normal cells but which are expressed at much higher levels on tumor cells. Because of the dynamic nature of tumors, in some instances, tumor cells may express unique antigens at certain stages, and at others also express antigens that are also expressed on non-tumor cells. Thus, inclusion of a certain marker as a TAA does not preclude it being considered a TSA. In some embodiments, the TAA and/or TSA that contains an antigenic determinant specifically bound by a CAR cell, Adapter, and/or CAR cell/Adapter composition provided herein, is selected from: BCMA, CD19, CD20, CD22, CD30, CD33/IL3Ra, CD70, CD123, CD171 (L1-CAM), CS1, EGFRvIII, GD2, Lewis^Y, ROR 1, mesothelin, IL13Ra2, cMet, PSMA, folate receptor alpha (FR-alpha), CEA, ErbB2 (HER-2/neu); EGFR (HER), PSCA, PSA, MUC1, MUC16, CD44v6, CD44v6/7, CD44v7/8, CD55, IL11Ra, EphA2, EGP40, TAG72, CAIX, HMW-MAA (CSPG4), MAGEA4, NKG2D ligands, beta-HCG, Glycolipid F77, HLA-A2 (NY-ESO- 1), HMW-MAA, GD3, TCR, MAGE A3, MART1, WT1, thyroglobulin, gp100 (Pmel 17), tyrosinase, TRP1, TRP2, HLA-A1, MAGE1, MAGE3, BAGE, GAGE1, GAGE2, pi5, p53, Ras, BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, MYL-RAR; VEGFR2, FAP, FAR, EBVA, HPV antigen E6, HPV antigen E7, TSP-180, MAGE4, MAGE5, MAGE6, RAGE, pl85erbB2, pl80erbB3, nm-23H1, CA 19-9, CA72-4, CAM 17.1, NuMa, K-ras, beta-Catenin, CDK4, Mum-1, p15, p16, 43-9F, alpha-fetoprotein, BCA225, BTAA, CA125, CA 15-3, CA 27.29(BCAA), CA195, CA242, CA50, CAM43, CD68, CO-029, FGF5, G250, HTgp-175, M344, MA50, MG7-Ag, NB/70K, NY-CO-1, RCAS1, SDCCAG16, M2BP, TAAL6, TLP, and TPS.

[0149] The term "CS1" as used herein refers to an NK cell receptor regulating immune functions that is also expressed on B cells, T cells, dendritic cells, NK-T cells, and monocytes. CS1 is overexpressed in multiple myeloma and has been successfully targeted for immunotherapy multiple myeloma. Malaer & Mathew, Am J

Cancer Res. 7(8): 1637–1641 (2017). CS1 is also known as SLAMF7, protein 19A, CRACC, and CD319. The term "CS1" includes variants, isoforms, homologues, orthologs and paralogs. CS1 is a transmembrane protein with various differentially spliced isoforms. In some embodiments, the amino acid sequence of human CS1, comprising a 22 amino acid residue N-terminal signal sequence (MAGSPTCLTLIYLWQLTGSA, SEQ ID NO: 1119) and an extracellular domain comprising the 226 N-terminal residues (SEQ ID NO: 1120), has Genbank Accession No. NP_067004 (SEQ ID NO: 1121). In some embodiments, the amino acid sequence of human CS1 has Genbank Accession No. NP_001269517, NP_001269518, NP_001269519, NP_001269520, NP_001269521, NP_001269522, NP_001269523, NP_001269524, or NP_001269525.

[0150] The term "autoimmune disease" as used herein is defined as a disorder that results from an autoimmune response. An autoimmune disease is the result of an inappropriate and excessive response to a self-antigen. Examples of autoimmune diseases include but are not limited to, Addison's disease, alopecia areata, ankylosing spondylitis, autoimmune hepatitis, autoimmune parotitis, Crohn's disease, diabetes (Type I), dystrophic epidermolysis bullosa, epididymitis, glomerulonephritis, Graves' disease, Guillain-Barré syndrome, Hashimoto's disease, hemolytic anemia, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, pemphigus vulgaris, psoriasis, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, Sjögren's syndrome, spondyloarthropathies, thyroiditis, vasculitis, vitiligo, myxedema, pernicious anemia, ulcerative colitis, among others.

[0151] The term "transduction" as used herein refers to the introduction of a foreign nucleic acid into a cell using a viral vector. "Transfection" as used herein refers to the introduction of a foreign nucleic acid into a cell using recombinant DNA technology. The term "transformation" means the introduction of a "foreign" (*e.g.*, extrinsic, extracellular, or otherwise non-endogenous) nucleic acid (DNA or RNA) sequence to a host cell, so that the host cell will express the introduced nucleic acid to produce a desired substance, such as a protein or enzyme coded by the introduced coding sequence. The introduced nucleic acid sequence can also be called a "cloned" or "foreign" gene or sequence, can include regulatory or control sequences, such as start, stop, promoter, signal, secretion, or other sequences used by a cell's genetic machinery. The nucleic acid sequence can include nonfunctional sequences or sequences with no known function. A host cell that receives and expresses introduced nucleic acid (*e.g.*, DNA or RNA) has been "transformed" and is a "transformant" or a "clone." The DNA or RNA introduced to a host cell can come from any source, including cells of the same genus or species as the host cell, or cells of a different genus or species or may be non-naturally occurring.

[0152] The term "D domain" refers to a target binding polypeptide sharing certain sequence and certain structural features of the reference scaffold sequence: MGSWAEFKQRLAAIK
TRLQALGGSEAELAAFEKEIAAFESLQAYKKGKNPEVEALRK EAAAIRDELQAYRHN (SEQ ID NO: 1) (*see* WO 2016/164305 and WO 2016/164308, each of which is incorporated by reference herein in its entirety). The reference scaffold is a variant of a non-naturally occurring and targetless antiparallel three

helical bundle reference polypeptide originally engineered as an exercise in protein folding (*see*, Walsh *et al.*, PNAS 96: 5486-5491 (1999) incorporated by reference herein in its entirety). It has been discovered that polypeptides containing modifications of the targetless reference scaffold having the amino acid sequence of SEQ ID NO: 1 are able to specifically bind targets of interest. Thus, a D domain, or a molecule comprising a D domain, can specifically (non-randomly) bind to a target molecule. While not wishing to be bound by theory, it is believed that in designing the D domain, the structural constraints of surface-exposed residues (that can be modified) confer the ability of the surface exposed residues to specifically bind a target of interest.

[0153] "Co-express" as used herein refers to expression of two or more protein coding sequences by the same cell or cell population. The coding sequences may be for example, nucleic acids that each encode a single protein or a chimeric protein as a single polypeptide chain.

[0154] "Antigen loss escape variants" as used herein refer to cells which exhibit reduced or loss of expression of the target antigen, which antigenic determinants are targeted by an Adapter or CAR provided herein.

II. Antigenic Determinants (ADs)

[0155] Antigenic determinants (ADs) are epitopes that are capable of being recognized and specifically bound by an antigenic determinant binding regions (ADBDS) (*e.g.*, antigen-binding fragments of an antibody or alternative scaffold binding domains (ASBDs) (*e.g.*, D domains)). The ADs in the Adapters and on the target cells provided herein can be bound by the CARs discussed below.

[0156] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an AD that is present in a naturally occurring protein or other molecule. In some embodiments, the AD is an AD that is endogenous to humans.

[0157] In some embodiments, the AD in the Adapter is an AD that is present on a target cell.

[0158] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an AD that is present in a transmembrane protein, *e.g.*, an AD that is present in the extracellular portion of a transmembrane protein. In some embodiments, the AD is a tumor antigen. In some embodiments, the AD is a tumor-associated antigen. In some embodiments, the AD is a tumor-specific antigen.

[0159] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is a cancer antigen. In some embodiments, the AD is a cancer-associated antigen. In some embodiments, the AD is a cancer-specific antigen.

[0160] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of BCMA. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 5.

[0161] In some embodiments, the AD is an epitope of CD19. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 3.

[0162] In some embodiments, the AD is an epitope of CD20. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 6-9, or 10.

[0163] In some embodiments, the AD is an epitope of CD22. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 41.

[0164] In some embodiments, the AD is an epitope of CD123. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 11.

[0165] In some embodiments, the AD is an epitope of CD37. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 12 or 13.

[0166] In some embodiments, the AD is an epitope of CS1. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1139. In further embodiments, the AD is an epitope of CS1 that is bound by elotuzumab.

[0167] In some embodiments, the AD is an epitope of HER2. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 42.

[0168] In some embodiments, the AD is an epitope of AFP. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 15.

[0169] In some embodiments, the AD is an epitope of AFP p26. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 16. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1117. In further embodiments, the AD comprises the amino acid residues of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123.

[0170] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is expressed on the surface of an immune effector cell.

[0171] In some embodiments, the AD is an epitope of the extracellular domain (ECD) of human CD45. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 29-766 of SEQ ID NO: 1106.

[0172] In some embodiments, the AD is an epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the AD is an epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0173] In some embodiments, the AD is an epitope of CD26. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 29-766 of SEQ ID NO: 1113.

[0174] In some embodiments, the AD is an epitope of CD30. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 19-379 of SEQ ID NO: 1114.

[0175] In some embodiments, the AD is an epitope of CD33. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 18-259 of SEQ ID NO: 1115.

[0176] In some embodiments, the AD is an epitope of CD38. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 43-300 of SEQ ID NO: 1116.

[0177] In some embodiments, the AD is an epitope of a human intracellular protein. In further embodiments, the AD is an epitope of an intracellular portion of a membrane associated receptor protein selected from the group: cytokine receptor, chemokine receptor, T cell receptor, B cell receptor, NK cell receptor, myeloid cell receptor, endothelial cell receptor, and epithelial cell receptor. In some embodiments, the AD is an epitope of the intracellular portion of CD3, CD137, CD279, CD223, CD152, CD28, and VEGFR-2. In some embodiments, the AD is an epitope of a human nuclear protein.

[0178] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of a tumor antigen associated with a malignant tumor. In some embodiments, the AD is an epitope of a tissue-specific antigen from a melanoma. In some embodiments, the AD is an epitope of a tissue-specific melanoma antigen selected from: MART-1, tyrosinase, and GP 100. In some embodiments, the AD is an epitope of a tissue-specific antigen from a prostate cancer. In some embodiments, the tissue-specific prostate cancer antigen is selected from: prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA). In some embodiments, the AD is an epitope of a transformation-related molecule. In further embodiments, the AD is an epitope of ErbB2 (HER2). In some embodiments, the AD is an epitope of an onco-fetal antigen. In some embodiments, the AD is an epitope of carcinoembryonic antigen (CEA). In some embodiments, the AD is an epitope of a B-cell lymphoma-specific idiotype immunoglobulin. In some embodiments, the AD is an epitope of a B-cell

differentiation antigen. In some embodiments, the AD is an epitope of a B-cell differentiation antigen selected from: CD19, CD20, and CD37. In some embodiments, the AD is an epitope of an antigen on myeloid cells. In some embodiments, the AD is an epitope of a myeloid cell antigen selected from: TSLPR and IL-7R. In some embodiments, the AD is an epitope of a cancer testis (CT) antigen. In some embodiments, the AD is an epitope of a cancer testis (CT) selected from: NY-ESO-1 and LAGE-1a. In some embodiments, the AD is an epitope of an antigen selected from: CS1, CD38, CD138, MUC1, HM1.24, CYP1B1, SP17, PRAME, Wilms' tumor 1 (WT1), and heat shock protein gp96 on multiple myeloma cells.

[0179] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of a TSA or TAA. In some embodiments, the AD is an epitope of a tumor differentiation antigen. In some embodiments, the AD is an epitope of a tumor differentiation antigen selected from: MART1/MelanA, gp100 (Pmel 17), tyrosinase, TRP1, and TRP2. In some embodiments, the AD is an epitope of a tumor-specific multilineage antigen. In some embodiments, the AD is an epitope of a tumor-specific multilineage antigen selected from: MAGE1, MAGE3, BAGE, GAGE1, GAGE2, and p15. In some embodiments, the AD is an epitope of an overexpressed embryonic antigen. In some embodiments, the AD is an epitope of CEA. In some embodiments, the AD is an epitope of an overexpressed oncogene or mutated tumor-suppressor gene product. In some embodiments, the AD is an epitope of an overexpressed oncogene or mutated tumor-suppressor gene product selected from: p53, Ras, and HER2/neu. In some embodiments, the AD is an epitope of a unique tumor antigen resulting from chromosomal translocations. In some embodiments, the AD is an epitope of a unique tumor antigen resulting from a chromosomal translocation selected from: BCR-ABL, E2A-PRL, H4-RET, IGH-IGK, and MYL-RAR. In some embodiments, the AD is an epitope of a viral antigen. In some embodiments, the AD is an epitope of the Epstein Barr virus antigen EBVA. In other embodiments, the AD is an epitope of the human papillomavirus (HPV) antigen E6 or E7. In some embodiments, the AD is an epitope of a large, protein-based antigen.

[0180] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of a hematological tumor antigen. In some embodiments, the AD is an epitope of an antigen selected from: BCMA, CD19, CD20, CD22, CD30, CD138, CD33, CD38, CD123, CS1, ROR1, Lewis^Y, Ig kappa light chain, TCR, BCMA, TACI, BAFFR (CD268), and a NKG2DL ligand.

[0181] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of a solid tumor antigen. In some embodiments, the AD is an epitope of an antigen selected from: disialoganglioside (GD2), o-acetyl GD2, EGFRvIII, HER2 (ErbB2), VEGFR2, FAP, mesothelin, IL13Ra2 (glioma), cMET, PSMA, folate receptor alpha, L1CAM, carcinoembryonic antigen (CEA), and EGFR.

[0182] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of an antigen selected from the group: CD137, PDL1, CTLA4, CD47, KIR, TNFRSF10B (DR5), TIM3, PD1, cMet, Glycolipid F77, EGFRvIII, HLAA2 (NY-ESO-1), LAG3, CD134 (OX40), HVEM, BTLA, TNFRSF25

(DR3), CD133, MAGE A3, PSCA, MUC1, CD44v6, CD44v6/7, CD44v7/8, IL11Ra, ephA2, CAIX, MNCAIX, CSPG4, MUC16, EPCAM (EGP2), TAG72, EGP40, ErbB receptor family, ErbB2 (HER2), ErbB3/4, RAGE1, GD3, FAR, Lewis^Y, NCAM, HLAA1/MAGE1, MAGEA1, MAGEA3, MAGE-A4, B7H3, WT1, MelanA (MART1), HPV E6, HPV E7, thyroglobulin, tyrosinase, PSA, CLL1GD3, Tn Ag, FLT3, KIT, PRSS21, CD24, PDGFR-beta, SSEA4, prostase, PAP, ELF2M, ephB2, IGF1, IGFII, IGF1 receptor, LMP2, gp100, bcr-ab1, Fucosyl GM1, sLe, GM3, TGS5, folate receptor beta, TEM1 (CD248), TEM7R, CLDN6, TSHR, GPRC5D, CXORF61, CD97, CD7a, HLE, CD179a, ALK, Physialic acid, PLAC1, GloboH, NY—BR-1, UPK2, HAVCR1, ADRB3, PANX3, GPR20, LY6K, OR51E2, TARP, LAGE1a, legumain, E7, ETV6-AML, sperm protein 17, XAGE1, Tie 2, MAD-CT1, MAD-CT2, Fos-related antigen 1, p53, p53 mutant, prostein, survivin, telomerase, PCTA1 (Galectin 8), Ras mutant, hTERT, sarcoma translocation breakpoints, ML-IAP, ERG (TMPRSS2 ETS fusion gene), NA17, PAX3, Androgen receptor, Cyclin B1, MYCN, RhoC, TRP2, CYP1B1, BORIS, SART3, PAX5, OY-TES1, LCK, AKAP4, SSX2, reverse transcriptase, RU1, RU2, intestinal carboxyl esterase, neutrophil elastase, mut hsp70-2, CD79a, CD79b, CD72, LAIR1, FCAR, LILRA2, CD300LF, CLEC12A, BST2, EMR2, LY75, GPC3, FCRLS, IGLL1, TSP-180, MAGE4, MAGE5, MAGE6, VEGFR1, IGF1R, hepatocyte growth factor receptor, p185ErbB2, p180ErbB-3, nm-23H1, CA 19-9, CA 72-4, CAM 17.1, NuMa, K-ras, beta-Catenin, CDK4, Mum1, p15, p16, 43-9F, 5T4, 791Tgp72, β -human chorionic gonadotropin, BCA225, BTAA, CA125, CA15-3, CA 27.29 (BCAA), CA195, CA242, CA-50, CAM43, CD68, CO-029, FGF5, G250, HTgp-175, M344, MA50, MG7-Ag, MOV18, NB/70K, NY-CO1, RCAS1, SDCCAG16, M2BP, TAAL6, TLP, and TPS, glioma-associated antigen, alpha-fetoprotein (AFP), a p26 fragment of AFP, or variants thereof, lectin-reactive AFP, and TLR4.

[0183] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of a TSA or TAA. In some embodiments the AD is an epitope of an antigen selected from: PTGER4, ITGA4, CD37, CD52, CD62L (L-selectin), CXCR4, CD69, EVI2B (CD361), SLC39A8, MICB, LRRC70, CLELC2B, HMHA1, LST1, and CMTM6 (CKLFSF6). In some embodiments the AD is an epitope of BCMA. In some embodiments the AD is an epitope of CS1.

[0184] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of an antigen selected from: PDGFRA, VEGFR1, VEGFR3, neuropilin 1 (NRP1), neuropilin 2 (NRP2), betacellulin, PLGF, RET (rearranged during transfection), TIE1, TIE2 (TEK), CA125, CD3, CD4, CD7, CD10, CD13, CD25 CD32, CD32b, CD44 (*e.g.*, CD44v6), CD47, CD49e (integrin alpha 5), CD54 (ICAM), CD55, CD64, CD74, CD80, CD90, CD200, CD147, CD166, CD200, ESA, SHH, DHH, IHH, patched 1 (PTCH1), smoothened (SMO), WNT1, WNT2B, WNT3A, WNT4, WNT4A, WNT5A, WNT5B, WNT7B, WNT8A, WNT10A, WNT10B, WNT16B, LKP5, LRP5, LRP6, FZD1, FZD2, FZD4, FZD5, FZD6, FZD7, FZD8, Notch, Notch1, Notch3, Notch4, DLL4, Jagged, Jagged1, Jagged2, Jagged3, TNFRSF1A (TNFR1, p55, p60), TNFRSF1B (TNFR2), TNFRSF6 (Fas, CD95), TNFRSF6B (DcR3), TNFRSF7 (CD27), TNFSF9 (41BB

Ligand), TNFRSF8 (CD30), TNFRSF10A (TRAILR1, DR4), TNFRSF11A (RANK), TNFRSF12 (TWEAKR), TNFRSF19L (KELT), TNFRSF19 (TROY), TNFRSF21 (DR6), IL1R1, IL1R2, IL2R, IL5R, IL6R, IL8R, IL10R, IL12R, IL13R, IL15R, IL18R, IL19R, IL21R, IL23R, XAG1, XAG3, REGIV, FGFR1, FGFR2, FGFR3, ALK, ALK1, ALK7, ALCAM, Axl, TGFb, TGFb2, TGFb3, TGFBR1, IGFIIR, BMPRI, N-cadherin, E-cadherin, VE-cadherin, ganglioside GM2, ganglioside GD3, PSGR, DCC, CDCP1, CXCR2, CXCR7, CCR3, CCR4, CCR5, CCR7, CCR10, Claudin1, Claudin2, Claudin3, Claudin4, TMEFF2, neuregulin, MCSF, CSF, CSFR (fms), GCSF, GCSFR, BCAM, BRCA1, BRCA2, HLA-DR, ABCC3, ABCB5, HM 1.24, LFA1, LYNX, S100A8, S100A9, SCF, Von Willebrand factor, Lewis Y6 receptor, CA G250 (CA9), CRYPTO, VLA5, HLADR, MUC18, mucin CanAg, EGFL7, integrin avb3, integrin $\alpha 5\beta$ activin Bl alpha, leukotriene B4 receptor (LTB4R), neurotensin NT receptor (NTR), 5T4 oncofetal antigen, Tenascin C, MMP, MMP2, MMP7, MMP9, MMP12, MMP14, MMP26, cathepsin G, SULF1, SULF2, MET, CA9, TM4SF1, syndecan (SDC1), Ephrin B4, TEM1, TGFbeta 1, and TGFBR11.

[0185] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of an antigen associated with an autoimmune disorder, associated with an inflammatory or other disorder of the immune system, or is associated with regulating an immune response.

[0186] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of an immunoinhibitory target. In another embodiment, the AD is an epitope of an immunoinhibitory target selected from: IL1Ra, IL6R, CD26L, CD28, CD80, FcGamma RIIB. In another embodiment, the AD in the Adapter is an epitope of an immunostimulatory target selected from: CD25, CD28, CTLA4, PD1, B7H1 (PDL1), B7H4 TGFbeta, TNFRSF4 (OX40), TNFRSF5 (CD40), TNFRSF9 (41BB, CD137), TNFRSF14 (HVEM), TNFRSF25 (DR3), and TNFRSF18 (GITR).

[0187] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of a target selected from: IL1Rb, C3AR, C5AR, CXCR1, CXCR2, CCR1, CCR3, CCR7, CCR8, CCR9, CCR10, ChemR23, MPL, GP130, TLR2, TLR3, TLR4, TLR5, TLR7, TLR8, TLR9, TREM1, TREM2, CD49a (integrin alpha 1), integrin $\alpha 5\beta 3$, alpha4 integrin subunit, A4B7 integrin, cathepsin G, TNFRSF3 (LTBR), TNFRSF6 (Fas, CD95), TNFRSF6B (DcR3), TNFRSF8 (CD30), TNFRSF11A (RANK), TNFRSF16 (NGFR), TNFRSF19L (RELt), TNFRSF19 (TROY), TNFRSF21 (DR6), CD14, CD23, CD36, CD36L, CD39, CD91, CD153, CD164, CD200, CD200R, B71 (CD80), B72 (CD86), B7h, B7DC (PDL2), ICOS, ICOSL, MHC, CD, B7H2, B7H3, B7x, SLAM, KIM1, SLAMF2, SLAMF3, SLAMF4, SLAMF5, SLAMF6, SLAMF7, TNFRSF1A (TNFR1, p55, p60), TNFRSF1B (TNFR2), TNFRSF7 (CD27), TNFRSF12 (TWEAKR), TNFRSF5 (CD40), IL1R, IL2R, IL4Ra, IL5R, IL6R, IL15R, IL17R, IL17Rb, IL17RC, IL22RA, IL23R, TSLPR, B7RP1, cKit, GMCSF, GMCSFR, CD2, CD4, CD11a, CD18, CD30, CD40, CD86, CXCR3, CCR2, CCR4, CCR5, CCR8, RhD, IgE, and Rh.

[0188] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of an antigen associated with a neurological disorder.

[0189] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of a target selected from: amyloid beta (Abeta), beta amyloid, PLP, ROBO4, ROBO, LINGO, gpIIb, gpIIIa, integrin $\alpha 2\beta 3$, AOC3, TNFRSF19L (RELT), TNFRSF19 (TROY), and sclerostin.

[0190] The above targets and those otherwise described herein are intended to be illustrative and not limiting.

[0191] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is bound by a chimeric antigen receptor (CAR). In some embodiments, the AD is bound by a cell expressing a chimeric antigen receptor. In some embodiments, the AD is bound by a scFv. In some embodiments, the AD is bound by an alternative scaffold binding domain (ASBD). In some embodiments, the AD is bound by a D domain. In some embodiments, the AD is bound by an antibody or an antigen-binding fragment thereof.

III. *Antigenic Determinant Binding Domains (ADBDS)*

[0192] A protein domain that binds to an antigenic determinant (AD) (*e.g.*, as described in Section II and Section XI) is referred to herein as an "antigenic-determinant binding domain" or "ADBDS." In some embodiments, the ADBDS is sufficient to confer recognition and specific binding to a target of interest. The ADBDS described herein can be present in an Adapter (*e.g.*, as described in Section V and Section XI) and/or in a chimeric antigen receptor (CAR) (*e.g.*, as described in Section VI and Section XI).

[0193] The target of interest specifically bound by the ADBDS (*e.g.*, of an Adapter and/or CAR) can be any molecule for which it is desirable for an Adapter and/or CAR to bind, *e.g.*, any of the ADs described herein (*e.g.*, as described in Section II and Section XI). In some embodiments, the target(s) specifically bound by the ADBDS can be any target of purification, manufacturing, formulation, therapeutic, diagnostic, or prognostic relevance or value. In some embodiments, the target of the ADBDS can be naturally occurring or synthetic. In some embodiments, the target of the ADBDS can be an extracellular component, an intracellular component, a soluble factor (*e.g.*, an enzyme, hormone, cytokine, growth factor, toxin, venom, pollutant, etc.), or a transmembrane protein (*e.g.*, a cell surface receptor).

[0194] In some embodiment, the ADBDS (*e.g.*, of an Adapter and/or CAR) specifically binds a target of interest on the surface of a target cell. In some embodiments, the ADBDS specifically binds a cell surface receptor. In some embodiments, the ADBDS specifically binds a target of interest that is a member of a family selected from: a phosphatase receptor, growth factor receptor, a tyrosine kinase receptor, a TNF family receptor, a G-protein-coupled receptor, and a chemokine receptor. In some embodiments, the ADBDS binds multiple members of the same family (*e.g.*, the TNF receptors TRAILR1 and TRAILR2). In some

embodiments, the ADBD binds members from different families. Thus, for example, in some embodiments, the ADBD can bind to a growth factor receptor and a TNF receptor or a G-protein-coupled receptor and a chemokine receptor.

[0195] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) binds to a tumor antigen. In some embodiments, the ADBD binds to a tumor-associated antigen. In some embodiments, the ADBD binds to a tumor-specific antigen.

[0196] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) binds a cancer antigen. In some embodiments, the ADBD binds to a cancer-associated antigen. In some embodiments, the ADBD binds to a cancer-specific antigen.

[0197] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) binds an antigen expressed on the surface of an immune effector cell.

[0198] In some embodiments, a target of interest bound by the ADBD (*e.g.*, of an Adapter and/or CAR) is a human protein. In one embodiment, the ADBD binds a human protein target of interest and its monkey (*e.g.*, cynomolgous monkey), mouse, rabbit, hamster and/or a rabbit ortholog.

[0199] In another embodiment, the ADBD (*e.g.*, of an Adapter and/or CAR) binds a peptide tag present on a target of interest. Such peptide tags provide a useful means by which to detect, monitor, and/or attach one or more additional moieties to the Adapter. In one embodiment, the ADBD specifically binds a peptide tag selected from: a hexahistidyl (His6) tag, a myc tag, and a FLAG tag. Other peptide tags are described herein or otherwise known in the art.

[0200] Affinity requirements for a given ADBD binding event are contingent on a variety of factors including, but not limited to: the composition and complexity of the binding matrix, the valency and density of both the ADBD and target molecules, and the functional application of the ADBD. In one embodiment, the ADBD binds a target of interest with a dissociation constant (KD) of less than or equal to 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, or 10^{-5} M. In an additional embodiment, the ADBD binds a target of interest with a KD of less than or equal to 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, or 10^{-8} M. In additional embodiments, a the ADBD binds a target of interest with a KD less than or equal to 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M. In several embodiments, the ADBD generated by the methods disclosed herein have a dissociation constant selected from the group: between 10^{-4} M and 10^{-5} M, between 10^{-5} M and 10^{-6} M, between 10^{-6} M and 10^{-7} M, between 10^{-7} M and 10^{-8} M, between 10^{-8} M and 10^{-9} M, between 10^{-9} M and 10^{-10} M, between 10^{-10} M and 10^{-11} M and between 10^{-11} M and 10^{-12} M.

[0201] In one embodiment the ADBD binds a target of interest in active form. In one embodiment the ADBD reversibly binds a target of interest in active form and also releases the bound target in active form. In one embodiment the ADBD binds a target of interest in the native form. In specific embodiments, the ADBD

bind targets of interest with off-rates or K_{off} of greater than or equal to $10^{-10} \text{ sec}^{-1}$, $5 \times 10^{-9} \text{ sec}^{-1}$, 10^{-9} sec^{-1} , $5 \times 10^{-8} \text{ sec}^{-1}$, 10^{-8} sec^{-1} , $5 \times 10^{-7} \text{ sec}^{-1}$, 10^{-7} sec^{-1} , $5 \times 10^{-6} \text{ sec}^{-1}$, 10^{-6} sec^{-1} , $5 \times 10^{-5} \text{ sec}^{-1}$, 10^{-5} sec^{-1} , $5 \times 10^{-4} \text{ sec}^{-1}$, 10^{-4} sec^{-1} , $5 \times 10^{-3} \text{ sec}^{-1}$, 10^{-3} sec^{-1} , $5 \times 10^{-2} \text{ sec}^{-1}$, 10^{-2} sec^{-1} , $5 \times 10^{-1} \text{ sec}^{-1}$, or 10^{-1} sec^{-1} .

[0202] Binding experiments to determine KD and off-rates can be performed in a number of conditions including, but not limited to, [pH 6.0, 0.01% Tween 20], [pH 6.0, 0.1% gelatin], [pH5.0, 0.01% Tween 20], [pH9.0, 0.1% Tween 20], [pH6.0, 15% ethylene glycol, 0.01% Tween 20], [pH5.0, 15% ethylene glycol, 0.01% Tween 20], and [pH9.0, 15% ethylene glycol, 0.01% Tween 20]. The buffers in which to make these solutions can readily be determined by one of skill in the art, and depend largely on the desired pH of the final solution. Low pH solutions (<pH 5.5) can be made, for example, in citrate buffer, glycine-HCl buffer, or in succinic acid buffer. High pH solutions can be made, for example, in Tris-HCl, phosphate buffers, or sodium bicarbonate buffers. A number of conditions may be used to determine KD and off-rates for the purpose of determining, for example, optimal pH and/or salt concentrations.

[0203] In one embodiment, the ADBD specifically binds a target of interest with a K_{off} ranging from 0.1 to 10^{-7} sec^{-1} , 10^{-2} to 10^{-7} sec^{-1} , or 0.5×10^{-2} to 10^{-7} sec^{-1} . In a specific embodiment, the ADBD binds a target of interest with an off rate (K_{off}) of less than $5 \times 10^{-2} \text{ sec}^{-1}$, 10^{-2} sec^{-1} , $5 \times 10^{-3} \text{ sec}^{-1}$, or 10^{-3} sec^{-1} . In an additional embodiment, the ADBD binds a target of interest with an off rate (K_{off}) of less than $5 \times 10^{-4} \text{ sec}^{-1}$, 10^{-4} sec^{-1} , $5 \times 10^{-5} \text{ sec}^{-1}$, or 10^{-5} sec^{-1} , $5 \times 10^{-6} \text{ sec}^{-1}$, 10^{-6} sec^{-1} , $5 \times 10^{-7} \text{ sec}^{-1}$, or 10^{-7} sec^{-1} .

[0204] In one embodiment, the ADBD specifically binds a target of interest with a K_{on} ranging from 10^3 to $10^7 \text{ M}^{-1}\text{sec}^{-1}$, 10^3 to $10^6 \text{ M}^{-1}\text{sec}^{-1}$, or 10^3 to $10^5 \text{ M}^{-1}\text{sec}^{-1}$. In other specific embodiments, the ADBD binds the target of interest its target of interest with an on rate (K_{on}) of greater than $10^3 \text{ M}^{-1}\text{sec}^{-1}$, $5 \times 10^3 \text{ M}^{-1}\text{sec}^{-1}$, $10^4 \text{ M}^{-1}\text{sec}^{-1}$, or $5 \times 10^4 \text{ M}^{-1}\text{sec}^{-1}$. In an additional embodiment, the ADBD binds a target of interest with a K_{on} of greater than $10^5 \text{ M}^{-1}\text{sec}^{-1}$, $5 \times 10^5 \text{ M}^{-1}\text{sec}^{-1}$, $10^6 \text{ M}^{-1} \text{sec}^{-1}$, or $5 \times 10^6 \text{ M}^{-1}\text{sec}^{-1}$, or $10^7 \text{ M}^{-1} \text{sec}^{-1}$.

[0205] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) is an antibody or an antigen-binding fragment thereof. In some embodiments, the ADBD is a scFv. In some embodiments, the ADBD is an alternative scaffold binding domain. In some embodiments, the ADBD is a D domain.

IIIa. Antibody-derived Antigenic Determinant Binding Domains (ADBD)

[0206] In some embodiments, one or more ADBDs (*e.g.*, of an Adapter and/or CAR) can be derived from an antibody molecule, *e.g.*, one or more of monoclonal antibodies, polyclonal antibodies, recombinant antibodies, human antibodies, humanized antibodies, single-domain antibodies *e.g.*, a heavy chain variable domain (VH), a light chain variable domain (VL) and a variable domain (VHH) from, *e.g.*, human or camelid origin. In some embodiments, the ADBD is derived from the same species in which the Adapter or CAR will ultimately be used, *e.g.*, for use in humans. It may be beneficial for Adapter and/or CAR to comprise a human

or a humanized ADBD. Compositions and techniques for routinely generating such ADBDs are known in the art.

[0207] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) comprises a fragment of an antibody that is sufficient to confer recognition and specific binding to the target antigen. Examples of an antibody fragment include, but are not limited to, an Fab, Fab', F(ab')₂, or Fv fragment, an scFv antibody fragment, a linear antibody, single domain antibody such as an sdAb (either VL or VH), a camelid VHH domain, and multi-specific antibodies formed from antibody fragments.

[0208] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) is a "scFv," which can comprise a fusion protein comprising a VL chain and a VH chain of an antibody, wherein the VH and VL are, *e.g.*, linked via a short flexible polypeptide linker, *e.g.*, a linker described herein. scFvs can routinely be prepared according to methods known in the art (*see, e.g.*, Bird *et al.*, Science 242: 423-426 (1988) and Huston *et al.*, Proc. Natl. Acad. Sci. USA 85: 5879-5883 (1988)).

[0209] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) is a single domain antigen binding (SDAB) molecule. A SDAB molecule includes molecules containing complementary determining regions that are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain variable domains, binding molecules naturally devoid of light chains, single domains derived from conventional 4-chain antibodies, engineered domains and single domain scaffolds other than those derived from antibodies. SDAB molecules can be derived from any species including, but not limited to mouse, human, camel, llama, fish, shark, goat, rabbit, and bovine. This term also includes naturally occurring single domain antibody molecules from species other than Camelidae and sharks.

[0210] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) comprises a human antibody or a fragment thereof. In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) comprises a humanized antibody or a fragment thereof.

[0211] Humanization of antibodies is well-known in the art and can essentially be performed following the method of Winter and co-workers (Jones *et al.*, Nature 321: 522-525 (1986); Riechmann *et al.*, Nature 332: 323-327 (1988); Verhoeyen *et al.*, Science 239: 1534-1536 (1988)), by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody, *i.e.*, CDR-grafting (EP 239,400; Intl. Appl. Publ. No. WO 91/09967; and U.S. Pat. Nos. 4,816,567; 6,331,415; 5,225,539; 5,530,101; 5,585,089; and 6,548,640; the contents of which are incorporated herein by reference herein in their entirety). Humanization of antibodies can also be achieved by veneering or resurfacing (EP 592,106; EP 519,596; Padlan, 1991, Molecular Immunology, 28(4/5): 489-498; Studnicka *et al.*, Protein Engineering 7(6): 805-814 (1994); and Roguska *et al.*, PNAS 91: 969-973 (1994)) or chain shuffling (U.S. Pat. No. 5,565,332), the contents of which are incorporated herein by reference herein in their entirety.

IIIb. Alternative scaffold binding domains

[0212] In some embodiments, the ADBD(s) (*e.g.*, of an Adapter and/or CAR) is an alternative scaffold binding domain (ASBD). An "alternative scaffold binding domain" or "ASBD" as used herein, is an antigen determinant binding domain that is derived from, or corresponds to, a non-antibody-based binding scaffold.

[0213] In some embodiments, the disclosure provides a CAR comprising an ADBD that is an ASBD. In some embodiments, the disclosure provides a cell comprising a CAR that comprises an ADBD that is an ASBD. In further embodiments, an immune effector cell that comprises a CAR comprising and ASBD is provided. In some embodiments, the disclosure provides an Adapter comprising an ADBD that is an ASBD.

[0214] In further embodiments, the disclosure provides a composition comprising an Adapter and a CAR that each comprise an ASBD.

[0215] In some embodiments, the binding of the ASBD (*e.g.*, of an Adapter and/or CAR) to the target AD is mediated by secondary structures of the binding scaffold, such as alpha helices or beta sheets. In some embodiments, the ASBD is a three-helix bundle-based binding domain. In some embodiments, the ASBD is a D domain-based binding domain. In other embodiments, the ASBD is a Z-domain (Affibody)-based binding domain.

[0216] In some embodiments, the ASBD (*e.g.*, of an Adapter and/or CAR) is a D domain (*de novo* binding domain)-based AD binding domain. The D domain scaffold-based binding domain generally consists of 70-75 amino acid residues in which substitutions of up to 20 positions corresponding to structurally constrained surface-exposed residues in a non-naturally occurring antiparallel three helical bundle reference scaffold (SEQ ID NO: 1) confer target recognition and binding specificity for the target (AD) of interest. D domain scaffold-based binding domains are further disclosed in Intl. Appl. Publ. No. WO2016164308, the contents of which are herein incorporated by reference in their entirety. In one embodiment, the D domain comprises an amino acid sequence that differs (*e.g.*, due to amino acid modifications) from that of a reference scaffold having the sequence of SEQ ID NO: 1 by up to 20 substitutions. In some embodiments, the D domain comprises a sequence selected from the group: SEQ ID NO: 17, 18, and 19. In some embodiments, the D domain comprises a sequence selected from the group: SEQ ID NO: 20-26, and 27. In further embodiments, the D domain comprises a sequence selected from the group: SEQ ID NO: 44-1078 and 1079.

[0217] In some embodiments the ASBD (*e.g.*, of an Adapter and/or CAR) is a Z-domain scaffold (Affibody)-based AD binding domain. Z-domain scaffold-based binding domains generally consist of 58 amino acid residues in which substitutions of up to 13 positions located in the first and second of three alpha helices, confer binding confer target (AD) recognition and binding specificity for the target (AD) of interest. In further embodiments, the Z-domain ASBD comprises a sequence selected from SEQ ID NO: 28 and 29. Z-domain (Affibody) scaffold-based binding domains are further described in U.S. Pat. No. 5,831,012, the entire contents of which are herein incorporated by reference in their entirety.

[0218] Additional examples of ASBDs that display secondary structure-mediated target binding include DARPin, affilins, and armadillo repeat-based binding scaffolds.

[0219] In some embodiments, the ASBD (*e.g.*, of an Adapter and/or CAR) is a DARPin-based AD binding domain. DARPin-based binding domains generally contain 2-3 repeats of the sequence of SEQ ID NO: 30 positioned between N- and C- terminal capping repeats (*e.g.*, the sequence MRGSHHHHHGSDLGKKLLEAARAGQDDEVRLMANGA DVNAX₃₃ (SEQ ID NO: 31) and the sequence QDKFGKTAFDISIDNGNEDLAELQ (SEQ ID NO: 32), respectively, wherein the first Gln corresponds to consensus repeat position X₃₃ of the preceding repeat). Each internal repeat consists of 27 framework residues and up to 6 substituted non-framework residues that form a β -turn followed by two antiparallel helices and a loop that connects to the β -turn of the next repeat. The collective substitutions and structure of the DARPin confers target (AD) recognition and binding specificity.

Table 1. Exemplary secondary structure-based ASBD Sequences

ADBD	Sequence
D-domain F1	MGSWX ₅ X ₆ FKX ₉ X ₁₀ LAX ₁₃ IKX ₁₆ X ₁₇ LEALGGSEAEALX ₃₀ FEX ₃₃ X ₃₄ IAX ₃₇ FEX ₄₀ X ₄₁ LQ X ₄₄ YKGGKNPEVEALRKEAAAIRDELQAYRHN (SEQ ID NO: 17)
D-domain F2	MGSWAEFKQRLAAIKTRLEALGGSEAEALAFX ₃₂ X ₃₃ EIX ₃₆ AFX ₃₉ X ₄₀ ELX ₄₃ AYKGGK NPEVEALX ₅₇ X ₅₈ EAX ₆₁ AIX ₆₄ X ₆₅ ELX ₆₈ AYRHN (SEQ ID NO: 18)
D-domain F3	MGSWX ₅ EFX ₈ X ₉ RLX ₁₂ AIX ₁₅ X ₁₆ RLX ₁₉ ALGGSEAEALAAFEKEIAAFESLQAYKGGKNP EVEX ₅₅ LRX ₅₈ X ₅₉ AAX ₆₂ IRX ₆₅ X ₆₆ LQAYRHN (SEQ ID NO: 19)
D-domain C1	MGSWX ₅ X ₆ FKX ₉ X ₁₀ LAX ₁₃ IKX ₁₆ X ₁₇ LEALGGSEAEALAFX ₃₂ X ₃₃ EIX ₃₆ AFX ₃₉ X ₄₀ ELX ₄₃ A YKGGKNPEVEX ₅₅ LRX ₅₈ X ₅₉ AAX ₆₂ IRX ₆₅ X ₆₆ LQAYRHN (SEQ ID NO: 20)
D-domain C2	MGSWX ₅ EFX ₈ X ₉ RLX ₁₂ AIX ₁₅ X ₁₆ RLX ₁₉ ALGGSEAEALX ₃₀ FEX ₃₃ X ₃₄ IAX ₃₇ FEX ₄₀ X ₄₁ LQ X ₄₄ YKGGKNPEVEALX ₅₇ X ₅₈ EAX ₆₁ AIX ₆₄ X ₆₅ ELX ₆₈ AYRHN (SEQ ID NO: 21)
D-domain FIL_{px}	MGSWX ₅ X ₆ FKX ₉ X ₁₀ LAX ₁₃ IKX ₁₆ X ₁₇ LEALZ ₁ EAELAX ₂₈ FEX ₃₁ X ₃₂ IAX ₃₅ FEX ₃₈ X ₃₉ LQ X ₄₂ Y Z ₂ NPEVEALRKEAAAIRDELQAYRHN (SEQ ID NO: 22)
D-domain F2L_{px}	MGSWAEFKQRLAAIKTRLEALZ ₁ EAELAAFX ₃₀ X ₃₁ EIX ₃₄ AFX ₃₇ X ₃₈ ELX ₄₁ AYZ ₂ NPEV EALX ₅₂ X ₅₃ EAX ₅₆ AIX ₅₉ X ₆₀ ELX ₆₃ AYRHN (SEQ ID NO: 23)
D-domain F3L_{px}	MGSWX ₅ EFX ₈ X ₉ RLX ₁₂ AIX ₁₅ X ₁₆ RLX ₁₉ ALZ ₁ EAELAAFEKEIAAFESLQAY Z ₂ NPEVE X ₅₀ LRX ₅₃ X ₅₄ AAX ₅₇ IRX ₆₀ X ₆₁ LQAYRHN (SEQ ID NO: 24)
D-domain C1L_{px}	MGSWX ₅ X ₆ FKX ₉ X ₁₀ LAX ₁₃ IKX ₁₆ X ₁₇ LEALZ ₁ EAELAAFX ₃₀ X ₃₁ EIX ₃₄ AFX ₃₇ X ₃₈ ELX ₄₁ AYZ ₂ NPEVEX ₅₀ LRX ₅₃ X ₅₄ AAX ₅₇ IRX ₆₀ X ₆₁ LQAYRHN (SEQ ID NO: 25)
D-domain C2L_{px}	MGSWX ₅ EFX ₈ X ₉ RLX ₁₂ AIX ₁₅ X ₁₆ RLX ₁₉ ALZ ₁ EAELAX ₂₈ FEX ₃₁ X ₃₂ IAX ₃₅ FEX ₃₈ X ₃₉ L QX ₄₂ Y Z ₂ NPEVEALX ₅₂ X ₅₃ EAX ₅₆ AIX ₅₉ X ₆₀ ELX ₆₃ AYRHN (SEQ ID NO: 26)
D-domain DD-WTF	MGSWX ₅ EFX ₈ X ₉ RLX ₁₂ X ₁₃ IX ₁₅ X ₁₆ RLX ₁₉ ALGGSEAEALAAFEKEIX ₃₆ AFX ₃₉ X ₄₀ ELX ₄₃ AYK GKNPEVEALRX ₅₈ EAX ₆₁ X ₆₂ IRX ₆₅ ELX ₆₈ X ₆₉ YRX ₇₂ X ₇₃ (SEQ ID NO: 27)
Z-Domain AFFa	VDNKFNKEX ₉ X ₁₀ X ₁₁ AX ₁₃ X ₁₄ EIX ₁₇ X ₁₈ LPNLNX ₂₄ X ₂₅ QX ₂₇ X ₂₈ AFIX ₃₂ SLX ₃₅ DDPSQSANLL AEAKKLNDQAQPK (SEQ ID NO: 28)
Z-Domain AFFb	NKEX ₄ X ₅ X ₆ AX ₈ X ₉ EIX ₁₂ X ₁₃ LPNLNX ₁₉ X ₂₀ QX ₂₂ X ₂₃ AFIX ₂₇ SLX ₃₀ DDP (SEQ ID NO: 29)
DARPin	DX ₂ X ₃ GX ₅ TPHLAAX ₁₃ X ₁₄ GHLEIVEVLLKZ ₂₆ GADVNX ₃₃ (SEQ ID NO: 30) wherein X is any amino acid but C, R or P and Z is H, N, or Y.
X = all amino acid residues, including natural and non-natural amino acids Z = amino acid sequence corresponding to loop1 (Z ₁) or loop2 (Z ₂) as described herein, comprising between about 2 to about 30 natural or non-natural amino acids	

[0220] In some embodiments, the binding specificity of the ASBD (*e.g.*, of an Adapter and/or CAR) to the target AD is mediated by amino acids in exposed loops on the ASBD. Examples of scaffolds having these binding properties include, adnectins, lipocalins, avimers, knottins, fynomers, atrimers, kunitz domain-based binders, and CTLA4-based binding scaffolds.

[0221] In some embodiments, the ASBD is an adnectin-based AD binding domain. The adnectin-based binding domain is derived from the tenth domain of fibronectin type III (10Fn3). This ADBD is generally a 94 amino acid binding domain that adopts a beta sandwich fold containing seven strands that are connected by six loops. Substitutions in three surface-exposed loops on one side of the adnectin domain generate target (AD) specific binding moieties.

[0222] In some embodiments, the ASBD (*e.g.*, of an Adapter and/or CAR) is a lipocalin-, affilin-, or anticalin-based AD-binding domain. The anticalin scaffold displays a conserved β -barrel structure made up of eight anti-parallel β -strands and generally consists of 160–180 amino acids. The ligand binding pocket of the anticalin-based binding scaffold is composed of four loops, each containing up to 24 substitutions, that collectively confer target (AD) recognition and binding specificity.

[0223] In some embodiments, the ASBD (*e.g.*, of an Adapter and/or CAR) is an Avimer scaffold-based AD-binding domain. Avimer scaffold-based binding domains are derived from the A-domain of cell surface receptors and are generally 35 amino acids in length. The structure of the Avimer-based binding domain is maintained by 12 conserved amino acids. Substitutions of up to all of the remaining 23 residues of the binding domain confer target (AD) recognition and binding specificity. In some embodiments, the Avimer scaffold-based binding domain comprises the sequence

EFX₃CX₅NGX₈CIPX₁₂X₁₃WX₁₅CDGX₁₉DDCGDX₂₅SDE, wherein X is any amino acid (SEQ ID NO: 33).

Avimer scaffold-based binding domains are further described in U.S. Appl. Nos. 20040175756, 20050053973, 20050048512, and 20060008844, the entire contents of each of which are herein incorporated by reference in their entireties.

[0224] In some embodiments, the ASBD (*e.g.*, of an Adapter and/or CAR) is a fynomer scaffold-based AD binding domain. The fynomer binding domain is generally 60-75 amino acids in length and is composed of a pair of anti-parallel beta sheets joined by two flexible loops. Substitutions/insertions in the loops confer AD target recognition and binding specificity. In some embodiments, the fynomer-based AD binding domain comprises the sequence GVTLFV ALYDYX₁₂X₁₃X₁₄X₁₅X₁₆ X₁₇X₁₈X₁₉ X₂₀X₂₁

X₂₂LSFHKGEKFQILSTHEYEX₄₁X₄₂X₄₃X₄₄X₄₅ X₄₆X₄₇X₄₈WEARSLTTGETGX₆₁IPSNYVAPVDSIQ,

wherein X is any amino acid residue and X₁₃-X₂₁ and X₄₂-X₄₆, are optionally absent (SEQ ID NO: 34). In some embodiments, the fynomer-based AD binding domain comprises the sequence

GVTLFVALYDYX₁₂X₁₃X₁₄X₁₅X₁₆ X₁₇X₁₈X₁₉X₂₀X₂₁X₂₂

LSFHKGEKFQILSTHEYEDWEARSLTTGETGYIPSNYVAPVDSIQ, wherein X is any amino acid residue and X₁₆-X₂₁ and are optionally absent (SEQ ID NO: 35).

[0225] In some embodiments the ASBD (*e.g.*, of an Adapter and/or CAR) is a knottin scaffold-based AD binding domain. Knottin scaffold-based binding domains correspond to a 30-amino-acid protein fold composed of three anti-parallel β -strands connected by loops of variable length and multiple disulfide bonds.

[0226] In some embodiments the ASBD (*e.g.*, of an Adapter and/or CAR) is a Kunitz domain-based AD binding domain. Kunitz domain-based binding domains are derived from the active motif of Kunitz-type protease inhibitors and are generally about 60 amino acids in length. The hydrophobic core of this ADBD is composed of a twisted two-stranded antiparallel β -sheet and two α -helices stabilized by three pairs of disulfide bonds. Substitutions and insertions in the three loops confer AD target recognition and binding specificity. In some embodiments, the Kunitz domain-based AD binding domain comprises the sequence MHSFCAFKADX₁₁GX₁₃C X₁₅

X₁₆X₁₇X₁₈X₁₉RFFNFIFTRQCEEFX₃₄YGGCX₃₉X₄₀NQNRFSLEECKKMCTRDGA (SEQ ID NO: 36) sequence that is at least 85% identical to at positions other than X; X₁₁ is one of: A, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y; X₁₃ is one of: A, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y; X₁₅ is one of: A, D, E, F, G, H, I, K, L, M, N, Q, R, S, T, V, W, Y; X₁₆ is one of: A, G, E, D, H, T; X₁₇ is one of: A, D, E, F, G, H, I, K, L, M, N, Q, R, S, T, V, W, Y; X₁₈ is one of: A, D, E, F, G, H, I, K, L, M, N, Q, R, S, T, V, W, Y; X₁₉ is one of: A, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y; X₃₄ is one of: A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y; X₃₉ is one of: A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y; and X₄₀ is one of: G, and A. Kunitz scaffold-based binding domains are further described in Intl. Appl. Publ. No. WO 2004063337, the entire contents of which are herein incorporated by reference in their entirety.

[0227] In some embodiments the ASBD (*e.g.*, of an Adapter and/or CAR) is a WW domain-based AD-binding domain. WW domain-based binding scaffolds are generally 30-35 amino acids in length. In some embodiments, the WW domain-based AD binding scaffold comprises the sequence

KLPPGWX₇KX₉WSX₁₂X₁₃X₁₄GRVX₁₈YX₂₀NX₂₂ITX₂₅AX₂₇QWERP (SEQ ID NO: 37), wherein X₇, X₉, X₁₂, X₁₃, X₁₄, X₁₈, X₂₀, X₂₂, X₂₅, and X₂₇ represent any amino acid, and X₁₄ is optionally absent.

[0228] In some embodiments, the WW domain-based AD binding scaffold comprises the sequence KLPPGWX₇KX₉WSX₁₂X₁₃GRVX₁₇YX₁₉NX₂₁ITX₂₄AX₂₆QWERP (SEQ ID NO: 38), wherein X₇, X₉, X₁₂, X₁₃, X₁₇, X₁₉, X₂₁, X₂₄, and X₂₆ represent any amino acid, and X₁₄ is optionally absent.

Table 2. Exemplary loop-based ASBDs

ASBD	Sequence
Avimer1	EFX ₃ CX ₅ NGX ₈ CIPX ₁₂ X ₁₃ WX ₁₅ C DGX ₁₉ DDCGDX ₂₅ SDE (SEQ ID NO: 33)
Fynomer1	GVTLFVALYDYX ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ X ₂₀ X ₂₁ X ₂₂ LSFHKGEK FQILSTHEYEX ₄₁ X ₄₂ X ₄₃ X ₄₄ X ₄₅ X ₄₆ X ₄₇ X ₄₈ WEARSLTTGETGX ₆₁ IPSNY VAPVDSIQ wherein X= any amino acid residue and X ₁₃ -X ₂₁ and X ₄₂ -X ₄₆ , are optionally absent (SEQ ID NO: 34)

Fynomer2	GVTLFVALYDYX ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ X ₂₀ X ₂₁ X ₂₂ LSFHKGEKFQILSTHEYEDWWE ARSLTTGETGYIPSNYVAPVDSIQ, wherein X ₁₆ -X ₂₁ are optionally absent (SEQ ID NO: 35)
Kunitz1	MHSFCAFKADX ₁₁ GXi3CX ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ RFFFNIFTRQCEEFX ₃₄ YGGCX ₃₉ X ₄₀ NQNR FES LEECKK MCTRDGA (SEQ ID NO: 36)
WW1	KLPPGWX ₇ KX ₉ WSX ₁₂ X ₁₃ X ₁₄ GRVX ₁₈ YX ₂₀ NX ₂₂ ITX ₂₅ AX ₂₇ QWERP (SEQ ID NO: 37)
WW2	KLPPGWX ₇ KX ₉ WSX ₁₂ X ₁₃ GRVX ₁₇ YX ₁₉ NX ₂₁ ITX ₂₄ AX ₂₆ QWERP (SEQ ID NO: 38)
X = all amino acid residues	

IV. Linkers

[0229] Linkers are peptide or other chemical linkages located between two or more otherwise independent functional domains of the Adapter or CAR.

[0230] Suitable linkers for operably linking two or more functional domains of the Adapter in a single-chain amino acid sequence include but are not limited to, polypeptide linkers such as glycine linkers, serine linkers, mixed glycine/serine linkers, glycine- and serine-rich linkers or linkers composed of largely polar polypeptide fragments.

[0231] In one embodiment, the linker is made up of a majority of amino acids selected from glycine, alanine, proline, asparagine, glutamine, and lysine. In one embodiment, one or more linkers in the Adapter or CAR is made up of a majority of amino acids selected from glycine, alanine, proline, asparagine, aspartic acid, threonine, glutamine, and lysine. In one embodiment, one or more linkers in the Adapter or CAR is made up of one or more amino acids selected from glycine, alanine, proline, asparagine, aspartic acid, threonine, glutamine, and lysine. In another embodiment, one or more linkers in the Adapter or CAR is made up of a majority of amino acids that are sterically unhindered. In another embodiment, a linker in which the majority of amino acids are glycine, serine, and/or alanine. In some embodiments, one or more linkers in an Adapter or CAR linker comprises polyglycines (such as (Gly)₅ (SEQ ID NO: 1099), and (Gly)₈ (SEQ ID NO: 1100), poly(Gly-Ala), and polyalanines. In some embodiments, the peptide linker contains the sequence of Gly-Gly-Gly-Gly-Thr-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 39). In some embodiments, one or more linkers in the Adapter or CAR comprises the sequence of Gly-Gly-Gly-Gly-Asp-Gly-Gly-Gly-Gly-Ser (SEQ ID NO: 40).

[0232] In one embodiment, the Adapter or CAR comprises an ADBD directly attached (*i.e.*, without a linker) to another component of the Adapter or CAR, respectively. In one embodiment, the Adapter or CAR contains at least 2, at least 3, at least 4, or at least 5 ADBDs directly attached to another domain of the Adapter or CAR, respectively.

[0233] In another embodiment, an ADBD can be operably linked to another component of the Adapter or CAR through a linker. Adapters or CARs can contain a single linker, multiple linkers, or no linkers. In one embodiment, the Adapter or CAR comprises an ADBD operably linked to another component of the Adapter or CAR, respectively, through a linker peptide. In one embodiment, the Adapter or CAR contains at least 2, at

least 3, at least 4, or at least 5 ADBDs operably linked to another domain of the Adapter or CAR, respectively, through the same or different linkers.

[0234] Linkers can be of any size or composition so long as they are able to operably link a functional domain of the Adapter or CAR in a manner that enables the functional domain to function (*e.g.*, the ability of an antigenic determinant binding domain to bind a target of interest). In some embodiments, linker(s) are about 1 to about 100 amino acids, about 1 to 50 amino acids, about 1 to 20 amino acids, about 1 to 15 amino acids, about 1 to 10 amino acids, about 1 to 5 amino acids, about 2 to 20 amino acids, about 2 to 15 amino acids, about 2 to 10 amino acids, or about 2 to 5 amino acids. It should be clear that the length, the degree of flexibility and/or other properties of the linker(s) may have some influence on the properties of the final polypeptide of the invention, including but not limited to the affinity, specificity or avidity for a target of interest, or for one or more other target proteins of interest. When two or more linkers are used in the Adapter or CAR, these linkers may be the same or different. In the context and disclosure provided herein, a person skilled in the art will be able to routinely determine the optimal linker composition and length for the purpose of operably linking the functional domains of an Adapter or CAR.

[0235] The linker can also be a non-peptide linker such as an alkyl linker, or a PEG linker. For example, alkyl linkers such as $\text{-NH-(CH}_2\text{)}_s\text{-C(0)-}$, wherein $s=2\text{-}20$ can be used. These alkyl linkers may further be substituted by any non-sterically hindering group such as lower alkyl *e.g.*, C1-C6 lower acyl, halogen (*e.g.*, Cl, Br), CN, NH₂, phenyl, etc. An exemplary non-peptide linker is a PEG linker. In certain embodiments, the PEG linker has a molecular weight of about 100 to 5000 kDa, or about 100 to 500 kDa.

[0236] Suitable linkers for coupling Adapter or CAR functional domains by chemical cross-linking include, but are not limited to, homo-bifunctional chemical cross-linking compounds such as glutaraldehyde, imidoesters such as dimethyl adipimidate (DMA), dimethyl suberimidate (DMS) and dimethyl pimelimidate (DMP) or N-hydroxysuccinimide (NHS) esters such as dithiobis(succinimidylpropionate)(DSP) and dithiobis(sulfosuccinimidylpropionate)(DTSSP). Examples of suitable linkers for coupling Adapter or CAR functional domains include but are not limited to cross-linkers with one amine-reactive end and a sulfhydryl-reactive moiety at the other end, or with a NHS ester at one end and an SH-reactive group (*e.g.*, a maleimide or pyridyl).

[0237] In additional embodiments, one or more of the linkers in the Adapter or CAR is cleavable. Examples of cleavable linkers include, include but are not limited to a peptide sequence recognized by proteases (in vitro or in vivo) of varying type, such as Tev, thrombin, factor Xa, plasmin (blood proteases), metalloproteases, cathepsins (*e.g.*, GFLG, etc.), and proteases found in other corporeal compartments.

[0238] In some embodiments, the linker is a "cleavable linker" that facilitates the release of an Adapter functional domain or cytotoxic agent in a cell or at the cell surface. For example, an acid-labile linker (*e.g.*, hydrazone), protease-sensitive (*e.g.*, peptidase-sensitive) linker, photolabile linker, dimethyl linker or

disulfide-containing linker (*see, e.g.*, Chari, Can. Res. 52: 127-131 (1992); U.S. Pat. No. 5,208,020; and U.S. Appl. Pub. No. 20090110753; the contents of each of which is herein incorporated by reference in its entirety) can be used wherein it is desirable that the covalent attachment between an Adapter or a cytotoxic agent is intracellularly cleaved when the composition is internalized into the cell. The terms "intracellularly cleaved" and "intracellular cleavage" refer to a metabolic process or reaction inside a cell on an Adapter drug conjugate whereby the covalent attachment, *i.e.*, linked via a linker between the Adapter and cytotoxic agent is broken, resulting in the free Adapter and/or cytotoxic agent dissociated inside the cell.

[0239] In additional embodiments, one or more of the linkers in the CAR is cleavable. Examples of cleavable linkers include, include but are not limited to a peptide sequence recognized by proteases (in vitro or in vivo) of varying type, such as T_{ev}, thrombin, factor Xa, plasmin (blood proteases), metalloproteases, cathepsins (*e.g.*, GFLG, etc.), and proteases found in other corporeal compartments.

[0240] In some embodiments, a short oligo- or polypeptide linker, from about 1 to 100 amino acids in length, is used to link together any of the domains of a CAR. Linkers can be composed of flexible residues like glycine and serine (or any other amino acid) so that the adjacent protein domains are free to move relative to one another. The amino acids sequence composition of the linker may be selected to minimize potential immunogenicity of the CAR. Longer linkers can be used when it is desirable to ensure that two adjacent domains do not sterically interfere with one another.

[0241] In some embodiments, preferably between 2 and 10 amino acids in length forms the linkage between the transmembrane domain and the cytoplasmic signaling domain of the CAR. In further embodiments, the linker is between 10 and 15 amino acids in length, or between 15 and 20, or between 20 and 30, or between 30 and 60, or between 60 and 100 amino acids in length (or any range in between those listed). In further embodiments, the linker is a glycine-serine doublet sequence. In some embodiments, the ESD corresponds to the human T cell surface glycoprotein CD8 alpha-chain ESD region (*e.g.*, amino acid residues 138 to 182 CD8 alpha chain; Swiss-Prot Acc. No. P01732). In some embodiments, the ESD corresponds to the CD8 ESD region that has been further modified, through amino acid substitution, to improve expression function or immunogenicity. In further embodiments, the ESD corresponds to the CD28 ESD or sequences containing modifications of the CD28 ESD that confer improved expression function or immunogenicity.

[0242] Linker optimization can be evaluated using techniques described herein and/or otherwise known in the art. In some embodiments, linkers do not disrupt the ability of an Adapter or CAR to bind a target antigenic determinant and/or another Adapter or CAR functional domain to function appropriately (*e.g.*, the ability of an effector functional domain in the Adapter to elicit an effector function or the ability of an FcRn binding domain in the Adapter to bind FcRn).

V. *Adapters - Soluble Proteins*

[0243] Provided herein are multi-domain soluble Adapter proteins. The Adapter comprises an antigenic determinant (AD) (*e.g.*, as described in Section II and Section XI) and an antigenic determinant binding domain (ADBBD) (*e.g.*, as described in Section III and Section XI). The Adapter can further comprise additional ADs, additional ADBBDs, and/or other additional domains.

[0244] In an Adapter provided herein, the AD can be N-terminal to ADBBD. Alternatively, the ADBBD can be N-terminal to the AD. In some embodiments, the AD and ADBBD are directly fused. In some embodiments, the AD and the ADBBD are fused via a linker (a protein linker or chemical linker) or another protein domain (*e.g.*, a functional domain).

[0245] In some embodiments, the Adapter comprises a linker located between an ADBBD and another functional domain of the Adapter. In some embodiments, the linker is located between two ADBBDs of the Adapter. In some embodiments, the linker is located between the AD and an ADBBD of the Adapter. Suitable linkers for coupling the two or more functional domains of the Adapter will be clear to persons skilled in the art and may generally be any linker used in the art to link peptides, proteins or other organic molecules. Exemplary linkers are provided in Section IV. In particular embodiments, the linker(s) is suitable for constructing proteins or polypeptides that are intended for pharmaceutical use.

[0246] In addition to the AD (or multiple ADs) and the ADBBD (or multiple ADBBDs), an Adapter provided herein can further comprise an additional domain or additional domains, *e.g.*, a domain that confers an extended half-life.

[0247] In some embodiments, the Adapter, or the ADBBD in the Adapter, is deimmunized.

[0248] The Adapters provided herein have uses that include but are not limited to diagnostic, analytic, and therapeutic applications. In particular embodiments, the Adapters are used in combination with chimeric antigen receptors (CARs) (*e.g.*, as described in Section VI and Section XI) expressed on the surface of cells (*e.g.*, as described in Section VII and Section XI), *e.g.*, to kill a target cell.

Va. Antigenic Determinants (ADs)

[0249] An Adapter provided herein comprises at least one antigenic determinant (AD). In some embodiments, the Adapter comprises a single AD. In some embodiments, the Adapter comprises two or more ADs. Where an Adapter comprises two or more ADs, the ADs can be the same or different.

[0250] In an Adapter provided herein, the AD can be any AD or combination of ADs (*e.g.*, as described in Section II and Section XI).

[0251] In some embodiments, the Adapter comprises the extracellular domain of BCMA (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 5. In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 5.

[0252] In some embodiments, Adapter comprises the extracellular domain of CD123 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 11). In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 11.

[0253] In some embodiments, the Adapter comprises the extracellular domain of CD19 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 2 or 3). In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 2 or 3.

[0254] In some embodiments, the Adapter comprises the extracellular domain of CD20. In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 6-9, or 10.

[0255] In some embodiments, the Adapter comprises the extracellular domain of CD22 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 41). In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 41.

[0256] In some embodiments, the Adapter comprises the extracellular domain of CD37 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 12 or 13). In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 12 or 13.

[0257] In some embodiments, the Adapter comprises the extracellular domain of CS1 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 1138). In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1138.

[0258] In some embodiments, the Adapter comprises the extracellular domain of HER2 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 42). In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 42.

[0259] In some embodiments, the Adapter comprises the extracellular domain of CD45 (*e.g.*, a polypeptide comprising the sequence of residues 29-766 of SEQ ID NO: 1106). In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 29-766 of SEQ ID NO: 1106.

[0260] In some embodiments, the Adapter comprises the extracellular domain of CD26, CD30, CD33, or CD38. In some embodiments, the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid

residues, more than 150 amino acid residues, or all of the amino acid residues of the extracellular domain of CD26, CD30, CD33, or CD38.

[0261] In some embodiments, the AD is an epitope of AFP. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 15.

[0262] In some embodiments, the AD is an epitope of AFP p26. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 16. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1117. In further embodiments, the AD comprises the amino acid residues of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123.

[0263] In some embodiments, Adapter comprises a p26 protein (*e.g.*, having the sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123). Such fusion proteins containing p26 sequences have been discovered herein to have surprisingly long serum half-life. In some embodiments, the Adapter has a plasma half-life *in vivo* of at least 1 hour, at least 2 hours, at least 4 hours, at least 8 hours, at least 16 hours, at least 32 hours, at least 64 hours, or more. In some embodiments, the Adapter has an *in vivo* plasma half-life of at least 1 hour, at least 2 hours, at least 4 hours, at least 8 hours, at least 16 hours, at least 32 hours, at least 64 hours, or more hours 65 hours, or 1-10 hours, 2-10 hours, 4-10 hours, 6-10 hours, or 6-9 hours in a mouse. In some embodiments, the Adapter has an *in vivo* plasma half-life of at least 1 hour, at least 2 hours, at least 4 hours, at least 8 hours, at least 16 hours, at least 32 hours, at least 64 hours, or more hours 65 hours, or 1-10 hours, 2-10 hours, 4-10 hours, 6-10 hours, or 6-9 hours, in a human.

[0264] In some embodiments, the disclosure provides a method for modifying the *in vivo* half-life (*e.g.*, in a mouse or human) of an Adapter comprising a p26 protein (*e.g.*, having the sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123). In some embodiments, the Adapter comprises one or more target-binding DDpp. In some embodiments, the half-life of the Adapter is increased or decreased by substituting or deleting one or more amino acid residues normally found in the human p26 protein, or by inserting one or more amino acid residues not normally found in the human p26 protein. In another embodiment, the p26 sequence of the Adapter is modified through 1, 2, 3, 5, 5, 10, or 1-20, 1-10, 3-10, or 3-5, amino acid substitutions (conservative and/or nonconservative substitutions), deletions, and/or insertions so as to increase or decrease the *in vivo* half-life of the Adapter. In a particular embodiment, the amino acid residue corresponding to the glutamine (Gln, Q) at position 217 of p26 (SEQ ID NO: 16) is substituted with another amino acid residues. In a further embodiment, the substitution is Gln217Pro. In another embodiment, the p26 sequence of the Adapter is modified through deletion of 1-150, 1-100, 1-50, 1-25 or 1-10 amino acid residues so as to increase or decrease the *in vivo* half-life of the Adapter. In additional embodiments, the p26 sequence

of the Adapter is modified through 1, 2, 3, 5, 5, 10 or 1-20, 1-10, 3-10, or 3-5, amino acid substitutions (conservative and/or nonconservative substitutions), deletions, and/or insertions so as to increase or decrease the interaction of the Adapter with FcRn.

[0265] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an AD that is present in a naturally occurring protein or other molecule. In some embodiments, the AD is an AD that is endogenous to humans.

[0266] In some embodiments, the AD is an epitope of a human intracellular protein. In further embodiments, the AD is an epitope of a human intracellular protein selected from: elastinTyk2, Jak1, Jak2, Jak3, LCK, ZAP-70, and GRB2. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of the intracellular protein.

[0267] In some embodiments, the target of interest specifically bound by the ADBD of an Adapter is itself an AD of another Adapter, having a different sequence.

Vb. Antigenic Determinant Binding Domains (ADBDS)

[0268] An Adapter provided herein comprises at least one antigenic determinant binding domain (ADBD). In some embodiments, the Adapter contains one ADBD. In some embodiments, the Adapter contains at least 2, 3, 4, or 5, or more than 5 ADBDs. In some embodiments, the Adapter contains 1-3, 1-4, 1-5, or more than 5 different ADBDs. In some embodiments, the Adapter contains at least 2, 3, 4, or 5, or more than 5 different ADBDs. Thus, an Adapter can comprise a monomeric ADBD (*i.e.*, containing one antigenic determinant binding domain) or multimeric ADBDs (*i.e.*, containing more than one antigenic determinant binding domains in tandem optionally operably connected by a linker). In some embodiments, the use of a multimeric Adapter provides enhanced (*e.g.*, synergistic) target binding. In additional embodiments, the use of a multimeric Adapter allows for targeting of more than one target using a single Adapter construct (*e.g.*, bi-, tri-specific, etc.).

[0269] The multimeric Adapter is homo-multimeric (*i.e.*, containing more than one of the same ADBD optionally connected by linker(s) (*e.g.*, homodimers, homotrimers, homotetramers etc.) or Adapter hetero-multimeric (*i.e.*, containing two or more antigenic determinant binding domains in which there are at least two different antigenic determinant binding domains). The number of ADBDs included in any particular Adapter may vary, depending on the embodiment, and may be defined, at least in part, by the expression system in which the Adapter is produced. In several embodiments, however, the fusion proteins may comprise multimers of about 5 to about 10 ADBDs, about 10 to about 15 ADBDs, about 15 to about 20 ADBDs, about 20 to about 25 ADBDs, or about 25 to about 30 ADBDs (including numbers in between those listed as well as endpoints). Moreover, multiple domains of an Adapter can contain the same or different ADBD(s). In some embodiments, 2, 3, 4, 5, or more than 5 domains are in tandem.

[0270] In one embodiment, the Adapter comprises two or more ADBDs that are operably linked. In one embodiment, the Adapter comprises two ADBDs that bind to the same or different ADs on a target antigen. The linkage of two or more identical ADBDs that bind to the same target antigen results in a multivalent molecule that provides distinct advantages (*e.g.*, increased binding avidity, target clustering and receptor activation) over compositions that only contain one ADBD for a target antigen. In another embodiment the Adapter comprises two ADBDs that bind to different antigens. In some embodiments the Adapter comprises two ADBDs that bind to different antigens on the same cell. In some embodiments the Adapter comprises two ADBDs that bind to different antigens on different cells. The linkage of two or more ADBDs results in a multivalent and multi-specific Adapter that has the potential to bind more than one target antigen, either independently or simultaneously. In some embodiments, the multivalent Adapter is able to bind the same target antigen simultaneously. In some embodiments, the multivalent Adapter is able to bind different target antigens simultaneously. In some embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by an Antigenic Determinant. In some embodiments, the Antigenic Determinant is at least 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, the Antigenic Determinant is 5-500, 5-400, 10-300, 5-200, 50-100, 5-50, 10-500, 10-400, 10-300, 10-200, 10-100, 10-50, 50-500, 50-400, 50-300, 50-200, 50-100, 50-75, 100-500, 100-400, 100-300, 100-200, or 100-150 amino acids in length. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a BCMA Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by an AFP P26 Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a CD45 Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a CD26, CD30, CD33, or CD38 Antigenic Determinant.

[0271] An ADBD in the Adapter provided herein can bind to any AD (*e.g.*, as described in Section II and Section XI). In some embodiments, the ADBD binds to BCMA (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 5). In some embodiments, the ADBD binds to CD123 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 11). In some embodiments, the ADBD binds to CD22 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 41). In some embodiments, the ADBD binds to CD19 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 3). In some embodiments, the ADBD binds to CD20 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 6-9 or 10). In some embodiments, the ADBD binds to CD37 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 12 or 13). In some embodiments, the ADBD binds to CS1 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 1138). In some embodiments, the ADBD binds to HER2 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 42). In some embodiments, the ADBD binds to CD45. In some embodiments, the ADBD in the Adapter provided herein specifically binds to an AD of human CD26, CD30, CD33, or CD38. An Adapter can be

"monospecific" or "multi-specific." An Adapter that is "multi-specific" (*e.g.*, bispecific, trispecific or of greater multi-specificity) recognizes and binds to two or more different epitopes present on one or more different molecules.

[0272] In some embodiments, the Adapter comprises a domain (*e.g.*, the extracellular domain) of BCMA (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO 4). In some embodiments, Adapter comprises a domain (*e.g.*, the extracellular domain) of CD123 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 11). In some embodiments, the Adapter comprises a domain (*e.g.*, the extracellular domain) of CD22 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 24). In some embodiments, the Adapter comprises a domain (*e.g.*, the extracellular domain) of CD19 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 3). In some embodiments, the Adapter comprises a domain (*e.g.*, the extracellular domain) of CS1 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 1138). In some embodiments, the Adapter comprises a domain (*e.g.*, the extracellular domain) of HER2 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 42). In some embodiments, the Adapter comprises a domain (*e.g.*, the extracellular domain) of CD45. In some embodiments, the Adapter comprises a domain (*e.g.*, the extracellular domain) of CD26, CD30, CD33, or CD38. In some embodiments, the Adapter comprises a fragment of a domain. In further embodiments, the Adapter comprises a fragment of a domain having an amino acid sequence selected from the group: SEQ ID NO: 4 or 5, SEQ ID NO: 11, SEQ ID NO: 24, and SEQ ID NO: 3. In some embodiments, the Adapter comprises a fragment of a domain that is at least 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, the Antigenic Determinant is 5-500, 5-400, 10-300, 5-200, 50-100, 5-50, 10-500, 10-400, 10-300, 10-200, 10-100, 10-50, 50-500, 50-400, 50-300, 50-200, 50-100 50-75, 100-500, 100-400, 100-300, 100-200, or 100-150, amino acids in length.

[0273] In some embodiments, the Adapter contains at least two ADBDs that bind and cross-link one or more target antigens bound by the ADBDs and/or complexes containing the target antigen(s). In some embodiments, the cross-linked antigen(s) is on the same cell. In some embodiments, the cross-linked antigen(s) is on different cells. In some embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by an Antigenic Determinant (*e.g.*, a domain described above). In some embodiments, the Antigenic Determinant is at least 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, the Antigenic Determinant is 5-500, 5-400, 10-300, 5-200, 50-100, 5-50, 10-500, 10-400, 10-300, 10-200, 10-100, 10-50, 50-500, 50-400, 50-300, 50-200, 50-100 50-75, 100-500, 100-400, 100-300, 100-200, or 100-150 amino acids in length. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a BCMA Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a CD45 Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a CD26, CD30, CD33, or CD38 Antigenic Determinant. In further

embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by an AFP P26 Antigenic Determinant.

[0274] In some embodiments, the Adapter contains at least two of the same ADBDs (*i.e.*, is multivalent). In some embodiments, the multivalent Adapter is able to bind two or more of the same target antigens simultaneously. In some embodiments, the Adapter is multivalent and is able to bind the same target antigen simultaneously. In some embodiments, the multi-multivalent Adapter comprises two or more operably linked ADBDs that are separated by an Antigenic Determinant. In some embodiments, the Antigenic Determinant is at least 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, the Antigenic Determinant is 5-500, 5-400, 10-300, 5-200, 50-100, 5-50, 10-500, 10-400, 10-300, 10-200, 10-100, 10-50, 50-500, 50-400, 50-300, 50-200, 50-100 50-75, 100-500, 100-400, 100-300, 100-200, or 100-150 amino acids in length. In further embodiments, the multivalent Adapter comprises two or more operably linked ADBDs that are separated by a BCMA Antigenic Determinant. In further embodiments, the multivalent Adapter comprises two or more operably linked ADBDs that are separated by a CD45 Antigenic Determinant. In further embodiments, the multivalent Adapter comprises two or more operably linked ADBDs that are separated by an AFP P26 Antigenic Determinant.

[0275] In some embodiments, the Adapter contains at least two ADBDs that bind to different antigens (*i.e.*, is multispecific). In some embodiments, the multi-specific Adapter is able to bind the different target antigens simultaneously. In some embodiments, the Adapter is also multivalent and is able to bind the same target antigen simultaneously. In some embodiments, the multi-specific Adapter comprises two or more operably linked ADBDs that are separated by an Antigenic Determinant. In some embodiments, the Antigenic Determinant is at least 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, the Antigenic Determinant is 5-500, 5-400, 10-300, 5-200, 50-100, 5-50, 10-500, 10-400, 10-300, 10-200, 10-100, 10-50, 50-500, 50-400, 50-300, 50-200, 50-100 50-75, 100-500, 100-400, 100-300, 100-200, or 100-150 amino acids in length. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a BCMA Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a CD45 Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by an AFP P26 Antigenic Determinant.

[0276] In one embodiment, a multi-specific Adapter contains at least two ADBDs that bind to at least two different epitopes on a single target of interest (*i.e.*, is multiepitopic for the same target antigen). In additional embodiments, a multi-specific Adapter comprises at least one ADBD that specifically binds one epitope on a target of interest and at least one other ADBD that specifically binds to a different epitope on the same target antigen. In one embodiment, a multi-specific Adapter comprises at least one ADBD that specifically binds to an epitope on a first target antigen and at least one ADBD that specifically binds to an epitope on a second

antigen. In some embodiments, the Adapter comprises at least one ADBD that specifically binds to an epitope on a first target antigen on a cell and at least one ADBD that specifically binds to an epitope on a second antigen on the same cell. In some embodiments, the Adapter comprises at least one ADBD that specifically binds to an epitope on a first target antigen on a cell and at least one ADBD that specifically binds to an epitope on a second antigen on a different cell.

[0277] In a further embodiment, the Adapter comprises 2 or more ADBDs that are operably linked with other heterologous proteins (or their subdomains) and in so doing, impart the multivalent, multi-specific, and/or functional properties (*e.g.*, pharmacokinetics such as increased half-life) of the fusion partner to the Adapter fusion protein. Examples of fusion partners of an Adapter include but are not limited to, antibodies, antibody subdomains (*e.g.*, scFv or Fc domains), serum albumin, serum albumin subdomains, cell surface receptors, an alpha chain of a T cell receptor (TCR), a beta chain of a T cell receptor, cell surface receptor subdomains, peptides, peptide tags (*e.g.*, FLAG or myc). The number and location of ADBDs and their respective positions within the Adapter can vary. For example, ADBDs can be located at one or all termini of a fusion partner and/or interspersed within heterologous subunits within the Adapter fusion partner. In some embodiments the Adapter comprises 2 or more ADBDs that are separated by a heterologous protein (*e.g.*, Antigenic Determinant). In some embodiments, the heterologous protein is at least 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, the heterologous protein is 5-500, 5-400, 10-300, 5-200, 50-100, 5-50, 10-500, 10-400, 10-300, 10-200, 10-100, 10-50, 50-500, 50-400, 50-300, 50-200, 50-100, 50-75, 100-500, 100-400, 100-300, 100-200, or 100-150 amino acids in length.

[0278] In one embodiment, the Adapter is bispecific and contains ADBDs that specifically bind to two different target antigens. In further embodiments, the bispecific Adapter specifically binds to two different target antigens expressed on the surface of two different cell types. In further embodiments, the bispecific Adapter specifically binds to two different target antigens expressed on the surface of a tumor cell. In further embodiments, the bispecific Adapter specifically binds to two different target antigens expressed on the surface of a multiple myeloma cell (*e.g.*, BCMA and CS1). In one embodiment, the bispecific Adapter binds to target antigens expressed on different cells. In a further embodiment, the bispecific Adapter binds to target antigens expressed on different cells of a tumor. In another embodiment, the bispecific Adapter binds to target antigens expressed on different cells within a tumor vasculature or tumor microenvironment. In one embodiment, the bispecific Adapter specifically binds to a cancer cell target and an immune effector cell target. In one embodiment the bispecific Adapter specifically binds a target expressed on a cancer cell (*e.g.* CD19) and a target expressed on the surface of a T lymphocyte (*e.g.*, CD3 or CD45). In some embodiments, the bispecific Adapter is able to bind the different target antigens simultaneously. In some embodiments, the bispecific Adapter comprises two or more operably linked ADBDs that are separated by an Antigenic Determinant. In some embodiments, the Antigenic Determinant is at least 50, 75, 100, 150, 200,

250, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, the Antigenic Determinant is 5-500, 5-400, 10-300, 5-200, 50-100, 5-50, 10-500, 10-400, 10-300, 10-200, 10-100, 10-50, 50-500, 50-400, 50-300, 50-200, 50-100 50-75, 100-500, 100-400, 100-300, 100-200, or 100-150 amino acids in length. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a BCMA Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a CD45 Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by an AFP P26 Antigenic Determinant.

[0279] In some embodiments where the Adapter comprises more than one ADBD, the ADBD can be any of the types of ADBD discussed herein (*e.g.*, any ADBD described in Section III above and in and Section XI). For example, an ADBD can be an antibody, an antigen-binding fragment thereof, a ScFv, an alternative scaffold binding domain, a D domain, a T cell receptor, or an antigen-binding fragment thereof.

[0280] In some embodiments, where an Adapter comprises more than one ADBD, those ADBD can be the same types of antigen-binding molecules or can be different. For example, an Adapter can comprise two ADBD that are D domains. The two ADBD that are D domains can be the same or different. An Adapter can also comprise an ADBD that is a D domain and an ADBD that is a scFv. An Adapter can also comprise an ADBD that is a T cell receptor or antigen-binding fragment thereof and an ADBD that is a scFv. In some embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by an Antigenic Determinant. In some embodiments, the Antigenic Determinant is at least 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, or 500 amino acids in length. In some embodiments, the Antigenic Determinant is 5-500, 5-400, 10-300, 5-200, 50-100, 5-50, 10-500, 10-400, 10-300, 10-200, 10-100, 10-50, 50-500, 50-400, 50-300, 50-200, 50-100 50-75, 100-500, 100-400, 100-300, 100-200, or 100-150 amino acids in length. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a BCMA Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by a CD45 Antigenic Determinant. In further embodiments, the Adapter comprises two or more operably linked ADBDs that are separated by an AFP P26 Antigenic Determinant.

[0281] In some embodiments, the ADBD of the Adapter is deimmunized.

[0282] In some embodiments, the Adapter comprises an ADBD that binds to an antigen target containing an AD of interest, and has no discernable impact on the function of the target. Alternatively, in some embodiments, the Adapter comprises an ADBD that binds to an antigen target containing an AD of interest and completely or partially inhibits, antagonizes, agonizes, blocks, increases, stimulates, or interferes with the biological activity of the target. Binding can be identified as agonistic or antagonistic and determined using or routinely modifying assays, bioassays, and/or animal models known in the art for evaluating such activity.

[0283] An Adapter agonist refers to an Adapter that in some way increases or enhances the biological activity of the Adapter target or has biological activity comparable to a known agonist of the Adapter target.

In another embodiment, the Adapter is an antagonist of the target it binds. An Adapter antagonist refers to an Adapter that completely or partially blocks or in some way interferes with the biological activity of the Adapter target or has biological activity comparable to a known antagonist or inhibitor of the Adapter target.

[0284] In one embodiment an Adapter specifically binds a target of interest that is a serum protein. In one embodiment, an Adapter specifically binds a serum protein selected from: serum albumin (*e.g.*, human serum albumin (HSA)), thyroxin-binding protein, transferrin, fibrinogen, and an immunoglobulin (*e.g.*, IgG, IgE and IgM). Without being bound by theory, the binding of an Adapter to a carrier protein is believed to confer upon the Adapter an improved pharmacodynamic profile that includes, but is not limited to, improved tumor targeting, tumor penetration, diffusion within the tumor, and enhanced therapeutic activity compared to the Adapter in which the carrier protein binding sequence is missing (*see, e.g.*, WO 01/45746, the contents of which are herein incorporated by reference in its entirety).

[0285] In one embodiment the target of interest specifically bound by an Adapter is a disease-related antigen. The antigen can be an antigen characteristic of a cancer, and/or of a particular cell type (*e.g.*, a hyperproliferative cell), and/or of a pathogen (*e.g.*, a bacterial cell (*e.g.*, tuberculosis, smallpox, and anthrax), a virus (*e.g.*, HIV and H), a parasite (*e.g.*, malaria and leishmaniosis), a fungal infection, a mold, a mycoplasma, a prion antigen, or an antigen associated with a disorder of the immune system.

[0286] In an additional embodiment, the target of interest bound by an Adapter (is a bacterial antigen, a viral antigen, a fungal antigen, a mycoplasma antigen, a prion antigen, or a parasite antigen (*e.g.*, one infecting a mammal)). In one embodiment, the target of an Adapter is human papillomavirus anthrax, hepatitis b, rabies, Nipah virus, west Nile virus, a meningitis virus, or CMV. In an additional embodiment, an Adapter specifically binds a pathogen.

Vc. Adapter functional domain(s)

[0287] In some embodiments, the Adapter comprises a first antigenic determinant (an AD), a domain that binds to a second antigenic determinant (an ADBD), and further comprises a functional domain that confers one or more additional desirable properties (*e.g.*, improved manufacturing) and/or pharmacokinetic properties (*e.g.*, improved half-life). The functional domain of the Adapter can be located between the AD and the ADBD. The Adapter can also be located N-terminal to both the AD and ADBD or C-terminal to both the AD and ADBD. In some embodiments, where the Adapter comprises two or more ADs, the functional domain of the Adapter can be located between two or more ADs, N-terminal to two or more ADs, or C-terminal to two or more ADs. In some embodiments, where the Adapter comprises two or more ADBDs, the functional domain of the Adapter can be located between two or more ADBDs, N-terminal to two or more ADBDs, or C-terminal to two or more ADBDs.

[0288] In some embodiments, the Adapter comprises a functional domain selected from: an Fc or variant Fc (*e.g.*, a human Fc or variant Fc domain) or a fragment thereof, a serum protein (*e.g.*, human serum albumin)

or a fragment thereof; an FcRn binding domain; a serum protein binding domain; a cytokine, growth factor, hormone, or enzyme; an imaging agent; a labeling agent; and a peptide tag.

[0289] The functional domain(s) of the Adapter can be naturally derived or the result of recombinant engineering (*e.g.*, phage display, xenomouse, or synthetic). In certain embodiments, the functional domain of the Adapter enhances half-life, increases or decreases antibody dependent cellular cytotoxicity (ADCC), and/or increases or decreases complement dependent cytotoxicity (CDC) activity.

[0290] In some embodiments, the Adapter comprises a functional domain selected from: an Fc or variant Fc (*e.g.*, a human Fc or variant human Fc domain) or a fragment or derivative thereof, a serum protein (*e.g.*, human serum albumin) or a fragment or derivative thereof (*e.g.*, a serum protein binding domain); an FcRn binding domain; and a serum protein binding domain.

[0291] In one embodiment, an Adapter comprises a functional domain that comprises an antibody effector domain or derivative of an antibody effector domain that confers one or more effector functions to the Adapter, such as the ability to bind to one or more Fc receptors. In some embodiments, the functional domain comprises one or more CH2 and/or CH3 domains of an antibody having effector function provided by the CH2 and CH3 domains. In some embodiments, the functional domain comprises one or more derivatives of CH2 and/or CH3 domains of an antibody having effector function provided by the CH2 and CH3 domains. Other sequences that can be included in the Adapter to provide an effector function and that are encompassed by the invention will be clear to those skilled in the art and can routinely be chosen and designed into an Adapter encompassed herein on the basis of the desired effector function(s).

[0292] In one embodiment, the Adapter comprises a functional domain that increases the antibody dependent cellular cytotoxicity (ADCC) conferred by the Adapter (*see, e.g.*, Bruhns *et al.*, Blood 113: 3716-3725 (2009); Shields *et al.*, J. Biol. Chem. 276: 6591-6604 (2001); Lazar *et al.*, PNAS 103: 4005-4010 (2006); Stavenhagen *et al.*, Cancer Res. 67: 8882-8890 (2007); Horton *et al.*, Cancer Res. 68: 8049-8057 (2008); Zalevsky *et al.*, Blood 113: 3735-3743 (2009); Bruckheimer, Neoplasia 11: 509-517 (2009); WO2006/020114; Strohl, Curr. Op. Biotechnol. 20: 685-691 (2009); and WO2004/074455, each of which is herein incorporated by reference in its entirety). Examples of fragment engineering modifications of effector function conferring portions of an Fc contained in the functional domain of an Adapter that increases ADCC include one or more modifications corresponding to: IgG1- S298A, E333A, K334A; IgG1-S239D, I332E; IgG1-S239D, A330L, I332E; IgG1-P247I, A339D or Q; IgG1-D280H, K290S with or without S298D or V; IgG1-F243L, R292P, Y300L; IgG1-F243L, R292P, Y300L, P396L; and IgG1-F243L, R292P, Y300L, V305I, P396L; wherein the numbering of the residues in the Fc region is that of the EU index of Kabat *et al.* (Kabat *et al.*, Sequences of proteins of Immunological Interest, 1991 Fifth edition).

[0293] Accordingly, in some embodiments, the Adapter comprises a functional domain that comprises an antibody fragment that confers upon the Adapter a biological or biochemical characteristic of an

immunoglobulin. In some embodiments, the antibody fragment confers a characteristic selected from: the ability to non-covalently dimerize, the ability to localize at the site of a tumor, and an increased serum half-life when compared to an Adapter without the antibody fragment. In certain embodiments, the Adapter is at least as stable as the corresponding antibody fragment without the Adapter. In certain embodiments, the Adapter is more stable than the corresponding antibody fragment without the Adapter. Adapter protein stability can be measured using established methods, including, for example, ELISA techniques. In some embodiments, the Adapter is stable in whole blood (*in vivo* or *ex vivo*) at 37° C for at least about 10 hours, at least about 15 hours, at least about 20 hours, at least about 24 hours, at least about 25 hours, at least about 30 hours, at least about 35 hours, at least about 40 hours, at least about 45 hours, at least about 48 hours, at least about 50 hours, at least about 55 hours, at least about 60 hours, at least about 65 hours, at least about 70 hours, at least about 72 hours, at least about 75 hours, at least about 80 hours, at least about 85 hours, at least about 90 hours, at least about 95 hours, or at least about 100 hours (including any time between those listed). In one embodiment, the Adapter contains an immunoglobulin effector domain or half-life influencing domain that corresponds to an immunoglobulin domain or fragment in which at least a fraction of one or more of the constant region domains has been altered so as to provide desired biochemical characteristics such as reduced or increased effector functions, the ability to non-covalently dimerize, increased ability to localize at the site of a tumor, reduced serum half-life, or increased serum half-life when compared with an immunoglobulin fragment having the corresponding unaltered immunoglobulin sequence. These alterations of the constant region domains can be amino acid substitutions, insertions, or deletions.

[0294] In one embodiment, the Adapter comprises a functional domain that comprises an amino acid sequence of an immunoglobulin effector domain or a derivative of an immunoglobulin effector domain that confers antibody dependent cellular cytotoxicity (ADCC) to the Adapter. In additional embodiments, the Adapter comprises a sequence of an immunoglobulin effector domain that has been modified to increase ADCC (*see, e.g.*, Bruhns, Blood 113: 3716-3725 (2009); Shields, J. Biol. Chem. 276: 6591-6604 (2001); Lazar, PNAS 103: 4005-4010 (2006); Stavenhagen, Cancer Res. 67: 8882-8890 (2007); Horton, Cancer Res. 68: 8049-8057 (2008); Zalevsky, Blood 113: 3735-3743 (2009); Bruckheimer, Neoplasia 11: 509-517 (2009); WO 06/020114; Strohl, Curr. Op. Biotechnol. 20: 685-691 (2009); and WO 04/074455, the contents of each of which is herein incorporated by reference in its entirety). Examples of immunoglobulin fragment engineering modifications contained in an amino acid sequence in the Adapter that increases ADCC include immunoglobulin effector domain sequences having one or more modifications corresponding to: IgG1-S298A, E333A, K334A; IgG1-S239D, I332E; IgG1-S239D, A330L, I332E; IgG1-P247I, A339D or Q; IgG1-D280H, K290S with or without S298D or V; IgG1-F243L, R292P, Y300L; IgG1-F243L, R292P, Y300L, P396L; and IgG1-F243L, R292P, Y300L, V305I, P396L; wherein the numbering of the residues in the Fc

region is that of the EU index of Kabat *et al.* (Kabat *et al.*, Sequences of proteins of Immunological Interest, 1991 Fifth edition, herein incorporated by reference).

[0295] In additional embodiments, the Adapter comprises a functional domain that comprises the amino acid sequence of an immunoglobulin effector domain, or a derivative of an immunoglobulin effector domain, that confers antibody-dependent cell phagocytosis (ADCP) to the Adapter. In additional embodiments, the Adapter comprises a sequence of an immunoglobulin effector domain that has been modified to increase antibody-dependent cell phagocytosis (ADCP); (*see, e.g.*, Shields *et al.*, J. Biol. Chem. 276: 6591-6604 (2001); Lazar *et al.*, PNAS 103: 4005-4010 (2006); Stavenhagen *et al.*, Cancer Res. 67: 8882-8890 (2007); Richards *et al.*, Mol. Cancer Ther. 7: 2517-2527 (2008); Horton *et al.*, Cancer Res. 68: 8049-8057 (2008), Zalevsky *et al.*, Blood 113: 3735-3743 (2009); Bruckheimer *et al.*, Neoplasia 11: 509-517 (2009); WO 06/020114; Strohl, Curr. Op. Biotechnol. 20: 685-691 (2009); and WO 04/074455, the contents of each of which is herein incorporated by reference in its entirety). Examples of immunoglobulin fragment engineering modifications contained in an amino acid sequence in the Adapter that increases ADCP include immunoglobulin effector domain sequences having one or more modifications corresponding to: IgG1-S298A, E333A, K334A; IgG1-S239D, I332E; IgG1-S239D, A330L, I332E; IgG1-P247I, A339D or Q; IgG1-D280H, K290S with or without S298D or V; IgG1-F243L, R292P, Y300L; IgG1-F243L, R292P, Y300L, P396L; IgG1-F243L, R292P, Y300L, V305I, P396L; and IgG1-G236A, S239D, I332E; wherein the numbering of the residues is that of the EU index of Kabat *et al.* (Kabat *et al.*, Sequences of proteins of Immunological Interest, 1991 Fifth edition, herein incorporated by reference).

[0296] In additional embodiments, the Adapter comprises a functional domain that comprises an amino acid sequence of an immunoglobulin effector domain, or a derivative of an immunoglobulin effector domain, that confers complement-dependent cytotoxicity (CDC) to the Adapter. In additional embodiments, the Adapter comprises a sequence of an immunoglobulin effector domain that has been modified to increase complement-dependent cytotoxicity (CDC) (*see, e.g.*, Idusogie *et al.*, J. Immunol. 166: 2571-2575 (2001); Strohl, Curr. Op. Biotechnol. 20: 685-691 (2009); and Natsume *et al.*, Cancer Res. 68: 3863-3872 (2008), the contents of each of which is herein incorporated by reference in its entirety). By way of example, Adapters can contain an antibody fragment or domain that contains one or more of the following modifications that increase CDC: IgG1-K326A, E333A; IgG1-K326W, E333S, IgG2-E333S; wherein the numbering of the residues is that of the EU index of Kabat *et al.* (Sequences of proteins of Immunological Interest, 1991 Fifth edition, herein incorporated by reference).

[0297] In additional embodiments, the Adapter comprises a functional domain that comprises an amino acid sequence of an immunoglobulin effector domain, or a derivative of an immunoglobulin effector domain, that confers the ability to bind FcγRIIb receptor to the Adapter. In additional embodiments, the Adapter comprises a sequence of an immunoglobulin effector domain that has been modified to increase inhibitory

binding to FcγRIIb receptor (*see, e.g.,* Chu *et al.*, Mol. Immunol. 45: 3926-3933 (2008)). An example of an immunoglobulin fragment engineering modification contained in an amino acid sequence in the Adapter that increases binding to inhibitory FcγRIIb receptor is IgG1- S267E, L328F.

[0298] The half-life of an IgG is mediated by its pH-dependent binding to the neonatal receptor FcRn. In certain embodiments the Adapter contains a functional domain that comprises an amino acid sequence of an immunoglobulin effector domain, or a derivative of an immunoglobulin effector domain, that confers the ability to bind neonatal receptor FcRn to the Adapter. In certain embodiments the Adapter contains a functional domain that comprises a sequence of an immunoglobulin FcRn binding domain that has been modified to enhance binding to FcRn (*see, e.g.,* Petkova *et al.*, Int. Immunol. 18: 1759-1769 (2006); Dall'Acqua *et al.*, J. Immunol. 169: 5171-5180 (2002); Oganessian *et al.*, Mol. Immunol. 46: 1750-1755 (2009); Dall'Acqua *et al.*, J. Biol. Chem. 281: 23514-23524 (2006), Hinton *et al.*, J. Immunol. 176: 346-356 (2006); Datta-Mannan *et al.*, Drug Metab. Dispos. 35: 86-94 (2007); Datta-Mannan *et al.*, J. Biol. Chem. 282: 1709-1717 (2007); WO 06/130834; Strohl, Curr. Op. Biotechnol. 20: 685-691 (2009); and Yeung *et al.*, J. Immunol. 182: 7663-7671 (2009), the contents of each of which is herein incorporated by reference in its entirety).

[0299] In additional embodiments, the Adapter comprises a functional domain that comprises a sequence of an immunoglobulin effector domain that has been modified to have a selective affinity for FcRn at pH 6.0, but not pH 7.4. By way of example, the Adapter functional domain can contain an antibody fragment or domain that contains one or more of the following modifications that increase half-life: IgG1-M252Y, S254T, T256E; IgG1-T250Q, M428L; IgG1-H433K, N434Y; IgG1-N434A; and IgG1-T307A, E380A, N434A; wherein the numbering of the residues is that of the EU index of Kabat *et al.* (Kabat *et al.*, Sequences of Proteins of Immunological Interest, 1991 Fifth edition, herein incorporated by reference).

[0300] According to another embodiment, the Adapter comprises a functional domain that comprises an amino acid sequence corresponding to a immunoglobulin effector domain that has been modified to contain at least one substitution in its sequence corresponding to the Fc region (*e.g.,* Fc γ1) position selected from: 238, 239, 246, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 276, 278, 280, 283, 285, 286, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 309, 312, 315, 320, 322, 324, 326, 327, 329, 330, 331, 332, 333, 334, 335, 337, 338, 340, 360, 373, 376, 378, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438, and 439, wherein the numbering of the residues in the Fc region is according to the EU numbering system; of Kabat *et al.* (Sequences of proteins of Immunological Interest, 1991 Fifth edition, herein incorporated by reference). In a specific embodiment, the Adapter contains a functional domain that comprises a sequence of an immunoglobulin effector domain derivative wherein at least one residue corresponding to position 434 is a residue selected from: A, W, Y, F and H. According to another embodiment, the Adapter comprises a sequence of an immunoglobulin effector fragment derivative having

the following respective substitutions S298A/E333A/K334A. In an additional embodiment, the Adapter comprises an immunoglobulin effector domain derivative having a substitution corresponding to K322A. In another embodiment, the Adapter comprises a sequence of an immunoglobulin effector domain derivative having one or any combination of the following substitutions K246H, H268D, E283L, S324G, S239D and I332E. According to yet another embodiment, the Adapter comprises a sequence of an immunoglobulin effector domain derivative having substitutions corresponding to D265A/N297A.

[0301] In certain embodiments, the Adapter comprises a functional domain that comprises a sequence of an immunoglobulin effector domain that has been glycoengineered or mutated to increase effector function using techniques known in the art. For example, the inactivation (through point mutations or other means) of a constant region domain sequence contained in the Adapter may reduce Fc receptor binding of the circulating Adapter thereby increasing tumor localization. In other cases it may be that constant region modifications consistent with certain embodiments of the instant invention moderate complement binding and thus reduce the serum half-life and nonspecific association of a conjugated cytotoxin. Yet other modifications of the constant region may be used to modify disulfide linkages or oligosaccharide moieties that allow for enhanced localization due to increased antigen specificity or antibody flexibility. The resulting physiological profile, bioavailability and other biochemical effects of the modifications, such as tumor localization, biodistribution and serum half-life, can easily be measured and quantified using well known immunological techniques without undue experimentation.

Adapter as Chemical Conjugates

[0302] Adapter that promote specific binding to targets of interest can be chemically conjugated with a variety of compound such as fluorescent dyes, radioisotopes, chromatography compositions (*e.g.*, beads, resins, gels, etc.) and chemotherapeutic agents. Adapter conjugates have uses that include but are not limited to purification, diagnostic, analytic, manufacturing and therapeutic applications.

[0303] The inherent lack of cysteines in the Adapter sequence provides the opportunity for introduction of unique cysteines for purposes of site-specific conjugation.

[0304] In some embodiments, the Adapter contains at least one reactive residue. Reactive residues are useful, for example, as sites for the attachment of conjugates such as chemotherapeutic drugs. The reactive residue can be, for example, a cysteine, a lysine, or another reactive residue. Thus, a cysteine can be added to an Adapter at either the N- or C- terminus, or within the Adapter sequence. A cysteine can be substituted for another amino acid in the sequence of an Adapter. In addition, a lysine can be added to an Adapter at either end or within the Adapter sequence and/or a lysine can be substituted for another amino acid in the sequence of an Adapter. In one embodiment, a reactive residue (*e.g.*, cysteine, lysine, etc.,) is located in a loop sequence of an ADBD (*e.g.*, Z1 and Z2 of SEQ ID NOS: 22-25, or 26). In one embodiment, a reactive residue is located between components of an Adapter, *e.g.*, in a linker located between an ADBD and other component

of an Adapter fusion protein. The reactive residue (*e.g.*, cysteine, lysine, etc.) can also be located within the sequence of an Adapter. In one embodiment, an Adapter comprises at least one, at least two, at least three reactive residues. In one embodiment, an Adapter comprises at least one, at least two, or at least three, cysteine residues.

Vd. Production of Adapters

[0305] The production of the Adapter, useful in practicing the provided methods, may be carried out using a variety of standard techniques for chemical synthesis, semi-synthetic methods, and recombinant DNA methodologies known in the art. Also provided is a method for producing the Adapter, individually or as part of multi-domain fusion protein, as soluble agents and cell associated proteins.

[0306] In several embodiments, the overall production scheme for the Adapter comprises obtaining a reference protein scaffold and identifying a plurality of residues within the scaffold for modification. Depending on the embodiment, the reference scaffold may comprise a protein structure with one or more alpha-helical regions, or other tertiary structure. Once identified, the plurality of residues can be modified, for example by substitution of an amino acid. In some embodiments substitution is conservative, while in other embodiments non-conservative substitutions are made. In some embodiments a natural amino acid (*e.g.*, one of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine) is substituted into the reference scaffold at the targeted position for modification. In certain embodiments, the modifications do not include substituting in either a cysteine or a proline. After modifications have been made at all the identified positions desired in a particular embodiment, the resulting modified polypeptides (*e.g.*, candidate Adapter) can be recombinantly expressed, for example in a plasmid, bacteria, phage, or other vector (*e.g.* to increase the number of each of the modified polypeptides). The modified polypeptides can then be purified and screened to identify those modified polypeptides that have specific binding to a particular target of interest. In several embodiments, certain modified polypeptides will show enhanced binding specificity for a target of interest vis-à-vis the reference scaffold, which in some embodiments may exhibit little or no binding to a given target of interest. In additional embodiments, depending on the target of interest the reference scaffold may show some interaction (*e.g.* nonspecific interaction) with a target of interest, while certain modified polypeptides will exhibit at least about two fold, at least about five fold, at least about 10 fold, at least about 20 fold, at least about 50 fold, or at least about 100 fold (or more) increased binding specificity for the target of interest. Optionally, the reference sequence and/or the modified polypeptides (*e.g.*, Adapter) can be de-immunized. For example, residues or motifs that are potentially immunogenic can be identified and modified in order to reduce or eliminate potential immune responses to the Adapter. Additional details regarding various embodiments of the production, selection, and isolation of Adapter are provided in more detail below.

Ve. Recombinant expression of Adapters

[0307] In some embodiments, the Adapter is "recombinantly produced," (*i.e.*, produced using recombinant DNA technology). Exemplary recombinant methods available for synthesizing Adapter fusion proteins, include, but are not limited to polymerase chain reaction (PCR) based synthesis, concatemerization, seamless cloning, and recursive directional ligation (RDL)(*see, e.g.*, Meyer *et al.*, *Biomacromolecules* 3: 357-367 (2002), Kurihara *et al.*, *Biotechnol. Lett.* 27: 665-670 (2005), Haider *et al.*, *Mol. Pharm.* 2: 139-150 (2005); and McMillan *et al.*, 32: 3643-3646 (1999), the contents of each of which is herein incorporated by reference in its entirety).

[0308] Nucleic acids comprising a polynucleotide sequence encoding the Adapter are also provided. Such polynucleotides optionally further comprise, one or more expression control elements. For example, the polynucleotide can comprise one or more promoters or transcriptional enhancers, ribosomal binding sites, transcription termination signals, and polyadenylation signals, as expression control elements. The polynucleotide can be inserted within any suitable vector, which can be contained within any suitable host cell for expression.

[0309] The expression of nucleic acids encoding the Adapter is typically achieved by operably linking a nucleic acid encoding the Adapter to a promoter in an expression vector. Typical expression vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the desired nucleic acid sequence. Methods known in the art can be used to routinely construct expression vectors containing the nucleic acid sequence encoding an Adapter along with appropriate transcriptional/ translational control signals. These methods include, but are not limited to in vitro recombinant DNA techniques, synthetic techniques and in vivo recombination/genetic recombination. The expression of the polynucleotide can be performed in any suitable expression host known in the art including, but not limited to bacterial cells, yeast cells, insect cells, plant cells or mammalian cells. In one embodiment, a nucleic acid sequence encoding the Adapter is operably linked to a suitable promoter sequence such that the nucleic acid sequence is transcribed and/or translated into the Adapter in a host. Promoters useful for expression in *E. coli*, include but are not limited to, the T7 promoter.

[0310] In one embodiment, a vector comprising the Adapter encoding nucleic acid is introduced into a host cell (*e.g.*, phagemid) for expression of the Adapter. The vector can remain episomal or become chromosomally integrated, as long as the insert encoding therapeutic agent can be transcribed. Vectors can be constructed by standard recombinant DNA technology. Vectors can be plasmids, phages, cosmids, phagemids, viruses, or any other types known in the art, which are used for replication and expression in prokaryotic or eukaryotic cells. It will be appreciated by one of skill in the art that a wide variety of components known in the art (such as expression control elements) can be included in such vectors, including a wide variety of transcription signals, such as promoters and other sequences that regulate the binding of

RNA polymerase onto the promoter. Any promoter known or demonstrated to be effective in the cells in which the vector will be expressed can be used to initiate expression of the Adapter. Suitable promoters can be inducible (*e.g.*, regulated) or constitutive. Non-limiting examples of suitable promoters include the SV40 early promoter region, the promoter contained in the 3' long terminal repeat of Rous sarcoma virus, the HSV-1 (herpes simplex virus-1) thymidine kinase promoter, the regulatory sequences of the metallothionein gene, etc., as well as the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: elastase I gene control region which is active in pancreatic acinar cells; insulin gene control region which is active in pancreatic beta cells, mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells, albumin gene control region which is active in liver, alpha-fetoprotein gene control region which is active in liver, alpha 1-antitrypsin gene control region which is active in the liver, beta-globin gene control region which is active in erythroid cells, myelin basic protein gene control region which is active in oligodendrocyte cells in the brain, myosin light chain-2 gene control region which is active in skeletal muscle, and gonadotropin releasing hormone gene control region which is active in the hypothalamus. In a particular embodiment, the promoter is an immunoglobulin gene control region which is active in lymphoid cells.

[0311] In one embodiment, one or several nucleic acids encoding the Adapter is expressed under the control of a constitutive promoter or, alternately, a regulated expression system. Suitable regulated expression systems include, but are not limited to, a tetracycline-regulated expression system, an ecdysone inducible expression system, a lac-switch expression system, a glucocorticoid-inducible expression system, a temperature-inducible promoter system, and a metallothionein metal-inducible expression system. If several different nucleic acids encoding the Adapter are contained within the host cell system, some of the nucleic acids may be expressed under the control of a constitutive promoter, while others may be expressed under the control of a regulated promoter. Expression levels may be determined by methods known in the art, including Western blot analysis and Northern blot analysis.

[0312] A variety of host-expression vector systems can be utilized to express a nucleic acid encoding the Adapter. Vectors containing the nucleic acids encoding the Adapter or portions or fragments thereof, include plasmid vectors, a single and double-stranded phage vectors, as well as single and double-stranded RNA or DNA viral vectors. Phage and viral vectors may also be introduced into host cells in the form of packaged or encapsulated virus using known techniques for infection and transduction. Moreover, viral vectors may be replication competent or alternatively, replication defective. Alternatively, cell-free translation systems may also be used to produce the protein using RNAs derived from the DNA expression constructs (*see, e.g.*, WO86/05807 and WO89/01036; and U.S. Pat. No. 5,122,464, each incorporated in its entirety by reference herein).

[0313] Generally, any type of cells or cultured cell line can be used to express the Adapter provided herein. In some embodiments the background cell line used to generate an engineered host cells is a phage, a bacterial cell, a yeast cell or a mammalian cell. A variety of host-expression vector systems may be used to express the coding sequence of the Adapter. Mammalian cells can be used as host cell systems transfected with recombinant plasmid DNA or cosmid DNA expression vectors containing the coding sequence of the target of interest and the coding sequence of the Adapter.

[0314] The cells can be primary isolates from organisms (including human), cultures, or cell lines of transformed or transgenic nature. In some embodiments the host cell is a human cell. In some embodiments, the host cell is human T cell. In some embodiments, the host cell is derived from a human patient.

[0315] Useful host cells include but are not limited to microorganisms such as, bacteria (*e.g.*, *E. coli* and *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing Adapter coding sequences; yeast (*e.g.*, *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing Adapter coding sequences; insect cell systems infected with recombinant virus expression vectors (*e.g.*, *Baculovirus*) containing Adapter coding sequences; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing Adapter coding sequences. In particular embodiments, the mammalian cell systems are used to produce the Adapter. Mammalian cell systems typically utilize recombinant expression constructs containing promoters derived from the genome of mammalian cells (*e.g.*, metallothionein promoter) or from mammalian viruses (*e.g.*, the adenovirus late promoter; the vaccinia virus 7.5K promoter).

[0316] Prokaryotes useful as host cells in producing the Adapter, include gram negative or gram positive organisms such as, *E. coli* and *B. subtilis*. Expression vectors for use in prokaryotic host cells generally contain one or more phenotypic selectable marker genes (*e.g.*, genes encoding proteins that confer antibiotic resistance or that supply an autotrophic requirement). Examples of useful prokaryotic host expression vectors include the pKK223-3 (Pharmacia, Uppsala, Sweden), pGEM1 (Promega, Wis., USA), pET (Novagen, Wis., USA) and pRSET (Invitrogen, Calif., USA) series of vectors (*see, e.g.*, Studier, J. Mol. Biol. 219: 37 (1991) and Schoepfer, Gene 124: 83 (1993)). Exemplary promoter sequences frequently used in prokaryotic host cell expression vectors include T7, (Rosenberg *et al.*, Gene 56: 125-135 (1987)), beta-lactamase (penicillinase), lactose promoter system (Chang *et al.*, Nature 275: 615 (1978)); and Goeddel *et al.*, Nature 281: 544 (1979)), tryptophan (trp) promoter system (Goeddel *et al.*, Nucl. Acids Res. 8: 4057, (1980)), and tac promoter (Sambrook *et al.*, 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.).

[0317] In one embodiment, a eukaryotic host cell systems is used, including yeast cells transformed with recombinant yeast expression vectors containing the coding sequence of an Adapter, such as, the expression

systems taught in U.S. Appl. No. 60/344,169 and WO03/056914 (methods for producing humanlike glycoprotein in a non-human eukaryotic host cell)(the contents of each of which are incorporated by reference in their entirety). Exemplary yeast that can be used to produce compositions of the invention, such as, DBD, include yeast from the genus *Saccharomyces*, *Pichia*, *Actinomyces* and *Kluyveromyces*. Yeast vectors typically contain an origin of replication sequence from a 2 μ yeast plasmid, an autonomously replicating sequence (ARS), a promoter region, sequences for polyadenylation, sequences for transcription termination, and a selectable marker gene. Examples of promoter sequences in yeast expression constructs include, promoters from metallothionein, 3-phosphoglycerate kinase (Hitzeman, J. Biol. Chem. 255: 2073 (1980)) and other glycolytic enzymes, such as, enolase, glyceraldehyde-3 -phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phospho glycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase. Additional suitable vectors and promoters for use in yeast expression as well as yeast transformation protocols are known in the art. *See, e.g.*, Fleer, Gene 107: 285-195 (1991) and Hinnen, PNAS 75: 1929 (1978).

[0318] Insect and plant host cell culture systems are also useful for producing the compositions of the invention. Such host cell systems include for example, insect cell systems infected with recombinant virus expression vectors (*e.g.*, baculovirus) containing the coding sequence of a DBD; plant cell systems infected with recombinant virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (*e.g.*, Ti plasmid) containing the coding sequence of a DBD, including, but not limited to, the expression systems taught in U.S. Pat. No. 6,815,184; U.S. Publ. Nos. 60/365,769, and 60/368,047; and WO2004/057002, WO2004/024927, and WO2003/078614, the contents of each of which is herein incorporated by reference in its entirety.

[0319] In an additional embodiment the host cell systems may be used, including animal cell systems infected with recombinant virus expression vectors (*e.g.*, adenoviruses, retroviruses, adeno-associated viruses, herpes viruses, lentiviruses) including cell lines engineered to contain multiple copies of the DNA encoding an Adapter either stably amplified (CHO/dhfr) or unstably amplified in double-minute chromosomes (*e.g.*, murine cell lines). In one embodiment, the vector comprising the polynucleotide(s) encoding the Adapter is polycistronic. Exemplary mammalian cells useful for producing these compositions include 293 cells (*e.g.*, 293T and 293F), CHO cells, BHK cells, NS0 cells, SP2/0 cells, YO myeloma cells, P3X63 mouse myeloma cells, PER cells, PER.C6 (Crucell, Netherlands) cells VERY, Hela cells, COS cells, MDCK cells, 3T3 cells, W138 cells, BT483 cells, Hs578T cells, HTB2 cells, BT20 cells, T47D cells, CRL7030 cells, HsS78Bst cells, hybridoma cells, and other mammalian cells. Additional exemplary mammalian host cells that are useful in practicing the invention include but are not limited, to T cells. Some examples of expression systems and selection methods are described in the following references and references cited therein: Borth *et al.*, Biotechnol. Bioen. 71(4): 266-73 (2000), in Werner *et al.*, Arzneimittelforschung/Drug Res. 48(8): 870-80

(1998), Andersen *et al.*, Curr. Op. Biotechnol. 13: 117-123 (2002), Chadd *et al.*, Curr. Op. Biotechnol. 12: 188-194 (2001), and Giddings, Curr. Op. Biotechnol. 12: 450-454 (2001). Additional examples of expression systems and selection methods are described in Logan *et al.*, PNAS 81: 355-359 (1984), Birtner *et al.* Methods Enzymol. 153: 51-544 (1987)). Transcriptional and translational control sequences for mammalian host cell expression vectors are frequently derived from viral genomes. Commonly used promoter sequences and enhancer sequences in mammalian expression vectors include, sequences derived from Polyoma virus, Adenovirus 2, Simian Virus 40 (SV40), and human cytomegalovirus (CMV). Exemplary commercially available expression vectors for use in mammalian host cells include pCEP4 (Invitrogen) and pcDNA3 (Invitrogen).

[0320] Physical methods for introducing a nucleic acid into a host cell (*e.g.*, a mammalian host cell) include calcium phosphate precipitation, lipofection, particle bombardment, microinjection, electroporation, and other methods known in the art. Methods for producing cells comprising vectors and/or exogenous nucleic acids are well-known in the art. *See*, for example, Sambrook *et al.* (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York).

[0321] Biological methods for introducing a polynucleotide of interest into a host cell include the use of DNA and RNA vectors. Viral vectors, and especially retroviral vectors, have become the most widely used method for inserting genes into mammalian (*e.g.*, human) cells. Other viral vectors can be derived from lentivirus, poxviruses, herpes simplex virus I, adenoviruses and adeno-associated viruses, and other viral vectors known in the art. *See*, for example, U.S. Pat. Nos. 5,350,674 and 5,585,362, the contents of each of which is herein incorporated by reference in its entirety.

[0322] Methods for introducing a DNA and RNA polynucleotides of interest into a host cell include electroporation of cells, in which an electrical field is applied to cells in order to increase the permeability of the cell membrane, allowing chemicals, drugs, or polynucleotides to be introduced into the cell. Adapter encoding DNA or RNA constructs may be introduced into mammalian or prokaryotic cells using electroporation.

[0323] In a preferred embodiment, electroporation of cells results in the expression of a CAR on the surface of T cells, NK cells, NKT cells. Such expression may be transient or stable over the life of the cell. Electroporation may be accomplished with methods known in the art including MaxCyte GT® and STX® Transfection Systems (MaxCyte, Gaithersburg, MD, USA).

[0324] Chemical means for introducing a polynucleotide into a host cell include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. An exemplary colloidal system for use as a delivery vehicle in vitro and in vivo is a liposome (*e.g.*, an artificial membrane vesicle). In the case where a non-viral delivery system is utilized, an exemplary delivery vehicle is a liposome. The use of lipid

formulations is contemplated for the introduction of the nucleic acids into a host cell (in vitro, ex vivo or in vivo). In another aspect, the nucleic acid can be associated with a lipid. The nucleic acid associated with a lipid can be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the oligonucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid. Lipid, lipid/DNA or lipid/expression vector associated compositions are not limited to any particular structure in solution. For example, they can be present in a bilayer structure, as micelles, or with a "collapsed" structure. They can also simply be interspersed in a solution, possibly forming aggregates that are not uniform in size or shape. Lipids are fatty substances which can be naturally occurring or synthetic lipids. For example, lipids include the fatty droplets that naturally occur in the cytoplasm as well as the class of compounds which contain long-chain aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes.

[0325] Lipids suitable for use can be obtained from commercial sources. For example, dimyristoyl phosphatidylcholine ("DMPC") can be obtained from Sigma, St. Louis, MO; dicetyl phosphate ("DCP") can be obtained from K & K Laboratories (Plainview, NY); cholesterol ("Choi") can be obtained from Calbiochem-Behring; dimyristoyl phosphatidylglycerol ("DMPG") and other lipids may be obtained from Avanti Polar Lipids, Inc. (Birmingham, AL). Stock solutions of lipids in chloroform or chloroform/methanol can be stored at about -20°C. Chloroform may be used as the only solvent since it is more readily evaporated than methanol. "Liposome" is a generic term encompassing a variety of single and multilamellar lipid vehicles formed by the generation of enclosed lipid bilayers or aggregates. Liposomes can be characterized as having vesicular structures with a phospholipid bilayer membrane and an inner aqueous medium. Multilamellar liposomes have multiple lipid layers separated by aqueous medium. They form spontaneously when phospholipids are suspended in an excess of aqueous solution. The lipid components undergo self-rearrangement before the formation of closed structures and entrap water and dissolved solutes between the lipid bilayers (Ghosh *et al.*, *Glycobiology* 5: 505-510 (1991)). However, compositions that have different structures in solution than the normal vesicular structure are also encompassed. For example, the lipids can assume a micellar structure or merely exist as non-uniform aggregates of lipid molecules. Also contemplated are lipofectamine-nucleic acid complexes.

[0326] Regardless of the method used to introduce exogenous nucleic acids into a host cell, or the presence of the recombinant nucleic acid sequence in the host cell can routinely be confirmed through a variety of assays known in the art. Such assays include, for example, "molecular biological" assays known in the art, such as Southern and Northern blotting, RT-PCR and PCR; "biochemical" assays, such as detecting the

presence or absence of a particular peptide, *e.g.*, by immunological means (ELISAs and Western blots) or by assays described herein to identify agents falling within the scope of the invention.

[0327] Reporter genes are used for identifying potentially transfected cells and for evaluating the functionality of regulatory sequences. In general, a reporter gene is a gene that is not present in or expressed by the recipient organism, tissue, or cell and that encodes a polypeptide whose expression is manifested by some easily detectable property, *e.g.*, enzymatic activity. Expression of the reporter gene is assayed at a suitable time after the DNA has been introduced into the recipient cells. A non-limiting list of suitable reporter genes can include genes encoding luciferase, beta-galactosidase, chloramphenicol acetyl transferase, secreted alkaline phosphatase, or the green fluorescent protein gene (*e.g.*, Ui-Tei *et al.*, FEBS Lett. 479: 79-82 (2000)). Suitable expression systems are known in the art and can be prepared using known techniques or obtained commercially. In general, the construct with the minimal 5' flanking region showing the highest level of expression of reporter gene is identified as the promoter. Such promoter regions can routinely be linked to a reporter gene and used to evaluate agents for the ability to modulate promoter-driven transcription.

[0328] A number of selection systems can be used in mammalian host-vector expression systems, including, but not limited to, the herpes simplex virus thymidine kinase, hypoxanthine-guanine phosphoribosyltransferase and adenine phosphoribosyltransferase (Lowy *et al.*, Cell 22: 817 (1980)) genes, which can be employed in tk⁻, hgp⁺ or apr⁺ cells, respectively. Additionally, antimetabolite resistance can be used as the basis of selection for *e.g.*, dhfr, gpt, neo, hyg^r, trpB, hisD, ODC (ornithine decarboxylase), and the glutamine synthase system.

Vf. Adapter purification

[0329] Once an Adapter has been produced by recombinant expression, it can be purified by any method known in the art for purification of a recombinant protein, for example, by chromatography (*e.g.*, ion exchange, affinity, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In additional embodiments, the Adapter is optionally fused to a heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification. More particularly, it is envisioned that ligands (*e.g.*, antibodies and other affinity matrices) for Adapter affinity columns for affinity purification and that optionally, the Adapter or other components of the Adapter fusion composition that are bound by these ligands are removed from the composition prior to final preparation of the Adapter using techniques known in the art.

Vg. Chemical Synthesis of Adapters

[0330] In addition to recombinant methods, Adapter production may also be carried out using organic chemical synthesis of the desired polypeptide using a variety of liquid and solid phase chemical processes known in the art. Various automatic synthesizers are commercially available and can be used in accordance

with known protocols. *See*, for example, Tam *et al.*, J. Am. Chem. Soc. 105: 6442 (1983); Merrifield, Science 232: 341-347 (1986); Barany and Merrifield, The Peptides, Gross and Meienhofer, eds, Academic Press, New York, 1-284; Barany *et al.*, Int. J. Pep. Protein Res. 30: 705-739 (1987); Kelley *et al.* in Genetic Engineering Principles and Methods, Setlow, J. K., ed. Plenum Press, NY. 1990, vol. 12, pp. 1-19; Stewart *et al.*, Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, 1989. One advantage of these methodologies is that they allow for the incorporation of non-natural amino acid residues into the sequence of the Adapter.

[0331] The Adapters that are used in the methods of the present invention may be modified during or after synthesis or translation, *e.g.*, by glycosylation, acetylation, benzylation, phosphorylation, amidation, pegylation, formylation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, ubiquitination, etc. (*see, e.g.*, Creighton, Proteins: Structures and Molecular Properties, 2d Ed. (W.H. Freeman and Co., N.Y., 1992); Postranslational Covalent Modification of Proteins, Johnson, ed. (Academic Press, New York, 1983), pp. 1-12; Seifter, Meth. Enzymol. 182: 626-646 (1990); Rattan, Ann. NY Acad. Sci. 663: 48-62 (1992).) In specific embodiments, the peptides are acetylated at the N-terminus and/or amidated at the C-terminus.

[0332] Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to acetylation, formylation, etc. Additionally, the derivative may contain one or more non-classical amino acids.

VI. Chimeric Antigen Receptors

[0333] As provided herein, chimeric antigen receptors (CARs) are multi-domain proteins that comprise an extracellular domain comprising an ADBD, a transmembrane domain, and an intracellular signaling domain. Such CARs can be expressed on the surface of cells (*e.g.*, as described in Section VII and Section XI) and used in combination with Adapters (*e.g.*, as described in Section V and Section XI), for example, to kill a target cell. In several embodiments, the ADBD is made up of, at least in part, a target-binding polypeptide as disclosed herein. In several embodiments, the intracellular signaling domain is selected from the group: a human CD3 zeta domain, 41BB domain, a CD28 domain and any combination thereof. Depending on the embodiment, the costimulatory signaling region comprises the intracellular domain of a costimulatory molecule selected from the group: CD27, CD28, 41BB, OX40, CD30, CD40, PD1, lymphocyte function-associated antigen-1 (LFA1), CD2, CD7, LIGHT, NKG2C, B7H3, a ligand that specifically binds with CD83, and any combination thereof. In several embodiments, the CAR comprises a fusion protein that includes an additional target-binding polypeptide. Also provided for are isolated nucleic acid sequences encoding CARs that include the target-binding polypeptides as part (or all) of the targeting region.

[0334] In some embodiments, the ADBD of a CAR comprises at least one alternative scaffold binding domain (*e.g.*, a D domain or affibody) designed to impart binding specificity to a membrane bound CAR. A receptor comprising an alternative scaffold binding domain may be expressed by any cell type.

[0335] In one embodiment, the CAR is composed of the following elements: an extracellular domain, a transmembrane domain and a cytoplasmic domain wherein the cytoplasmic domain comprises the signaling domain. In another embodiment the CAR is composed of an extracellular domain and a transmembrane domain. In a further embodiment the CAR is comprised of an extracellular domain composed of one or more ADBDs with the same or different specificities. In one embodiment, the intracellular domain (*e.g.*, the cytoplasmic domain) of the CAR comprises the intracellular domain of CD3 zeta chain. In another embodiment the intracellular signaling domain of the CAR is comprised of part of the intracellular domain of CD3 zeta chain. In a further embodiment, the intracellular domain of the CAR comprises the intracellular domain of CD3 zeta chain and a costimulatory signaling region. The costimulatory signaling region refers to a portion of the CAR comprising all or part of the intracellular domain of a costimulatory molecule. Costimulatory molecules and portions of these molecules that are able to confer costimulatory properties to a CAR are known in the art and can routinely be incorporated into the CAR. In addition, truncations or mutation to these intracellular signaling and costimulatory domains may be incorporated to further enhance or reduce receptor signaling. In preferred embodiments, a T cell is genetically modified to stably express a CAR. In such embodiments the cytoplasmic domain of the CAR can be designed to comprise the CD28 and/or 41BB signaling domain by itself or be combined with any other desired cytoplasmic domain(s) useful in the context of the invention. In one embodiment, the cytoplasmic domain of the CAR can be designed to further comprise the signaling domain of CD3-zeta. In one embodiment, the CAR comprises an extracellular domain, an extracellular protein linker with a transmembrane domain that passes through the cellular membrane (such as found in T cells or NK cells), and a cytoplasmic domain, optionally comprising multiple signaling modules. In several embodiments, the CAR may also comprise an epitope tag. In several embodiments, the cytoplasmic domain of the CAR can include but is not limited to CD3-zeta, 41BB and CD28 signaling modules and combinations thereof.

VIa. CAR Extracellular Antigenic Determinant Binding Domain

[0336] The CARs provided herein comprise one or more antigenic determinant binding domains (ADBDs). The ADBD of the CAR can be any ADBD described herein (*e.g.*, as described in Section III and Section XI). An exemplary ADBD comprises a polypeptide, *e.g.*, an antibody molecule (which includes an antibody, and antigen binding fragments thereof, *e.g.*, an immunoglobulin, single domain antibody (sdAb), and a scFv), or a non-antibody scaffold (*e.g.*, a D domain, or affibody).

[0337] Depending on the desired antigen(s) to be targeted, the extracellular domain of the CAR can be engineered to include one or more antigenic determinant binding domains (ADBDs) that specifically bind the

desired antigen target(s). For example, in one embodiment, the CAR is engineered to target CD19 and a CD19-binding ADBD is incorporated into the extracellular domain of the CAR. Alternatively, an extracellular domain of a CAR may include more than one ADBD, thereby imparting multi-specificity or multi-valency to the CAR.

[0338] The choice of ADBDs in the extracellular domain of the CAR depends upon the identity of the cell or cells to be targeted. For example, the extracellular domain of the CAR may be engineered to specifically bind to cell surface proteins, such as a receptor, on the same cell or another cell. In other embodiments, the extracellular domain of the CAR is engineered to specifically bind to a soluble molecule, such as an immunoglobulin. In other embodiments the targets of interest bound by the CAR include those associated with viral, bacterial and parasitic infections, diseases and disorders of the immune system (*e.g.*, autoimmune disease).

[0339] In other embodiments, the extracellular domain of the CAR contains one or more ADBDs that bind a ligand that acts as a cell surface marker on target cells associated with a cancer. In some embodiments, ADBD(s) target and bind a tumor or cancer antigen (*e.g.*, a TAA, TSA, CAA, CSA or other tumor antigen described herein or otherwise known in the art). Accordingly, provided herein are methods for creating CAR, their use in creating chimeric cells such as, human T cells and natural killer cells, and the use of these chimeric T and NK cells in adoptive immunotherapy.

[0340] The choice of an ADBD can depend upon the type and number of ligands or receptors that define the surface of a target cell. For example, the ADBD may be chosen to recognize a ligand or receptor that acts as a cell surface marker on target cells associated with a particular disease state. Examples of cell surface markers that may act as ligands or receptors include a cell surface marker associated with a particular disease state, *e.g.*, cell surface makers for viral diseases, bacterial diseases parasitic infections, autoimmune diseases and disorders associated with unwanted cell proliferation, *e.g.*, a cancer, such as, a cancer described herein.

[0341] The target of interest specifically bound by the ADBD of the CAR can be any molecule for which it is desirable for a CAR or an Adapter to bind, *e.g.*, any of the ADs described in Section IIa and Section XI.

[0342] In some embodiments, the ADBD binds to a target listed in Table 4. In further embodiments, the ADBD comprises 1, 2, 3, 4, 5, 1-5, 1-10, or more than 10, D domain sequences listed in Table 3 (*e.g.*, SEQ ID NO: 44-1078, or 1079). In some embodiments, the ADBD comprises 1, 2, 3, 4, 5, 1-5, 1-10, or more than 10, different D domain sequences listed in Table 3.

[0343] In some embodiments, the ADBD binds to BCMA (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 5). In some embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 44-338, and 339.

[0344] In some embodiments, the ADBD binds to CS1 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 1138). In some embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 780-794, and 795

[0345] In some embodiments, the ADBD binds to HER2 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 42). In some embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 800-839, and 840

[0346] In some embodiments, the ADBD binds to CD123 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 11). In some embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 340-772 and 773.

[0347] In some embodiments, the ADBD binds to AFP (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 14 or 15). In some embodiments, the ADBD binds to AFP p26 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123). In some embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 841-983 and 984.

[0348] In some embodiments, the ADBD binds to CD137 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 1081). In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 985-990 and 991.

[0349] In some embodiments, the ADBD binds to CD47. In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 992-995 and 996.

[0350] In some embodiments, the ADBD binds to CTLA4. In further embodiments, the ADBD comprises a DD sequence of SEQ ID NO: 997.

[0351] In some embodiments, the ADBD binds to DR5. In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 998-1006, 1070-1072, and 1073.

[0352] In some embodiments, the ADBD binds to KIR. In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 1007, 1008, and 1009.

[0353] In some embodiments, the ADBD binds to PDL1. In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079.

[0354] In some embodiments, the ADBD binds to TIM3. In further embodiments, the ADBD comprises the DD sequence of SEQ ID NO: 1017.

[0355] In some embodiments, the ADBD binds to PD1. In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 1018, 1019, and 1020.

[0356] In some embodiments, the ADBD binds to CD137. In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 985-990 and 991.

[0357] In some embodiments, the ADBD binds to CD19 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 3). In some embodiments, the ADBD binds to CD20 (*e.g.*, a polypeptide comprising the

sequence of SEQ ID NO: 6-9 or 10). In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 1030-1058, and 1059.

[0358] In some embodiments, the ADBD binds to CD22 (*e.g.*, a polypeptide comprising the sequence of SEQ ID NO: 41). In further embodiments, the ADBD comprises a DD sequence selected from the group: SEQ ID NO: 1060-1068, and 1069.

[0359] In some embodiments, the ADBD binds an intracellular protein. In further embodiments, the ADBD comprises a DD sequence that binds an intracellular protein selected from the group: elastin, Tyk2, Jak1, Jak2, Jak3, LCK, ZAP-70, and GRB2.

[0360] In some embodiments, the ADBD binds to the extracellular domain (ECD) of human CD45 (*e.g.*, residues 29-766 of SEQ ID NO: 1106).

[0361] In some embodiments, the ADBD binds to CD26 (*e.g.*, residues 29-766 of SEQ ID NO: 1113).

[0362] In some embodiments, the ADBD binds to CD30 (*e.g.*, residues 19-379 of SEQ ID NO: 1114).

[0363] In some embodiments, the ADBD binds to CD33 (*e.g.*, residues 18-259 of SEQ ID NO: 1115).

[0364] In some embodiments, the ADBD binds to CD38 (*e.g.*, residues 43-300 of SEQ ID NO: 1116).

[0365] In some embodiments, the ADBD binds a tumor antigen or cancer antigen that comprises one or more antigenic cancer epitopes immunologically recognized by tumor infiltrating lymphocytes (TIL) derived from a cancer or tumor of a mammal.

[0366] In some embodiments, the ADBD binds an AD expressed on the surface of an immune effector cell.

[0367] In some embodiments, the CAR binds to an AD (*e.g.*, in an Adapter and/or on a target cell) that is present in a naturally occurring protein or other molecule. In some embodiments, the CAR binds to an AD that is endogenous to humans.

[0368] In some embodiments, a CAR provided herein comprises an ADBD (*e.g.*, an antibody fragment or ASBD) that binds to a MHC presented-peptide. Normally, peptides derived from endogenous proteins fill the pocket of Major histocompatibility complex (MHC) class I molecules, and are recognized by T cell receptors (TCRs) on CD8⁺T lymphocytes. The MHC class I complexes are constitutively expressed by all nucleated cells. In cancer, virus-specific and/or tumor-specific peptide/MHC complexes represent a unique class of cell surface targets for immunotherapy. TCR-like antibodies targeting peptides derived from viral or tumor antigenic determinants in the context of human leukocyte antigen (HLA)-A1 or HLA-A2 have been described (*see, e.g.*, Sastry *et al.*, J. Virol. 85(5): 1935-1942 (2011); Sergeeva *et al.*, Blood 117(16): 4262-4272 (2011); Verma *et al.*, J. Immunol. 184(4): 2156-2165(2010); Willemsen *et al.*, Gene Ther. 8(21): 1601-1608 (2001); Dao *et al.*, Sci. Transl. Med. 5(176): 176ra33 (2013); Tassev *et al.*, Cancer Gene Ther. 19(2): 84-100 (2012)). For example, TCR-like antibody can be identified from screening a library, such as a human scFv phage displayed library. Accordingly, in some embodiments, the disclosure provides a CAR that comprises an

ABBD that binds to a MHC presented peptide of a molecule selected from any tumor antigen described above that is expressed intracellularly, *e.g.*, p53, BCR-Ab1, Ras, K-ras, NY-ESO-1, and c-met.

[0369] In some embodiments, the CAR comprises an ABBBD that is an antibody or an antigen-binding fragment thereof. In some embodiments, the CAR comprises an ABBBD that is a scFv. In some embodiments, the CAR comprises an ABBBD that is an alternative scaffold binding domain. In some embodiments, the CAR comprises an ABBBD that is a D domain. In some embodiments, the CAR comprises a T cell receptor, or an antigen-binding fragment thereof.

[0370] Also provided herein are CAR wherein the CAR comprises a plurality of ABBBDs. In some embodiments, the CAR comprises a plurality of the same ABBBD. In some embodiments, the CAR comprises a plurality of different ABBBDs. In some embodiments, the CAR comprises a plurality of ABBBDs that bind the same antigenic determinant. In some embodiments, the CAR comprises a plurality of ABBBDs, wherein the binding domains bind to different ADs. In some embodiments, the CAR comprises a plurality of ABBBDs, wherein the binding domains bind to different ADs on the same cell. In some embodiments, the CAR comprises a plurality of ABBBDs, wherein the binding domains bind to different ADs on different cells.

[0371] In some embodiments, a CAR comprises a plurality of, *e.g.*, 2, 3, 4, 5, or more than 5, ABBBDs (*e.g.*, D domains, affibodies, or scFvs), wherein each ABBBD(s) are able to bind to a target antigen. In one embodiment, two or more of the ABBBDs of a CAR can bind to different ADs. In an additional embodiment, two or more of the ABBBDs of the CAR can bind to the same antigen, *e.g.*, the same or different epitopes on the same antigen. In one embodiment, a plurality of ABBBDs of the CAR are linked to each other, *e.g.*, the C-terminus of a first ABBBD is linked to the N-terminus of a second ABBBD. In an embodiment, the C-terminus of a first ABBBD is linked to the N-terminus of a second ABBBD by a covalent bond, *e.g.*, a peptide bond.

[0372] In some embodiments, a linker or hinge region is contained between one or more of the ABBBDs, *e.g.*, a linker or hinge region is located between the C-terminus of a first ABBBD and the N-terminus of a second ABBBD. By way of example, an antigen binding member comprising two ABBBDs (*e.g.*, ABBBD₁ and ABBBD₂) can be arranged in the following configuration: [ABBD₁]-[linker/hinge]-[ABBD₂]. Additional ABBBDs can be added in a similar manner, optionally with linker or hinge regions located between the C-terminus of an ABBBD and the N-terminus of the next ABBBD. Linkers or hinge regions suitable for use in linking a plurality of antigen binding members are flexible, non-cleavable, and allow near-free motion of each ABBBD independent from the other ABBBDs to encourage binding with multiple target ADs simultaneously. Any flexible linker or hinge region known in the art can be used. Examples of linkers include peptide linkers comprising glycine and serine residues, *e.g.*, (GGGGS)_n, where *n* is a positive integer equal to or greater than 1, *e.g.*, *n*=1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 (SEQ ID NO: 43).

Vib. Extracellular Spacer Domain

[0373] In some embodiments, the CARs comprise an extracellular spacer domain. As used herein, the term "extracellular spacer domain" or "ESD" refers to a polypeptide sequence of a CAR disposed between the ADBD and the transmembrane domain. In an embodiment the extracellular spacer domain allows sufficient distance from the outer surface of the cell and the ADBD as well as flexibility to minimize steric hindrance between the cell and the ADBD.

[0374] In particular embodiments, the extracellular spacer domain is sufficiently short or flexible that it does not interfere with engagement of the cell that includes the CAR with a cell bearing an AD, *e.g.*, a target cell. In an embodiment, the extracellular spacer domain is from 2 to 20, 5 to 15, 7 to 12, or 8 to 10 amino acids in length. In some embodiments, the ESD domain includes at least 50, 20, or 10 residues. In some embodiments the ESD is 10 to 300, 10 to 250, or 10 to 200 residues in length.

[0375] In some embodiments the distance from which the ESD extends from the cell is sufficiently short that the hinge does not hinder engagement of the CAR ADBD with the surface of a target cell. In some embodiment the ESD extends less than 20, 15, or 10 nanometers from the surface of the cytotoxic cell. Thus, suitability for an ESD can be influenced by both linear length, the number of amino acid residues and flexibility of the ESD. By way of example, an IgG4 ESD can be as long as 200 amino acids in length, but the distance it extends from the surface of the cytotoxic cell is smaller due to Ig-domain folding. A CD8 alpha ESD, which is ~43 amino acids at ~8 nm in length. In contrast, the IgG4 C2 & C3 ESD is ~ 200 amino acids in length, but has a distance from the cytotoxic cell surface that is comparable to that of the CD8 alpha ESD. While not wishing to be bound by theory, the similarity in extension is influenced by flexibility.

[0376] In some embodiments, the extracellular spacer domains include but are not limited to Fc fragments of antibodies or fragments or derivatives thereof, hinge regions of antibodies or fragments or derivatives thereof, CH2 regions of antibodies, CH3 regions of antibodies, artificial spacer sequences or combinations thereof. Additional examples of extracellular spacer domains include but are not limited to CD8a hinge, and artificial spacers made of polypeptides which may be as small as, for example, Gly3 or CH1 and CH3 domains of IgGs (such as human IgG4). In some embodiments, the extracellular spacer domain is any one or more of (i) a hinge, CH2 and CH3 regions of IgG4, (ii) a hinge region of IgG4, (iii) a hinge and CH2 of IgG4, (iv) a hinge region of CD8a, (v) a hinge, CH2 and CH3 regions of IgG1, (vi) a hinge region of IgG1 or (vi) a hinge and CH2 region of IgG1. Other extracellular spacer domains will be apparent to those of skill in the art and may be used in connection with alternate embodiments provided herein.

[0377] In some embodiments, the ESD is a naturally occurring sequence. In some embodiments, the ESD of the CAR corresponds to an ESD from a human protein, a fragment thereof, or a short oligo- or polypeptide linker. In some embodiments, the CAR ESD corresponds to a human Ig (immunoglobulin) ESD (hinge), or fragment thereof. In one embodiment, the ESD comprises (*e.g.*, consists of) the amino acid sequence of the IgG4 ESD. In one embodiment, for example, the hinge comprises (*e.g.*, consists of) the amino acid sequence

of the IgD hinge. In some embodiments, the hinge can be a human CD8 hinge, or fragment thereof. In one embodiment, for example, the hinge comprises (*e.g.*, consists of) the amino acid sequence of the CD8 hinge.

[0378] In some embodiments, the ESD is an artificial sequence. In one embodiment, the ESD is a short oligopeptide linker comprising a glycine-serine doublet.

[0379] In some embodiments, the CARs do not contain an extracellular spacer domain.

VIc. Transmembrane domain

[0380] The term "transmembrane domain" (TMD) as used herein refers to the region of a cell surface expressed protein, such as a CAR, which spans the plasma membrane. In some embodiments, the TMD links an extracellular sequence, *e.g.*, an extracellular ADBD, and an intracellular sequence, such as an intracellular signaling domain. In some embodiments, the transmembrane domain of the CAR is the transmembrane region of a transmembrane protein (for example Type I transmembrane proteins), an artificial hydrophobic sequence or a combination thereof. Other transmembrane domains will be apparent to those of skill in the art and may be used in connection with alternate embodiments of the invention.

[0381] The CAR can be designed to contain a transmembrane domain that is fused to the extracellular domain of the receptor. As described above, the fusion of the extracellular and transmembrane domains can be accomplished with or without a linker. In one embodiment, the transmembrane domain that is naturally associated with one of the domains in the CAR is used. In a specific embodiment, the transmembrane domain in the CAR is the CD8 transmembrane domain. In some instances, the transmembrane domain of the CAR comprises the CD8 hinge domain. In some embodiments, the transmembrane domain is selected or modified by amino acid substitution to promote or inhibit association with other surface membrane proteins.

[0382] The transmembrane domain can be derived either from a natural or from a synthetic source. Where the source is natural, the domain can be derived from any membrane-bound or transmembrane protein. Transmembrane regions of particular use for the purposes herein may be derived from (*i.e.*, comprise at least the transmembrane region(s) of) a member selected from the group: the alpha, beta or zeta chain of the T cell receptor; CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD16, CD22, CD33, CD37, CD64, CD80, CD86, CD134, CD137, and CD154. In some embodiments, the transmembrane domain is derived from the transmembrane region(s) of a NKR. In further embodiments, the transmembrane domain is derived from the transmembrane region of a molecule selected from the group consisting of, KIRDS2, OX40, TNFR2, LFA1 (CD11a, CD18), ICOS, 41BB, GITR, LTBR, BAFRR, HVEM, NKp80 (KLRF1), IL2R beta, IL2R gamma, IL7R α , ITGA1, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGB7, VLA1, VLA6, IA4, ITGAX, CD11c, ITGB1 CD27, CD29, ITGB2, CD2, CD11a, CD11b, CD11d, CD18, CD19, CD40, CD49a, CD49d, CD49f, CD84, CD96, CD100, CD103, CD160, CD162, CD226, CD229, CEACAM1, CRTAM, PSGL1, SLAM (SLAMF1), SLAMF4, SLAMF6 (NTB-A, Ly108), SLAMF7, SLAMF8, SELPLG, and PAG/Cbp. Alternatively, the transmembrane domain can be synthetic, and preferably predominantly comprises

hydrophobic residues such as leucine and valine. In further embodiments, the transmembrane domain comprises the triplet of FWV (phenylalanine, tryptophan and valine) at each end of the transmembrane domain.

[0383] Exemplary NKR domains, *e.g.*, transmembrane, hinge or stem, or intracellular (*e.g.*, cytoplasmic) domains (identified by the NKR from which the domain is derived) Killer immunoglobulin KIR2DL1 receptors (KIRs) include KIR2DL2/L3, KIR2DL4, KIR2DL5A, KIR2DL5B, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS4, KIR2DS5, KIR3DL1/S1, KIR3DL2, KIR3DL3, KIR2DP1, KIR2DP1, NCRs: , NKp30, NKp44, NKp46, SLAM; Receptors SLAM, CD48, CD229, 2B4, CD84, NTB-A, CRACC, BLAME, CD2F-10, SLAMF6, SLAMF7; Fc-binding Receptors CD16, FcγRIII, CD64, Ly49; Receptors Ly49, Lectin-related NK Ly49A cell receptor, Ly49C; other NK receptors NKG2D, CD160 (TM containing splice variant(s)) DNAM1, CRTAM, CD27, PSGL1, CD96, CD100, NKp80, CEACAM1, and CD244.

VId. Intracellular signaling domain

[0384] Described herein are intracellular signaling domains that can be used in a chimeric antigen receptor (CAR) according to the present invention.

[0385] "Intracellular signaling domain" (ISD) or "cytoplasmic domain" as used herein refer to the portion of the CAR which transduces the effector function signal and directs the cell to perform its specialized function (*e.g.*, cytolytic activity and helper activity, including cytokine secretion).

[0386] The cytoplasmic domain (*i.e.*, intracellular signaling domain) of a CAR is responsible for activation of at least one of the normal effector functions of an immune cell engineered to express a CAR. The term "effector function" refers to a specialized function of a cell. The effector function of a T cell, for example, includes cytolytic activity and helper activity including the secretion of cytokines. Thus the term "intracellular signaling domain" refers to the portion of a CAR protein which transduces the effector function signal and directs the cell to perform a specialized function. While typically the entire intracellular signaling domain corresponding to a naturally occurring receptor can be employed, in many cases it is not necessary to use the entire chain. To the extent that a truncated portion of the intracellular signaling domain is used, such truncated portion can be used in place of the intact chain as long as it transduces the effector function signal. The term intracellular signaling domain is thus meant to include any truncated portion of the intracellular signaling domain sufficient to transduce the effector function signal. In one embodiment, an intracellular signaling domain in the CAR includes the cytoplasmic sequences of the T cell receptor (TCR) and also the sequence of co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, or any derivative or variant of these sequences that has functional capability. Examples of domains that transduce an effector function signal include but are not limited to the ζ chain of the T cell receptor complex or any of its homologues (*e.g.*, η chain, FcγRI and β chains, MB 1 (Iga) chain, B29 (Ig) chain, etc.), human CD3 zeta chain, CD3 polypeptides (Δ, δ and ε), syk family tyrosine kinases (Syk, ZAP 70, etc.), src family tyrosine

kinases (Lck, Fyn, Lyn, etc.) and other molecules involved in T cell transduction, such as CD2, CD5 and CD28.

[0387] In some embodiments, the intracellular signaling domain of the CAR produces an intracellular signal when an extracellular domain (*e.g.*, an ADBD) to which it is fused, binds a cognate AD. The Intracellular signaling domains of the CAR can include primary intracellular signaling domains and costimulatory signaling domains. In one embodiment, the CAR is constructed for expression in an immune cell (*e.g.*, a T or NK cell), such that the expressed CAR comprises a domain such as a primary intracellular signaling domain and/or costimulatory signaling domain, that is derived from a polypeptide typically associated with the immune cell. For example, in some embodiments, the CAR is for expression in a T cell and comprises a 41BB domain and a CD3 zeta domain. In another embodiment, the CAR molecule is constructed for expression in an immune cell such that the expressed CAR comprises a domain that is derived from a polypeptide that is not typically associated with the immune cell. For example, in some embodiments the CAR for expression in a T cell comprises a KIR domain derived from a NK cell. In an alternative embodiment, the CAR for expression in an NK cell comprises a 41BB domain and a CD3 zeta domain derived from a T cell (*See e.g.* WO2013/033626, incorporated herein by reference).

[0388] The intracellular signaling domain of the CAR comprises sufficient primary stimulatory molecule sequence to produce an intracellular signal, *e.g.*, when an ADBD to which it is fused binds a cognate AD. In particular embodiments, the intracellular signal of the CAR mediates a T cell response selected from the group: proliferation, cytokine secretion, killing, activation, and differentiation.

[0389] In one embodiment, the intracellular signaling region of the CAR comprises a domain that contains an immunoreceptor tyrosine-based activation motif (ITAM). In a further embodiment, the CAR intracellular signaling region comprises ITAM containing domain from a molecule selected from: TCR zeta (CD3 zeta), FcR gamma (FCER1G), Fc gamma RIIa, FcR beta (FCER1B), CD3 gamma, CD3 delta, CD3 epsilon, CD3 gamma, CD5, CD22, CD79a, CD79b, DAP10, DAP12, CD32 (Fc gamma RIIa), CD79a, and CD79b. In a specific embodiment, the intracellular signaling domain of the CAR comprises a CD3 zeta signaling domain. In another specific embodiment, the intracellular signaling domain of the CAR comprises a DAP12 signaling domain. In some embodiments, the ITAM containing signaling domain has at least 70, 75, 80, 85, 90, 95, 98, or 99% sequence identity with, or differs by no more than 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 amino acid residues from the corresponding residues of a naturally occurring ITAM containing domain.

[0390] Examples of ITAM containing primary cytoplasmic signaling sequences that are of particular use in the invention include those derived from TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD22, CD79a, CD79b, and CD66d. It is particularly preferred that a cytoplasmic signaling molecule in the CAR comprises a cytoplasmic signaling sequence derived from CD3 zeta.

[0391] In a preferred embodiment, the cytoplasmic domain of the CAR comprises the CD3-zeta signaling domain by itself or combined with any other desired cytoplasmic domain(s) useful in the context of the CAR. For example, the cytoplasmic domain of the CAR can comprise a CD3 zeta chain portion and a costimulatory signaling region. The costimulatory signaling region refers to a portion of the CAR comprising the intracellular domain of a costimulatory molecule. A costimulatory molecule is a cell surface molecule other than an antigen receptor or their ligands that is required for an efficient response of lymphocytes to an antigen. Examples of such molecules include CD27, CD28, 41BB (CD 137), OX40, CD30, CD40, PD1, ICOS, lymphocyte function-associated antigen-1 (LFA1), CD2, CD7, LIGHT, NKG2C, B7H3, TIM1, and LAG3.

[0392] "Co-stimulatory domain" (CSD) as used herein refers to the portion of the CAR which enhances the proliferation, survival and/or development of memory cells. The CAR may comprise one or more co-stimulatory domains. Each co-stimulatory domain comprises the costimulatory domain of any one or more of, for example, a member of the TNFR superfamily, selected from CD28, CD137 (41BB), CD134 (OX40), Dap10, CD27, CD2, CD5, ICAM1, LFA1(CD1 la/CD18), Lck, TNFR1, TNFR2, Fas, CD30, and CD40 or a combination thereof. Other co-stimulatory domains (*e.g.*, from other proteins) will be apparent to those of skill in the art and may be used in connection with alternate embodiments of the invention.

[0393] In some embodiments, the intracellular domain of the CAR comprises an ITAM containing domain and a costimulatory signaling domain that comprises a functional fragment or analog of a costimulatory molecule that is sufficient to produce an intracellular signal when an extracellular ADBD to which it is fused, binds cognate ligand. In some embodiments, the CAR comprises a costimulatory signaling domain corresponding to that found in a molecule selected from: CD137 (41BB), OX40, LIGHT, TNFR2, TRANCE/RANKL, GITR, BAFFR, HVEM, B7H3, CDS, IL2R beta, IL2R gamma, IL7R alpha, ITGA4, ITGA6, ITGAD, ITGAE, ITGAL, ITGAM, ITGAX, ITGB1, ITGB2, ITGB7, VLA1, VLA6, C49f, IA4, LFA1, CD2, CD4, CD7, CD8 alpha, CD8 beta, CD11A, CD11B, CD11C, CD11D, CD18, CD19, CD27, CD28, CD29, CD30, CD40, CD49A, CD49D, CD69, CD84, CD96, CD100, CD103, CD150, CD160, CD162, CD226, CD229, CD278, ICAM1, CEACAM1, CRTAM, PSGL1, SLAMF1, SLAMF4, SLAMF6, SLAMF7, SLAMF8, LTBR, LAT, GADS, PAG/Cbp, SLP76, NKG2C, NKp30, NKp44, NKp46 and NKp80.

[0394] In some embodiments, the CAR comprises a costimulatory domain corresponding to that found in a molecule selected from the group consisting 41BB, CD28, CD27, ICOS, and OX40.

[0395] In some embodiments, the CAR comprises a plurality of costimulatory domains. In particular embodiments, the CAR comprises the following costimulatory signaling domains, from the extracellular to intracellular direction: 41BB-CD27, CD27-41BB, 41BB-CD28, CD28-41BB, OX40-CD28, CD28-OX40, CD28-41BB; or 41BB-CD28.

[0396] In some embodiments the costimulatory signaling domain of the CAR has at least 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identity with, or differs by no more than 30, 25, 20, 15, 10, 5, 4, 3, 2, or 1 amino acid residues from the corresponding residues of a naturally occurring costimulatory domain.

[0397] Polypeptide linkers may be positioned between adjacent elements of the CAR. For example linkers may be positioned between adjacent ADBDs or between an ADBD and the transmembrane domain or between the transmembrane domain and the cytoplasmic domain or between adjacent cytoplasmic domains. The cytoplasmic signaling sequences within the cytoplasmic signaling portion of the CAR may be linked to each other in a random or specified order. Optionally, a short linker, preferably between 2 and 10 amino acids in length may form the linkage. A glycine-serine doublet provides a particularly suitable linker.

VIe. Expression of CARs

[0398] CARs are intentionally cell associated and used in the context of the cell in which they are expressed. One particular embodiment relates to a strategy of adoptive cell transfer of T cells which have been transduced to express a CAR. Preferably, the cell can be genetically modified to stably express a CAR on its surface, conferring novel target specificity that is MHC independent.

[0399] A variety of viral-derived vectors can be used in applications in which viruses are used for transfection and integration into a mammalian cell genome. Viruses, which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. Lentiviral vectors are particularly suitable to achieving long-term gene transfer (*e.g.*, adoptive T cell immune therapy) since they allow long-term, stable integration of a transgene and its propagation in daughter cells. Lentiviral vectors have the added advantage over vectors derived from onco-retroviruses such as murine leukemia viruses in that they can transduce non-proliferating cells, such as hepatocytes. They also have the added advantage of low immunogenicity. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers, (*e.g.*, Intl. Appl. Publ. Nos. WO 01/96584 and WO 01/29058; and U.S. Pat. No. 6,326,193). Several vector promoter sequences are available for expression of the transgenes. One example of a suitable promoter is the immediate early cytomegalovirus (CMV) promoter sequence. This promoter sequence is a strong constitutive promoter sequence capable of driving high levels of expression of any polynucleotide sequence operatively linked thereto. Another example of a suitable promoter is EF- 1a. However, other constitutive promoter sequences can also be used, including, but not limited to the simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and

the creatine kinase promoter. Inducible promoters include, but are not limited to a metallothionein promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

[0400] In order to assess the expression of a CAR polypeptide or portions thereof, the expression vector introduced into a cell can also contain either a selectable marker gene or a reporter gene or both to facilitate identification and selection of expressing cells from the population of cells sought to be transfected or infected through viral vectors. In other aspects, the selectable marker may be carried on a separate piece of DNA and used in a co- transfection procedure. Both selectable markers and reporter genes may be flanked with appropriate regulatory sequences to enable expression in the host cells. Useful selectable markers include, for example, antibiotic-resistance genes, such as neo and are otherwise known in the art.

[0401] Prior to expansion and genetic modification of the T cells of the invention, a source of T cells is obtained from a subject. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments provided herein, any number of T cell lines available in the art, may be used.

[0402] A full discussion of T cell isolation, culturing, activation and expansion methods may be found in WO 2012079000, the contents of which is herein incorporated by reference in its entirety.

[0403] Additionally provided is a host cell comprising nucleic acids encoding a CAR described herein. Further provided is a composition comprising a nucleic acid sequence encoding the CAR.

VII. Chimeric antigen receptor cells

[0404] The disclosure provides compositions and methods to regulate the specificity and activity of cells modified to express one or more different CAR(s).

[0405] In some embodiments, cells are engineered to express one or more of the CARs described herein. Such CAR-containing cells, referred to as "CAR cells" have uses in monotherapy and in combination therapies that include other therapeutic agents, such as the Adapters described herein, for example, to kill a target cell.

[0406] In some embodiments, a CAR cell comprises a nucleic acid sequence encoding a CAR, wherein the CAR comprises an extracellular domain made up of, at least in part, an ADBD that binds a target of interest, a transmembrane domain, and a signaling domain. In several embodiments, the encoded CAR polypeptide binds specifically to a tumor antigen (and thus functions to deliver the cell expressing the CAR to the tumor). In several embodiments, the tumor antigen bound by the CAR is associated with a hematologic malignancy. In additional embodiments, tumor antigen bound by the CAR is associated with a solid tumor. In further embodiments the CAR is engineered to bind both solid and hematologic tumors. Depending on the embodiment, the cell expressing the CAR can be an immune effector cell (e.g., a T cell or a natural killer (NK) cell) or another cell type. In several embodiments, the cell (whether T cell, NK cell or other cell type)

exhibits an anti-tumor immunity when the antigen-binding domain of the CAR binds to its targeted tumor antigen(s).

[0407] In some embodiments, prior to expansion and genetic modification or other modification, a source of cells (*e.g.*, T cells or natural killer cells), can routinely be obtained from a subject using techniques known in the art. The term "subject" is intended to include living organisms in which an immune response can be elicited (*e.g.*, mammals). T cells can be obtained from sources, including but not limited to peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors.

[0408] In some embodiments, the CAR cell is capable of killing a target cell, *e.g.*, when the ADBD of the CAR interacts with an AD, which can be present on the surface of a target cell and/or in an Adapter. In some embodiments, the CAR cell is capable of degranulating, *e.g.*, when the ADBD of the CAR interacts with an AD, which can be present on the surface of a target cell and/or in an Adapter. In some embodiments, the CAR cell is capable of secreting a cytokine or cytokines, *e.g.*, when the ADBD of the CAR interacts with an AD, which can be present on the surface of a target cell and/or in an Adapter.

[0409] In some embodiments, the CAR-containing cell is an immune cell. In some embodiments, the CAR-containing cell is an immune effector cell. In further embodiments, the CAR-containing immune cell is a cytotoxic cell. In further embodiments, the cytotoxic cell is selected from a T cell, NK cell, or a cultured NK cell (*e.g.*, a NK92 cell).

[0410] In certain embodiments, an immune effector cell comprises a cell surface receptor for an immunoglobulin or other peptide binding molecule, such as a receptor for an immunoglobulin constant region and including the class of receptors commonly referred to as "Fc receptors" ("FcR"s). A number of FcRs have been structurally and/or functionally characterized and are known in the art, including FcR having specific abilities to interact with a restricted subset of immunoglobulin heavy chain isotypes, or that interact with Fc domains with varying affinities, and/or which may be expressed on restricted subsets of immune effector cells under certain conditions (*e.g.*, Kijimoto-Ochichai *et al.*, Cell Mol. Life. Sci. 59: 648 (2002); Davis *et al.*, Curr. Top. Microbiol. Immunol. 266: 85 (2002); Pawankar, Curr. Opin. Allerg. Clin. Immunol. 1: 3 (2001); Radaev *et al.*, Mol. Immunol. 38: 1073 (2002); Wurzburg *et al.*, Mol. Immunol. 38: 1063 (2002); Sulica *et al.*, Int. Rev. Immunol. 20: 371 (2001); Underhill *et al.*, Ann. Rev. Immunol. 20: 825 (2002); Coggeshall, Curr. Dir. Autoimm. 5: 1 (2002); Mimura *et al.*, Adv. Exp. Med. Biol. 495: 49 (2001); Baumann *et al.*, Adv. Exp. Med. Biol. 495: 219 (2001); Santoso *et al.*, Ital. Heart J. 2: 811 (2001); Novak *et al.*, Curr. Opin. Immunol. 13: 721 (2001); Fossati *et al.*, Eur. J. Clin. Invest. 31: 821 (2001)), the contents of each of which is herein incorporated by reference in its entirety.

[0411] Cells that are capable of mediating ADCC are examples of immune effector cells. Other immune effector cells include Natural Killer cells, tumor-infiltrating T lymphocytes (TILs), cytotoxic T lymphocytes,

and granulocytic cells such as cells that comprise allergic response mechanisms. Immune effector cells thus include, but are not limited to, cells of hematopoietic origin including cells at various stages of differentiation within myeloid and lymphoid lineages and which may (but need not) express one or more types of functional cell surface FeR, such as T lymphocytes, B lymphocytes, NK cells, monocytes, macrophages, dendritic cells, neutrophils, basophils, eosinophils, mast cells, platelets, erythrocytes, and precursors, progenitors (*e.g.*, hematopoietic stem cells), as well as quiescent, activated, and mature forms of such cells. Other immune effector cells may include cells of non-hematopoietic origin that are capable of mediating immune functions, for example, endothelial cells, keratinocytes, fibroblasts, osteoclasts, epithelial cells, and other cells. Immune effector cells can also include cells that mediate cytotoxic or cytostatic events, or endocytic, phagocytic, or pinocytotic events, or that effect induction of apoptosis, or that effect microbial immunity or neutralization of microbial infection, or cells that mediate allergic, inflammatory, hypersensitivity and/or autoimmune reactions.

[0412] In some embodiments, the CAR-containing cell is a T cell. In some embodiments, the CAR-containing cell is a NK cell. In additional embodiments, the CAR-containing cell is a B cell. Other immune cells, and/or combinations of different immune cell types can optionally be used. In some embodiments, combinations of cell types (*e.g.*, NK cells and T cells) are advantageous because they act synergistically to treat a disease or condition (*e.g.*, a hyperproliferative disease such as cancer). When combinations are used, the various cell types can target the same, different, or overlapping tumor antigenic determinants.

[0413] In some embodiments, the CAR-containing immune cell is a T cell, and the binding of the ADBD of the CAR to a cognate ligand (*i.e.*, target of interest) stimulates the T cell to initiate intracellular signaling. In further embodiments, binding of the ADBD of the CAR to a cognate ligand stimulates the T cell to produce cytokines and degranulate, leading to the cytotoxic effects on the cell expressing the target of interest on its surface (*e.g.*, a cancer cell). In additional embodiments, the CAR-containing T cell proliferates in response to binding the target of interest. In some embodiments, the activity of the CAR-containing T cell does not result in the T cells exhibiting a phenotype associated with T cell exhaustion. In some embodiments where the CAR cell is a T cell, the transmembrane domain of the CAR comprises 41BB or CD28, and the cytoplasmic domain comprises a T cell receptor alpha, beta, or zeta chain.

[0414] In some embodiments, the CAR-containing immune cell is a NK cell, the transmembrane domain comprises CD28, and the cytoplasmic domain comprises a zeta chain of a T cell receptor.

[0415] In some embodiments, the CAR-containing immune cell has been engineered to bind to a target of interest expressed by a cancer cell. In further embodiments the CAR-containing cell binds a tumor antigen selected from the group: CD137, PDL1, CD123, CTLA4, CD47, KIR, DR5, TIM3, PD1, EGFR, TCR, CD19, CD20, CD22, ROR1, mesothelin, CD33, IL3Ra, cMet, PSMA, Glycolipid F77, EGFRvIII, GD2, NY-ESO- 1,

and MAGE A3. In further embodiments the CAR-containing cell binds 2, 3, 4, 5 or more of the above tumor antigens.

[0416] In some embodiments, the CAR of the CAR cell binds two or more targets of interest. In further embodiments, the CAR further comprises a second polypeptide comprising the amino acid of SEQ ID NO: 17-26, or 27, the polypeptide being able to specifically bind a second target of interest expressed by a cancer cell, and wherein the second polypeptide's specific binding the second target of interest is greater than binding of a polypeptide according to SEQ ID NO: 1 to the second target of interest.

[0417] In some embodiments, the CAR cell is engineered to express an Adapter disclosed herein (*e.g.*, as described in Section V and Section XI).

[0418] In additional embodiments, the CAR cell is engineered to express a second CAR. In some embodiments, the second CAR comprises an extracellular domain comprising an ADBD, a transmembrane domain, and an intracellular signaling domain. In an additional embodiment the second CAR is comprised of an extracellular domain composed of one or more ADBDs (*e.g.*, as described in Section VI herein and in Section XI) with the same or different specificities. In some embodiments, the second CAR is able to transduce an effector function signal upon binding a target of interest. In further embodiments, the second CAR comprises an extracellular domain comprising an ADBD, and transmembrane or other cell-surface associating domain, but is unable to signal upon binding a target of interest.

[0419] In some embodiments the CAR cell is engineered such that the CAR coding sequence is site specifically introduced into a locus of a gene highly expressed in the corresponding host cell. In some embodiments the CAR coding sequence is introduced into a T cell receptor locus. In further embodiments, the CAR coding sequence is introduced into the T cell receptor α constant (*TRAC*) of the cell. Modified cells that lack expression of a functional TCR and/or HLA can routinely be obtained using any suitable means known in the art, including for example, siRNA, shRNA, CRISPR, TALEN, and/or ZFN.

[0420] In some embodiments, the immune effector cell can be an allogeneic immune effector cell, *e.g.*, T cell or NK cell.

VIIa. Genetic modifications of CAR cells

[0421] To avoid or reduce the possibility that CAR cells disclosed herein target an immune response (*e.g.*, kill) to themselves, a CAR cell can be genetically modified to reduce or eliminate the expression of one or more AD targeted by the CAR cell directly by a CAR provided herein or indirectly through an Adaptor provided herein. For example, a CAR cell provided herein with an ADBD that specifically binds to an AD of human CD45 or a CAR cell provided herein suited to be used in combination with an Adapter comprising an ADBD that specifically binds to an AD of human CD45 can be engineered to reduce or eliminate the expression of the human CD45 AD recognized by the ADBD. In some embodiments, the CAR cell is a human immune effector cell.

[0422] In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of one AD bound by a CAR or Adapter provided herein. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of more than one AD bound by a CAR or Adapter provided herein. In some embodiments, the CAR cell comprises more than one genetic modification that reduces or eliminates the expression of more than one AD bound by a CAR or Adapter provided herein. In some embodiments, the more than one AD is comprised by a single antigen. In some embodiments, the AD is a human CD45 AD. In some embodiments, the AD is a human CD26, CD30, CD33, or CD38 AD. In some embodiments, the CAR cell is a human immune effector cell.

[0423] In some embodiments, the genetic modification reduces expression of the AD by about 50%, about 60%, about 70%, about 80%, about 90%, about 95% compared to a reference cell without the genetic modification. In some embodiments, the genetic modification eliminates expression of the AD.

[0424] In some embodiments, the genetic modification reduces expression of the polypeptide comprising the AD by about 50%, about 60%, about 70%, about 80%, about 90%, about 95% compared to a reference cell without the genetic modification. In some embodiments, the genetic modification eliminates expression of the polypeptide comprising the AD. In some embodiments, the AD is a human CD45 AD. In some embodiments, the AD is a human CD26, CD30, CD33, or CD38 AD.

[0425] In some embodiments, the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding the AD. In some embodiments, the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding the AD that eliminates expression of the AD. In some embodiments, the AD is a human CD45 AD. In some embodiments, the AD is a human CD26, CD30, CD33, or CD38 AD.

[0426] In some embodiments, the genetic modification is a substitution of a gene or fragment thereof encoding a polypeptide comprising the AD with a nucleotide sequence encoding a homologue, variant, or derivative of the polypeptide comprising the AD, wherein the encoded homologue, variant, or derivative does not comprise the AD. In some embodiments, the homologue is a non-human primate homologue. In some embodiments, the homologue is derived from rhesus macaque. In some embodiments, the homologue is derived from cynomolgus monkey. In some embodiments, the variant is a naturally occurring variant. In some embodiments, the variant is a splice variant. In some embodiments, the variant has altered glycosylation pattern. In some embodiments, the variant or derivative is capable of signaling. In some embodiments, the AD is a human CD45 AD. In some embodiments, the AD is a human CD26, CD30, CD33, or CD38 AD.

[0427] The genetic modification can reduce or eliminate the expression of any AD for which it is desirable for a CAR or an Adapter to bind, *e.g.*, any of the ADs described in Section IIa and in Section XI.

[0428] The production of CAR cells comprising a genetic modification useful in practicing the provided methods may be carried out using a variety of standard techniques for recombinant DNA methodologies,

genetic manipulation, and genome editing known in the art. Genetically modified CAR cells described herein that lack expression of an AD can routinely be obtained using any suitable means known in the art, including for example, siRNA, shRNA, CRISPR, TALEN, and/or ZFN. Methods for genetic manipulation of CAR cells is described, for example, in U.S. Patent Appl. Pub. 20170204372, which is incorporated herein by reference in its entirety.

[0429] In some embodiments the CAR cell is engineered to eliminate or reduce the expression of a functional T cell receptor (TCR) and/or human leukocyte antigen (HLA), *e.g.*, HLA class I and/or HLA class II. Modified cells that lack expression of a functional TCR and/or HLA can routinely be obtained using any suitable means known in the art, including for example, siRNA, shRNA, CRISPR, TALEN, and/or ZFN.

[0430] In some embodiments, the CAR cell is engineered to eliminate or reduce the expression of a molecule that may decrease the ability of a CAR cell to mount an immune effector response. In further embodiments, the CAR cell is engineered to eliminate or reduce the expression of a molecule selected from: PD1, PDL1, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR beta. In some embodiments, the CAR cell has been engineered to eliminate or reduce the expression of 2, 3, 4, 5 or more of the above molecules. Modified cells that lack expression of one or more of the above molecules can routinely be obtained using any suitable means known in the art, including for example, siRNA, shRNA, CRISPR, TALEN, and/or ZFN.

[0431] In further embodiments, the CAR cell is engineered to eliminate or reduce the expression of one or more of (a) a functional TCR and an HLA; and (b) a molecule selected from: PD1, PDL1, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR beta. In further embodiments, the CAR cell has been engineered to eliminate or reduce the expression of 2, 3, 4, 5, 6 or more of the above molecules.

VIII. Compositions

[0432] Described herein are compositions comprising a CAR cell (*e.g.*, as described in Section VII and Section XI) and an Adapter (*e.g.*, as described in Section V and Section XI).

[0433] For example, in one embodiment a composition comprises (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell. The CAR cell can be any CAR cell described herein (*e.g.*, as described in Section VII and Section XI) and/or the Adapter can be any Adapter described herein (*e.g.*, as described in Section V and Section XI). In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the first or second AD.

[0434] In one embodiment, a composition comprises (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell. The CAR cell can be any CAR cell described herein (*e.g.*, as described in Section VII and Section XI) and/or the Adapter can be any Adapter described herein (*e.g.*, as described in Section V and Section XI). In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the first or second AD.

[0435] In one embodiment, a composition comprises (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell. The CAR cell can be any CAR cell described herein (*e.g.*, as described in Section VII and Section XI) and/or the Adapter can be any Adapter described herein (*e.g.*, as described in Section V and Section XI). In some embodiments, the binding of the Adapter cross-links the second AD on the target cell or complexes containing the second AD. In some embodiments, the Adapter contains an ADBD that is derived from a non-naturally occurring scaffold. In some embodiments, the Adapter contains an AD that is not expressed by the target cell. In some embodiments the Adapter contains an AD is on a secreted protein. In some embodiments the Adapter contains an alfafetoprotein AD. In some embodiments, the AD of the Adapter is not a nuclear protein. In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the first or second AD.

[0436] In one embodiment, a composition comprises (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an alternative scaffold binding domain (ASBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell. The CAR cell can be any CAR cell described herein (*e.g.*, as described in Section VII and Section XI) and/or the Adapter can be any Adapter described herein (*e.g.*, as described in Section V and Section XI). In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the first or second AD.

[0437] In one embodiment, a composition comprises (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD comprising an ASBD that binds to a second AD on a target cell. The CAR cell can be any CAR cell described herein (*e.g.*, as described in Section VII and

Section XI) and/or the Adapter can be any Adapter described herein (*e.g.*, as described in Section V and Section XI). In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the first or second AD.

[0438] In one embodiment a composition comprises (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; (b) an Adapter which comprises (i) said first AD and (ii) a D domain that binds to a second AD on a target cell. The CAR cell can be any CAR cell described herein (*e.g.*, as described in Section VII and Section XI) and/or the Adapter can be any Adapter described herein (*e.g.*, as described in Section V and Section XI). In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the first or second AD.

[0439] In one embodiment, the composition comprises (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a D domain that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell. The CAR cell can be any CAR cell described herein (*e.g.*, as described in Section VII and Section XI) and/or the Adapter can be any Adapter described in Section V and Section XI. In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the first or second AD.

[0440] In one embodiment, a composition comprises (a) a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a first D domain that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) an Adapter which comprises (i) said first AD and (ii) a second D domain that binds to a second AD on a target cell. The CAR cell can be any CAR cell described herein (*e.g.*, as described in Section VII and Section XI) and/or the Adapter can be any Adapter described herein (*e.g.*, as described in Section V and Section XI). In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the first or second AD.

[0441] In certain embodiments, the CAR comprises a single-chain variable fragment (scFv) ADBD. In other embodiments, the CAR comprises an alternative scaffold binding domain (ASBD) ADBD. In further embodiments, the CAR comprises a D domain.

[0442] In some embodiments, the CAR comprises 2 ADBDs. In other embodiments, the CAR comprises an ASBD and a scFv. In further embodiments, the CAR comprises a D domain and a scFv. In some embodiments, the CAR comprises 2 ASBDs. In further embodiments, the CAR comprises 2 D domains.

[0443] In some embodiments, the CAR intracellular domain is a signaling domain. In further embodiments, the CAR intracellular domain comprises a primary signaling domain. In certain embodiments, the CAR intracellular domain comprises a CD3 ζ primary signaling domain. In some embodiments, the CAR

intracellular domain further comprises a costimulatory signaling domain. In further embodiments, the costimulatory signaling domain is selected from: CD28, 41BB, CD27, and CD134. In particular embodiments, the CAR intracellular signaling domain comprises a 41BB costimulatory signaling domain.

[0444] In some embodiments, the CAR binds to an antigen selected from: CD45, CD26, CD30, CD33, and CD38. In some embodiments, the CAR binds to CD26. In some embodiments, the CAR binds to CD30. In some embodiments, the CAR binds to CD33. In some embodiments, the CAR binds to CD38. In further embodiments, the CAR binds to CD45.

[0445] In some embodiments, the CAR binds to an antigen selected from: CD19, CD22, CD123, BCMA, CS1, HER2, TACI, BAFFR, and PDL1. In further embodiments, the CAR binds to BCMA. In further embodiments, the CAR binds to CS1. In other embodiments, the CAR binds to CD123. In other embodiments, the CAR binds to CD19. In other embodiments, the CAR binds to CD22. In other embodiments, the CAR binds to TACI. In other embodiments, the CAR binds to BAFFR. In other embodiments, the CAR binds to PDL1. In other embodiments, the CAR binds to HER2.

[0446] In some embodiments, the CAR comprises 2 ADBDs that bind to separate targets. In further embodiments, the CAR binds to BCMA and CS1. In further embodiments, the CAR binds to CD19 and CD123. In other embodiments, the CAR binds to CD22 and CD123. In other embodiments, the CAR binds to PDL1 and CD123. In some embodiments, the CAR binds to CD45 and a second target. In certain embodiments, the CAR comprises a first ASBD that binds to BCMA and a second ASBD that binds to CS1. In other embodiments, the CAR comprises a first D domain that binds to BCMA and a second D domain that binds to CS1. In other embodiments, the CAR comprises a D domain that binds to BCMA and a scFv that binds to CS1. In other embodiments, the CAR comprises a D domain that binds to CS1 and a scFv that binds to BCMA. In certain embodiments, the CAR comprises a first ASBD that binds to CD19 and a second ASBD that binds to CD123. In other embodiments, the CAR comprises a first D domain that binds to CD19 and a second D domain that binds to CD123. In some embodiments, the CAR comprises a first D domain that binds to a CD45 AD and a second D domain that binds to a second AD. In other embodiments, the CAR comprises a D domain that binds to CD19 and a scFv that binds to CD123. In other embodiments, the CAR comprises a first ASBD that binds to CD22 and a second ASBD that binds to CD123. In other embodiments, the CAR comprises a first D domain that binds to CD22 and a second D domain that binds to CD123. In other embodiments, the CAR comprises a D domain that binds to CD22 and a scFv that binds to CD123. In some embodiments, the CAR comprises a first ASBD that binds to PDL1 and a second ASBD that binds to CD123. In some embodiments, the CAR comprises a first D domain that binds to PDL1 and a second D domain that binds to CD123. In some embodiments, the CAR comprises a D domain that binds to PDL1 and a scFv that binds to CD123. In some embodiments, the CAR comprises an ASBD that binds to CD19 and a scFv that binds to CD123.

[0447] In some embodiments, the Adapter comprises an AD of a tumor antigen. In further embodiments, the tumor antigen is selected from the group: BCMA, CD123, CD19, CD22, CS1, TACI, BAFFR, and PDL1. In further embodiments, the tumor antigen is HER2.

[0448] In some embodiments, the Adapter comprises an ADBD that is a scFv. In further embodiments, the Adapter comprises an ADBD that is an ASBD. In some embodiments, the Adapter comprises a D domain.

[0449] In some embodiments, the Adapter comprises two ADBDs. In further embodiments, the Adapter comprises two ADBDs that (a) are the same, (b) bind to the same antigenic determinant, (c) bind to different ADs of the same antigen, (d) bind to different antigens on the same cell, or (d) bind to different antigens on different cells. In further embodiments, the Adapter comprises two ASBDs. In certain embodiments, the Adapter comprises two D domains. In some embodiments, the Adapter comprises an ADBD that is a scFv and an ADBD that is an ASBD. In other embodiments, the Adapter comprises an ADBD that is a scFv and an ADBD that is a D domain.

[0450] In some embodiments, the Adapter comprises an ADBD that binds to a member selected from: CD45, CD26, CD30, CD33, and CD38. In certain embodiments, the Adapter comprises an ADBD binds to CD45. In other embodiments, the Adapter comprises an ADBD that binds to CD26. In some embodiments, the Adapter comprises an ADBD that binds to CD30. In other embodiments, the Adapter comprises an ADBD that binds to CD33. In other embodiments, the Adapter comprises an ADBD that binds to CD38. In some embodiments, the Adapter comprises an ADBD that binds to CD45.

[0451] In some embodiments, the Adapter comprises an ADBD that binds to a member selected from: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1. In certain embodiments, the Adapter comprises an ADBD binds to BCMA. In other embodiments, the Adapter comprises an ADBD that binds to CD123. In some embodiments, the Adapter comprises an ADBD that binds to CD19. In other embodiments, the Adapter comprises an ADBD that binds to CD22. In other embodiments, the Adapter comprises an ADBD that binds to CS1. In other embodiments, the Adapter comprises an ADBD that binds to HER2. In other embodiments, the Adapter comprises an ADBD that binds to TACI. In other embodiments, the Adapter comprises an ADBD that binds to BAFFR. In other embodiments, the Adapter comprises an ADBD that binds to PDL1.

[0452] In some embodiments, the Adapter is bispecific. In further embodiments, the Adapter comprises an ADBD that binds to CD19 and an ADBD that binds to CD123. In other embodiments, the Adapter comprises an ADBD that binds to BCMA and an ADBD that binds to CS1. In other embodiments, the Adapter comprises an ADBD that binds to CD22 and an ADBD that binds to CD123. In other embodiments, the Adapter comprises an ADBD that binds to PDL1 and an ADBD that binds to CD123. In some embodiments, the Adapter binds to a human CD45 AD and a second AD.

[0453] In some embodiments, the target cell is a tumor cell. In further embodiments, the tumor cell is selected from the group: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia. In further embodiments, the tumor cell is selected from the group: acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the tumor cell is an AML tumor cell. In some embodiments, the tumor cell is an CLL tumor cell. In some embodiments, the tumor cell is an MM tumor cell.

[0454] In some embodiments, the target cell is a cancer cell. In further embodiments, the cancer cell is selected from the group: breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, colon cancer, and lung cancer. In further embodiments, the cancer cell is breast cancer. In some embodiments, the cancer cell is ovarian cancer.

[0455] In some embodiments, the composition comprises at least two target cells. In some embodiments, at least one target cell is a tumor cell. In further embodiments, the first and second target cells are tumor cells. In certain embodiments, the first and second tumor cells are of the same tumor type. In other embodiments, the first and second tumor cells are of a different tumor type. In some embodiments, the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia. In some embodiments, the tumor cells are selected from: acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM).

[0456] In some embodiments, the cell expressing the CAR is an immune effector cell. In further embodiments, the immune effector cell is a T cell. In other embodiments, the immune effector cell is an NK cell. In some embodiments, the cell expressing the CAR kills the target cell. In some embodiments, binding of the Adapter to an AD blocks the activity of the antigen comprising the AD. In some embodiments, the cell expressing the CAR comprises a genetic modification that reduces or eliminates the expression of an AD described herein. In some embodiments, the cell expressing the CAR comprises a genetic modification that reduces or eliminates the expression of a human CD45 AD.

[0457] In one embodiment, the composition is within a patient, *e.g.*, a human patient.

[0458] In some embodiments, the CAR cell binds to an AD that is present on both a target cell and an Adapter. In other embodiments, the CAR cell binds to an AD that is present on an Adapter, but is not present on a target cell. In some embodiments, the AD is a naturally occurring protein/molecule. In some embodiments, the AD is a human protein/molecule.

IX. Methods that Comprise Contacting a Target Cell

[0459] Described herein are methods of use comprising contacting a target cell with a CAR cell (*e.g.*, as described above in Section VII and Section XI) and an Adapter (*e.g.*, as described above in Section V and Section XI) or a composition (*e.g.*, as described above in Section VIII and Section XI).

[0460] For example, in one embodiment, a method of delivering an immune response to a target cell comprises contacting the target cell with any of the compositions described herein (*e.g.*, as described in Section VIII and Section XI). In another embodiment, a method of killing a target cell comprises contacting the target cell with any of the compositions described herein (*e.g.*, as described in Section VIII and Section XI). As used herein, "contacting" can refer to contacting a target cell *in vitro* (*e.g.*, in a cell culture) or contacting a target cell *in vivo* (*e.g.*, in a patient).

[0461] In one embodiment, a method of delivering an immune response to a target cell comprises contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0462] In one embodiment, a method of delivering an immune response to one or more target cells comprises contacting a composition comprising a first target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0463] In one embodiment, method of delivering an immune response to a target cell comprises contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0464] In one embodiment, a method of delivering an immune response to a target cell comprises contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell.

[0465] In one embodiment, a method of delivering an immune response to a target cell comprises contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein (a) a first antigenic determinant (AD) is present on the target cell; (b) the composition comprising the first target cell further comprises an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on the target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0466] In one embodiment, a method of delivering an immune response to one or more target cells comprises contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein (a) a first AD is present on the first target cell; (b) the composition comprising the first target cell further comprises a second target cell and an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on a second target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the first target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0467] In one embodiment, a method of delivering an immune response to a target cell comprises contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein (a) a first antigenic determinant (AD) is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0468] In one embodiment, a method of delivering an immune response to a target cell comprises contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein (a) a first antigenic determinant (AD) is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0469] In one embodiment, a method of killing a target cell comprises contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0470] In one embodiment, a method of killing one or more target cells comprising contacting a composition comprising a first target cell with an Adapter, wherein, wherein (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an

antigenic determinant binding domain (ADBD) that binds to a first AD on said first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell.

[0471] In one embodiment, a method of killing a target cell comprises contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell.

[0472] In one embodiment, a method of killing a target cell comprises contacting a composition comprising a target cell with an Adapter, wherein (a) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD (*e.g.*, D domain) that binds to a second AD on said target cell.

[0473] In one embodiment, a method of killing a target cell comprises contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) said first AD and (ii) an ADBD that binds to a second AD on the target cell and (c) the comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0474] In one embodiment, a method of killing one or more target cells comprises contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the first target cell, (b) the composition comprising a first target cell further comprises a second target cell and an Adapter comprising (i) said first AD and (ii) an ADBD that binds to a second AD on the second target cell; and (c) the CAR comprises (i) an ADBD that binds to said first AD on the first target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0475] In one embodiment, a method of killing a target cell comprises contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an ADBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0476] In one embodiment, a method of killing a target cell comprises contacting a composition comprising a target cell with a cell expressing a CAR, wherein (a) a first AD is present on the target cell; (b) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant

binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and (c) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.

[0477] The contacting can occur *in vitro*, *ex vivo*, or *in vivo*. In one embodiment, the contacting occurs in a patient, *e.g.* a human patient, for example after administration of an Adapter to a patient who has received a cell expressing a CAR or after administration of a cell expressing a CAR to a patient who has received an Adapter.

[0478] In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of an AD recognized by a CAR described herein or by an Adapter described herein. In some embodiments, the AD is a human CD45 AD. In some embodiments, the CAR cell comprises a genetic modification that eliminates the expression of the AD recognized by the CAR or by an Adapter bound by the CAR. In some embodiments, the AD is a human CD45 AD.

[0479] In certain embodiments, the CAR comprises a single-chain variable fragment (scFv) ADBD. In other embodiments, the CAR comprises an alternative scaffold binding domain (ASBD) ADBD. In further embodiments, the CAR comprises a D domain.

[0480] In some embodiments, the CAR comprises 2 ADBDs. In other embodiments, the CAR comprises an ASBD and a scFv. In further embodiments, the CAR comprises a D domain and a scFv. In some embodiments, the CAR comprises 2 ASBDs. In further embodiments, the CAR comprises 2 D domains.

[0481] In some embodiments, the CAR intracellular domain is a signaling domain. In further embodiments, the CAR intracellular domain comprises a primary signaling domain. In certain embodiments, the CAR intracellular domain comprises a CD3 ζ primary signaling domain. In some embodiments, the CAR intracellular domain further comprises a costimulatory signaling domain. In further embodiments, the costimulatory signaling domain is selected from: CD28, 41BB, CD27, and CD134. In particular embodiments, the CAR intracellular signaling domain comprises a 41BB costimulatory signaling domain.

[0482] In some embodiments, the CAR binds to an antigen selected from: CD45, CD26, CD30, CD33, and CD38. In further embodiments, the CAR binds to CD26. In other embodiments, the CAR binds to CD30. In other embodiments, the CAR binds to CD33. In other embodiments, the CAR binds to CD38. In some embodiments, the CAR binds to CD45.

[0483] In some embodiments, the CAR binds to an antigen selected from: CD19, CD22, CD123, BCMA, CS1, HER2, TACI, BAFFR, and PDL1. In further embodiments, the CAR binds to BCMA. In other embodiments, the CAR binds to CS1. In other embodiments, the CAR binds to CD123. In other embodiments, the CAR binds to CD19. In other embodiments, the CAR binds to CD22. In other embodiments, the CAR binds to TACI. In other embodiments, the CAR binds to BAFFR. In other embodiments, the CAR binds to PDL1. In other embodiments, the CAR binds to HER2.

[0484] In some embodiments, the CAR comprises 2 ADBDs that bind to separate targets. In further embodiments, the CAR binds to CD19 and CD123. In other embodiments, the CAR binds to BCMA and CS1. In other embodiments, the CAR binds to CD22 and CD123. In other embodiments, the CAR binds to PDL1 and CD123. In some embodiments, the CAR binds to CD45 and second target. In certain embodiments, the CAR comprises a first ASBD that binds to CD19 and a second ASBD that binds to CD123. In other embodiments, the CAR comprises a first D domain that binds to CD19 and a second D domain that binds to CD123. In certain embodiments, the CAR comprises a first ASBD that binds to BCMA and a second ASBD that binds to CS1. In other embodiments, the CAR comprises a first D domain that binds to BCMA and a second D domain that binds to CS1. In other embodiments, the CAR comprises a D domain that binds to CS1 and a scFv that binds to BCMA. In some embodiments, the CAR comprises a first D domain that binds to a CD45 AD and a second D domain that binds to a second AD. In other embodiments, the CAR comprises a D domain that binds to CD19 and a scFv that binds to CD123. In other embodiments, the CAR comprises a first ASBD that binds to CD22 and a second ASBD that binds to CD123. In other embodiments, the CAR comprises a first D domain that binds to CD22 and a second D domain that binds to CD123. In other embodiments, the CAR comprises a D domain that binds to CD22 and a scFv that binds to CD123. In some embodiments, the CAR comprises a first ASBD that binds to PDL1 and a second ASBD that binds to CD123. In some embodiments, the CAR comprises a first D domain that binds to PDL1 and a second D domain that binds to CD123. In some embodiments, the CAR comprises a D domain that binds to PDL1 and a scFv that binds to CD123. In some embodiments, the CAR comprises an ASBD that binds to CD19 and a scFv that binds to CD123.

[0485] In some embodiments, the Adapter comprises an AD of a tumor antigen. In further embodiments, the tumor antigen is selected from the group: CD45, CD26, CD30, CD33, and CD38.

[0486] In some embodiments, the Adapter comprises an AD of a tumor antigen. In further embodiments, the tumor antigen is selected from the group: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1.

[0487] In some embodiments, the Adapter comprises an ADBD that is a scFv. In further embodiments, the Adapter comprises an ADBD that is an ASBD. In some embodiments, the Adapter comprises a D domain.

[0488] In some embodiments, the Adapter comprises two ADBDs. In further embodiments, the Adapter comprises two ADBDs that (a) are the same, (b) bind to the same antigenic determinant, (c) bind to different ADs of the same antigen, (d) bind to different antigens on the same cell, or (e) bind to different antigens on different cells. In some embodiments, the Adapter comprises two ASBDs. In certain embodiments, the Adapter comprises two D domains. In some embodiments, the Adapter comprises an ADBD that is a scFv and an ADBD that is an ASBD. In other embodiments, the Adapter comprises an ADBD that is a scFv and an ADBD that is a D domain.

[0489] In some embodiments, the Adapter comprises an ADBD that binds to a member selected from: CD45, CD26, CD30, CD33, and CD38. In certain embodiments, the Adapter comprises an ADBD binds to CD26. In other embodiments, the Adapter comprises an ADBD that binds to CD30. In some embodiments, the Adapter comprises an ADBD that binds to CD38. In other embodiments, the Adapter comprises an ADBD that binds to CD45.

[0490] In some embodiments, the Adapter comprises an ADBD that binds to a member selected from: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1. In certain embodiments, the Adapter comprises an ADBD binds to BCMA. In other embodiments, the Adapter comprises an ADBD that binds to CD123. In some embodiments, the Adapter comprises an ADBD that binds to CD19. In other embodiments, the Adapter comprises an ADBD that binds to CD22. In other embodiments, the Adapter comprises an ADBD that binds to CS1. In other embodiments, the Adapter comprises an ADBD that binds to HER2. In other embodiments, the Adapter comprises an ADBD that binds to TACI. In other embodiments, the Adapter comprises an ADBD that binds to BAFFR. In other embodiments, the Adapter comprises an ADBD that binds to PDL1.

[0491] In some embodiments, the Adapter is bispecific. In further embodiments, the Adapter comprises an ADBD that binds to CD19 and an ADBD that binds to CD123. In other embodiments, the Adapter comprises an ADBD that binds to BCMA and an ADBD that binds to CS1. In other embodiments, the Adapter comprises an ADBD that binds to CD22 and an ADBD that binds to CD123. In other embodiments, the Adapter comprises an ADBD that binds to PDL1 and an ADBD that binds to CD123. In some embodiments, the Adapter binds to a human CD45 AD and a second AD.

[0492] In some embodiments, the target cell is a tumor cell. In further embodiments, the tumor cell is selected from the group: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia. In further embodiments, the tumor cell is selected from the group: acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the tumor cell is an AML tumor cell. In some embodiments, the tumor cell is an CLL tumor cell. In some embodiments, the tumor cell is an MM tumor cell.

[0493] In some embodiments, the composition comprises at least two target cells. In some embodiments, at least one target cell is a tumor cell. In further embodiments, the first and second target cells are tumor cells. In certain embodiments, the first and second tumor cells are of the same tumor type. In other embodiments, the first and second tumor cells are of a different tumor type. In some embodiments, the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia. In some embodiments, the tumor cells are selected from:

acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the tumor cells are multiple myeloma (MM). In the methods of killing a target cell provided herein, the target cell can be a cancer cell. Exemplary cancer cells that can be targeted according to the methods provided herein are discussed in Section X and Section XI.

[0494] In some embodiments, the target cell is a tumor cell. In further embodiments, the tumor cell is selected from the group: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia. In some embodiments, the tumor cell is selected from: acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the tumor cell is multiple myeloma (MM).

[0495] In some embodiments, the target cell is a cancer cell. In further embodiments, the cancer cell is selected from the group: breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, colon cancer, and lung cancer. In some embodiments, the cancer cell is breast cancer. In some embodiments, the cancer cell is ovarian cancer.

[0496] In some embodiments, the composition comprises at least two target cells. In some embodiments, at least one target cell is a tumor cell. In further embodiments, the first and second target cells are tumor cells. In certain embodiments, the first and second tumor cells are of the same tumor type. In other embodiments, the first and second tumor cells are of a different tumor type. In some embodiments, the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia. In some embodiments, the tumor cells are selected from: acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the tumor cells are multiple myeloma (MM).

[0497] In the methods of killing a target cell provided herein, the target cell can be a cell of the immune system. In some embodiments, the target cell is a B cell. In some embodiments, the target cell is a T cell. In some embodiments, the target cell is a naïve T cell. In some embodiments, the target cell is a memory T cell.

[0498] In the methods of killing a target cell provided herein, the target cell can be a bacterial cell (*e.g.*, tuberculosis, smallpox, and anthrax), a cell of a parasite (*e.g.*, malaria or leishmaniasis), a fungal cell, a mold, a mycoplasma, or a cell infected with a virus (*e.g.*, HIV, hepatitis b, rabies, Nipah virus, west Nile virus, a meningitis virus, or CMV).

[0499] In some embodiments, the cell expressing the CAR is an immune effector cell. An immune effector cell is a cell that is involved in an immune response, *e.g.*, in the promotion of an immune effector response. Examples of immune effector cells include T cells (*e.g.*, alpha/beta T cells and gamma/delta T cells), B cells, natural killer (NK) cells, natural killer T (NKT) cells, mast cells, and myeloid-derived phagocytes. An

immune effector function or immune effector response is a function or response of for example, an immune effector cell *that* enhances or promotes an immune attack of a target cell. In some embodiments, the immune effector function or response refers a property of a T or NK cell that promotes killing, or the inhibition of growth or proliferation, of a target cell. For example, primary stimulation and costimulation are examples of immune effector function or response of a T cell. In particular embodiments, an immune effector function or response is promoted by the action of the disclosed CAR, Adapter, and/or CAR and Adapter compositions. Such function or response results in, for example, a CAR cell that is more effective at proliferation, cytokine production, cytotoxicity or upregulation of cell surface markers such as CD25, CD69, and CD107a.

[0500] In some embodiments, the immune effector cell is a T cell. In other embodiments, the immune effector cell is an NK cell. In some embodiments, the cell expressing the CAR kills the target cell. In some embodiments, binding of the Adapter to an AD blocks the activity of the antigen comprising the AD.

[0501] In some embodiments, the CAR cell kills the target cell upon direct binding to the target cell. In some embodiments, the CAR cell kills the target cell upon binding to the Adapter, wherein the Adapter is bound to the target cell (*e.g.*, as depicted in FIGS. 3A-3C).

[0502] In some embodiments, binding of CAR to the target cell and/or to the Adapter results in intracellular signaling in the cell expressing the CAR.

[0503] In some embodiments, binding of the CAR to the target cell and/or to the Adapter results in degranulation. Degranulation can result in the release of, depending on the cell type, antimicrobial, cytotoxic or other molecules from secretory granules in the immune cell. Molecules like perforin (a pore forming cytotoxin) or granzymes (serine proteases that induce apoptosis in the target cell) aid T cells and NK cells in killing tumor cells (or other cell types).

[0504] In some embodiments, binding of the CAR to the target cell and/or to the Adapter results in cytokine secretion by the cell expressing the CAR. The cytokine can be, for example, interferon gamma (IFN γ).

[0505] In some embodiments, binding of the CAR to the target cell and/or to the Adapter results in proliferation of the cell expressing the CAR.

X. Therapeutic Uses

[0506] Described herein are methods of delivering an immune response to a target cell in a patient and/or killing a target cell in a patient comprising administering an Adapter (as described herein (*e.g.*, as described in Section V and Section XI)) and/or a CAR cell described herein (*e.g.*, as described in Section VII and Section XI) to the patient. Also described herein are methods of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter described herein (*e.g.*, as described in Section V and Section XI) and/or a CAR cell described herein (*e.g.*, as described in Section VII and Section XI) to the patient. In particular embodiments, provided herein are methods of treating hematological cancer or autoimmune disease comprising administering an Adapter described herein (*e.g.*, as

described in Section V and Section XI) and/or a CAR cell described herein (*e.g.*, as described in Section VII and Section XI) to the patient.

[0507] In one embodiment, a method of delivering an immune response to a target cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of killing a target cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of depleting lymphocytes in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a patient comprises administering a cell expressing a CAR to the patient. In certain embodiments, a method of treating hematological cancer comprises administering a cell expressing a CAR to the patient. In certain embodiments, a method of treating an autoimmune disease or disorder comprises administering a cell expressing a CAR to the patient. In one embodiment, a first AD is present on the target cell, and the CAR comprises (i) an ADBD that binds to said first AD on the target cell, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the target cell; and the CAR comprises (i) an ADBD that is an ASBD that binds to said first AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In the methods of killing a target cell in a patient comprising administering a cell expressing a CAR the cell expressing a CAR can be any of the cells expressing CARs described herein (*e.g.*, as described in Section VII and Section XI). In the methods of killing a target cell in a patient comprising administering a cell expressing a CAR the cell expressing a CAR can be in a pharmaceutically acceptable composition. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD bound by the CAR.

[0508] In one embodiment, a method of delivering an immune response to a target cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of killing a target cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of depleting lymphocytes in a patient comprises administering an Adapter to the patient. In another embodiment, a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a patient comprises administering an Adapter to the patient. In certain embodiments, a method of treating hematological cancer comprises administering an Adapter to the patient. In certain embodiments, a method of treating an autoimmune disease or disorder comprises administering an Adapter to the patient. In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell. In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first

antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell. In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell. In the methods of killing a target cell in a patient comprising administering an Adapter to a patient, the Adapter can be any of the Adapters described herein (*e.g.*, as described in Section V and Section XI) and/or the patient can have been treated with any of the cells expressing CARS described herein (*e.g.*, as described in Section VII and Section XI). In some embodiments of the methods of killing a target cell in a patient comprising administering an Adapter to a patient, the patient has previously been treated with an Adapter (in addition to the cell expressing a CAR). In some embodiments, the Adapter that is administered to the patient and the Adapter that was previously administered to the patient bind to different ADs (*e.g.*, on the same or different target cells). In the methods of killing a target cell in a patient comprising administering an Adapter to a patient, the Adapter can be in a pharmaceutically acceptable composition. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD bound by the CAR or the Adapter.

[0509] In one embodiment, a method of delivering an immune response to a target cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of killing a target cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of depleting lymphocytes in a patient comprises administering an Adapter to the patient. In another embodiment, a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a patient comprises administering an Adapter to the patient. In certain embodiments, a method of treating hematological cancer comprises administering an Adapter to the patient. In certain embodiments, a method of treating an autoimmune disease or disorder comprises administering an Adapter to the patient. In one embodiment, the patient comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell. In one embodiment, the patient comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell. In one embodiment, the patient comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an

antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell. In the methods of killing a target cell in a patient comprising administering an Adapter to a patient, the Adapter can be any of the Adapters described herein (*e.g.*, as described in Section V and Section XI) and/or the patient can comprise any of the cells expressing CARS described herein (*e.g.*, as described in Section VII and Section XI). In some embodiments of the methods of killing a target cell in a patient comprising administering an Adapter to a patient, the patient comprises an Adapter (in addition to the cell expressing a CAR). In some embodiments, the Adapter that is administered to the patient and the Adapter comprised by the patient bind to different ADs (*e.g.*, on the same or different target cells). In the methods of killing a target cell in a patient comprising administering an Adapter to a patient, the Adapter can be in a pharmaceutically acceptable composition. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD bound by the CAR or the Adapter.

[0510] In one embodiment, a method of redirecting an immune response to a target cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of redirecting target cell killing in a patient comprises administering an Adapter to the patient. In another embodiment, a method of redirecting lymphocyte depletion in a patient comprises administering an Adapter to the patient. In another embodiment, a method of redirecting treatment of a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprises administering an Adapter to the patient. In certain embodiments, a method of redirecting treatment of a hematological cancer comprises administering an Adapter to the patient. In certain embodiments, a method of redirecting treatment of an autoimmune disease or disorder comprises administering an Adapter to the patient. In one embodiment, the patient has been treated with a cell expressing a CAR, wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell. In the methods of redirecting target cell killing in a patient comprising administering an Adapter to a patient, the Adapter can be any of the Adapters described herein (*e.g.*, as described in Section V and Section XI) and/or the patient can have been treated with any of the cells expressing CARS described herein (*e.g.*, as described in Section VII and Section XI). In one embodiment, the patient comprises a cell expressing a CAR, wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell. In the methods of redirecting target cell killing in a patient comprising administering an Adapter to a patient, the Adapter can be any of the Adapters described herein (*e.g.*, as described in Section

V and Section XI) and/or the patient can comprise any of the cells expressing CARs described herein (*e.g.*, as described in Section VII and Section XI). In the methods of redirecting target cell killing in a patient comprising administering an Adapter to a patient, the Adapter can be in a pharmaceutically acceptable composition. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD bound by the CAR or the Adapter.

[0511] In one embodiment, a method of delivering an immune response to a target cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of killing a target cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of depleting lymphocytes in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a patient comprises administering a cell expressing a CAR to the patient. In certain embodiments, a method of treating hematological cancer comprises administering a cell expressing a CAR to the patient. In certain embodiments, a method of treating an autoimmune disease or disorder comprises administering a cell expressing a CAR to the patient. In one embodiment, a first AD and a second AD are present on the target cell, the patient has been treated with an Adapter comprising (i) said first AD and (ii) an ADBD that binds to the second AD on said target cell; and the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, the patient has been treated with an Adapter comprising (i) a first AD and (ii) an ADBD that binds to a second AD on the target cell; and the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the target cell; the patient has been treated with an Adapter comprising (i) an ADBD that binds to the first AD on said target cell and (ii) a second AD; and the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the target cell; the patient has been treated with an Adapter comprising (i) an ADBD comprising an ASBD that binds to the first AD on the target cell and (ii) a second AD; and the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In the methods of killing a target cell in a patient comprising administering a cell expressing a CAR to a patient, the cell expressing a CAR can be any of the cells expressing CARs described herein (*e.g.*, as described in Section VII and Section XI) and/or the patient can have been treated with any of Adapters described herein (*e.g.*, as described in Section V and Section XI). In the methods of killing a target cell in a patient comprising administering a cell expressing a CAR to a patient, the cell expressing a CAR can be in a pharmaceutically acceptable composition. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD bound by the CAR or the Adapter.

[0512] In one embodiment, a method of delivering an immune response to a target cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of killing a target cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of depleting lymphocytes in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a patient comprises administering a cell expressing a CAR to the patient. In certain embodiments, a method of treating hematological cancer comprises administering a cell expressing a CAR to the patient. In certain embodiments, a method of treating an autoimmune disease or disorder comprises administering a cell expressing a CAR to the patient. In one embodiment, a first AD and a second AD are present on the target cell, the patient comprises an Adapter comprising (i) said first AD and (ii) an ADBD that binds to the second AD on said target cell; and the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, the patient comprises an Adapter comprising (i) a first AD and (ii) an ADBD that binds to a second AD on the target cell; and the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the target cell; the patient comprises an Adapter comprising (i) an ADBD that binds to the first AD on said target cell and (ii) a second AD; and the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the target cell; the patient comprises an Adapter comprising (i) an ADBD comprising an ASBD that binds to the first AD on the target cell and (ii) a second AD; and the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In the methods of killing a target cell in a patient comprising administering a cell expressing a CAR to a patient, the cell expressing a CAR can be any of the cells expressing CARs described herein (*e.g.*, as described in Section VII and Section XI) and/or the patient can comprise any of Adapters described herein (*e.g.*, as described in Section V and Section XI). In the methods of killing a target cell in a patient comprising administering a cell expressing a CAR to a patient, the cell expressing a CAR can be in a pharmaceutically acceptable composition. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD bound by the CAR or the Adapter.

[0513] In one embodiment, a method of delivering an immune response to a target cell in a patient comprises administering a cell expressing a CAR and an Adapter to the patient. In another embodiment, a method of killing a target cell in a patient comprises administering a cell expressing a CAR and an Adapter to the patient. In another embodiment, a method of depleting lymphocytes in a patient comprises administering a cell expressing a CAR and an Adapter to the patient. In another embodiment, a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a patient comprises

administering a cell expressing a CAR and an Adapter to the patient. In certain embodiments, a method of treating hematological cancer comprises administering a cell expressing a CAR and an Adapter to the patient. In certain embodiments, a method of treating an autoimmune disease or disorder comprises administering a cell expressing a CAR and an Adapter to the patient. In one embodiment, a first AD and a second AD are present on the target cell, the Adapter comprises (i) said first AD and (ii) an ADBD that binds to the second AD on said target cell; and the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, the Adapter comprises (i) a first AD and (ii) an ADBD that binds to a second AD on the target cell; and the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the target cell; the Adapter comprises (i) an ADBD that binds to the first AD on said target cell and (ii) a second AD; and the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the target cell; the Adapter comprises (i) an ADBD comprising an ASBD that binds to the first AD on the target cell and (ii) a second AD; and the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In the methods of killing a target cell in a patient comprising administering a cell expressing a CAR and an Adapter to a patient, the cell expressing a CAR can be any of the cells expressing CARs described herein (*e.g.*, as described in Section VII and Section XI) and the Adapter can be any of the Adapters described herein (*e.g.*, as described in Section V and Section XI). In the methods of killing a target cell in a patient comprising administering a cell expressing a CAR and an Adapter to a patient, the cell expressing a CAR and the Adapter can be in a pharmaceutically acceptable composition. In some embodiments, the cell expressing a CAR and the Adapter are in a single pharmaceutically acceptable composition. In some embodiments, the cell expressing a CAR and the Adapter are in separate pharmaceutically acceptable compositions. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD bound by the CAR or the Adapter.

[0514] In certain embodiments, the CAR comprises a single-chain variable fragment (scFv) ADBD. In other embodiments, the CAR comprises an alternative scaffold binding domain (ASBD) ADBD. In further embodiments, the CAR comprises a D domain.

[0515] In some embodiments, the CAR comprises 2 ADBDs. In other embodiments, the CAR comprises an ASBD and a scFv. In further embodiments, the CAR comprises a D domain and a scFv. In some embodiments, the CAR comprises 2 ASBDs. In further embodiments, the CAR comprises 2 D domains.

[0516] In some embodiments, the CAR intracellular domain is a signaling domain. In further embodiments, the CAR intracellular domain comprises a primary signaling domain. In certain embodiments, the CAR intracellular domain comprises a CD3 ζ primary signaling domain. In some embodiments, the CAR

intracellular domain further comprises a costimulatory signaling domain. In further embodiments, the costimulatory signaling domain is selected from: CD28, 41BB, CD27, and CD134. In particular embodiments, the CAR intracellular signaling domain comprises a 41BB costimulatory signaling domain.

[0517] In some embodiments, the CAR binds to an antigen selected from: CD45, CD26, CD30, CD33, and CD38. In further embodiments, the CAR binds to CD45. In other embodiments, the CAR binds to CD26. In other embodiments, the CAR binds to CD30. In other embodiments, the CAR binds to CD33. In other embodiments, the CAR binds to CD38. In some embodiments, the CAR binds to a CD45 AD.

[0518] In some embodiments, the CAR binds to an antigen selected from: CD19, CD22, CD123, BCMA, CS1, HER2, TACI, BAFFR, and PDL1. In further embodiments, the CAR binds to BCMA. In other embodiments, the CAR binds to CS1. In other embodiments, the CAR binds to CD123. In other embodiments, the CAR binds to CD19. In other embodiments, the CAR binds to CD22. In other embodiments, the CAR binds to TACI. In other embodiments, the CAR binds to BAFFR. In other embodiments, the CAR binds to PDL1. In other embodiments, the CAR binds to HER2.

[0519] In some embodiments, the CAR comprises 2 ADBDs that bind to separate targets. In further embodiments, the CAR binds to CD19 and CD123. In other embodiments, the CAR binds to BCMA and CS1. In other embodiments, the CAR binds to CD22 and CD123. In other embodiments, the CAR binds to PDL1 and CD123. In some embodiments, the CAR binds to CD45 and second target. In certain embodiments, the CAR comprises a first ASBD that binds to CD19 and a second ASBD that binds to CD123. In other embodiments, the CAR comprises a first D domain that binds to CD19 and a second D domain that binds to CD123. In other embodiments, the CAR comprises a D domain that binds to CD19 and a scFv that binds to CD123. In certain embodiments, the CAR comprises a first ASBD that binds to BCMA and a second ASBD that binds to CS1. In other embodiments, the CAR comprises a first D domain that binds to BCMA and a second D domain that binds to CS1. In other embodiments, the CAR comprises a D domain that binds to CS1 and a scFv that binds to BCMA. In other embodiments, the CAR comprises a first ASBD that binds to CD22 and a second ASBD that binds to CD123. In other embodiments, the CAR comprises a first D domain that binds to CD22 and a second D domain that binds to CD123. In some embodiments, the CAR comprises a first D domain that binds to a CD45 AD and a second D domain that binds to a second AD. In other embodiments, the CAR comprises a D domain that binds to CD22 and a scFv that binds to CD123. In some embodiments, the CAR comprises a first ASBD that binds to PDL1 and a second ASBD that binds to CD123. In some embodiments, the CAR comprises a first D domain that binds to PDL1 and a second D domain that binds to CD123. In some embodiments, the CAR comprises a D domain that binds to PDL1 and a scFv that binds to CD123. In some embodiments, the CAR comprises an ASBD that binds to CD19 and a scFv that binds to CD123.

[0520] In some embodiments, the Adapter comprises an AD of a tumor antigen. In further embodiments, the tumor antigen is selected from the group: CD45, CD26, CD30, CD33, and CD38.

[0521] In some embodiments, the Adapter comprises an AD of a tumor antigen. In further embodiments, the tumor antigen is selected from the group: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1.

[0522] In some embodiments, the Adapter comprises an ADBD that is a scFv. In further embodiments, the Adapter comprises an ADBD that is an ASBD. In some embodiments, the Adapter comprises a D domain.

[0523] In some embodiments, the Adapter comprises two ADBDs. In further embodiments, the Adapter comprises two ADBDs that (a) are the same, (b) bind to the same antigenic determinant, (c) bind to different ADs of the same antigen, (d) bind to different antigens on the same cell, or (e) bind to different antigens on different cells. In some embodiments, the Adapter comprises two ASBDs. In certain embodiments, the Adapter comprises two D domains. In some embodiments, the Adapter comprises an ADBD that is a scFv and an ADBD that is an ASBD. In other embodiments, the Adapter comprises an ADBD that is a scFv and an ADBD that is a D domain.

[0524] In some embodiments, the Adapter comprises an ADBD that binds to a member selected from: CD45, CD26, CD30, CD33, and CD38. In certain embodiments, the Adapter comprises an ADBD binds to CD26. In other embodiments, the Adapter comprises an ADBD that binds to CD30. In some embodiments, the Adapter comprises an ADBD that binds to CD33. In other embodiments, the Adapter comprises an ADBD that binds to CD38. In other embodiments, the Adapter comprises an ADBD that binds to CD45.

[0525] In some embodiments, the Adapter comprises an ADBD that binds to a member selected from: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1. In certain embodiments, the Adapter comprises an ADBD binds to BCMA. In other embodiments, the Adapter comprises an ADBD that binds to CD123. In some embodiments, the Adapter comprises an ADBD that binds to CD19. In other embodiments, the Adapter comprises an ADBD that binds to CD22. In other embodiments, the Adapter comprises an ADBD that binds to CS1. In other embodiments, the Adapter comprises an ADBD that binds to TACI. In other embodiments, the Adapter comprises an ADBD that binds to BAFFR. In other embodiments, the Adapter comprises an ADBD that binds to PDL1.

[0526] In some embodiments, the Adapter is bispecific. In further embodiments, the Adapter comprises an ADBD that binds to CD19 and an ADBD that binds to CD123. In other embodiments, the Adapter comprises an ADBD that binds to BCMA and an ADBD that binds to CS1. In other embodiments, the Adapter comprises an ADBD that binds to CD22 and an ADBD that binds to CD123. In other embodiments, the Adapter comprises an ADBD that binds to PDL1 and an ADBD that binds to CD123. In some embodiments, the Adapter comprises an ADBD that binds to a CD45 AD and an ADBD that binds to a second AD.

[0527] In some embodiments, the target cell is a tumor cell. In further embodiments, the tumor cell is selected from the group: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia. In further embodiments, the tumor cell is selected from the group: acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the tumor cell is an AML tumor cell. In some embodiments, the tumor cell is a CLL tumor cell. In some embodiments, the tumor cell is an MM tumor cell.

[0528] In some embodiments, the target cell is a cancer cell. In further embodiments, the cancer cell is selected from the group: breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, colon cancer, and lung cancer. In further embodiments, the cancer cell is breast cancer. In some embodiments, the cancer cell is ovarian cancer.

[0529] In some embodiments, the composition comprises at least two target cells. In some embodiments, at least one target cell is a tumor cell. In further embodiments, the first and second target cells are tumor cells. In certain embodiments, the first and second tumor cells are of the same tumor type. In other embodiments, the first and second tumor cells are of a different tumor type. In some embodiments, the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia. In some embodiments, the tumor cells are selected from: acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the tumor cells are multiple myeloma (MM).

[0530] In some embodiments, the cell expressing the CAR is an immune effector cell. In further embodiments, the immune effector cell is a T cell. In other embodiments, the immune effector cell is an NK cell. In some embodiments, the cell expressing the CAR kills the target cell. In some embodiments, binding of the Adapter to an AD blocks the activity of the antigen comprising the AD.

[0531] In embodiments, a method of killing a target cell in a patient comprises administering an Adapter and a cell expressing a CAR to the patient. The Adapter and the cell expressing the CAR can be administered in the same pharmaceutical composition or in different pharmaceutical compositions. The Adapter and the cell expressing the CAR can be administered in different pharmaceutical compositions. The Adapter and the cell expressing the CAR can be administered simultaneously or consecutively.

[0532] In one embodiment of the methods of killing a target cell in a patient or the methods of redirecting target cell killing in a patient, the patient has been diagnosed with cancer and the target cell is a cancer cell. In one embodiment, the cancer cell is a prostate cancer cell, a breast cancer cell, a colorectal cancer cell, a lung cancer cell, an osteosarcoma cell, or a glioblastoma cell. Thus, in some embodiments, the methods provided herein treat cancer.

[0533] Cancers that can be treated include tumors that are not vascularized, or not yet substantially vascularized, as well as vascularized tumors. The cancers can comprise non-solid tumors (such as hematological tumors, for example, leukemias and lymphomas) or can comprise solid tumors. Types of cancers to be treated include, but are not limited to, carcinoma, blastoma, and sarcoma, and certain leukemia or lymphoid malignancies, benign and malignant tumors, and malignancies *e.g.*, sarcomas, carcinomas, and melanomas. Adult tumors/cancers and pediatric tumors/cancers are also included.

[0534] Examples of solid tumors, such as sarcomas and carcinomas, include fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, and other sarcomas, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, lymphoid malignancy, pancreatic cancer, breast cancer, lung cancers, ovarian cancer, prostate cancer, hepatocellular carcinoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, pheochromocytomas sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, Wilms' tumor, cervical cancer, testicular tumor, seminoma, bladder carcinoma, melanoma, and CNS tumors (such as a glioma (such as brainstem glioma and mixed gliomas), glioblastoma (also known as glioblastoma multiforme) astrocytoma, CNS lymphoma, germinoma, medulloblastoma, Schwannoma craniopharyngioma, ependymoma, pineaioma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, retinoblastoma and brain metastases). In some embodiments, the solid tumor is breast cancer. In some embodiments, the solid tumor is ovarian cancer.

[0535] In another embodiment, the methods described herein are useful for treating a patient having a hematological cancer. Examples of hematological (or hematogenous) cancers include leukemias, including acute leukemias (such as acute lymphocytic leukemia, acute myelocytic leukemia, acute myelogenous leukemia and myeloblasts, promyelocytic, myelomonocytic, monocytic and erythroleukemia), chronic leukemias (such as chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia), polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (indolent and high grade forms), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia and myelodysplasia. Further examples of hematological (or hematogenous) cancers include acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the hematological (or hematogenous) cancer is AML. In some embodiments, the hematological (or hematogenous) cancer is CLL. In some embodiments, the hematological (or hematogenous) cancer is MM.

[0536] In some embodiments, the cancer is a relapsed or refractory cancer. In some embodiments, the cancer is a relapsed cancer. In some embodiments, the cancer has relapsed following chemotherapy. In some embodiments, the cancer has relapsed following treatment with a biological agent. In some embodiments, the

biological agent is a therapeutic antibody or a CAR-T cell. In some embodiments, the cancer is a refractory cancer. In some embodiments, the cancer is refractory to chemotherapy. In some embodiments, the cancer is refractory to treatment with a biological agent. In some embodiments, the biological agent is a therapeutic antibody or a CAR-T cell.

[0537] In some embodiments, the cancer is a relapsed of refractory hematological cancer. In some embodiments, the cancer is a relapsed hematological cancer. In some embodiments, the cancer is a hematological cancer that has relapsed following chemotherapy. In some embodiments, the cancer is a hematological cancer that has relapsed following treatment with a biological agent. In some embodiments, the biological agent is a therapeutic antibody or a CAR-T cell. In some embodiments, the cancer is a hematological cancer that has relapsed following autologous bone marrow transplantation. In some embodiments, the cancer is a hematological cancer that has relapsed following allogeneic bone marrow transplantation. In some embodiments, the cancer is a hematological cancer that has relapsed following hematopoietic stem cell transplantation (HSCT). In some embodiments, the HSCT is autologous HSCT. In some embodiments, the cancer is a refractory hematological cancer. In some embodiments, the cancer is a hematological cancer that is refractory to chemotherapy. In some embodiments, the cancer is a hematological cancer that is refractory to treatment with a biological agent. In some embodiments, the biological agent is a therapeutic antibody or a CAR-T cell. In some embodiments, the hematological cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), or multiple myeloma (MM). In some embodiments, the hematological cancer is AML. In some embodiments, the hematological cancer is CLL. In some embodiments, the hematological cancer is MM. In some embodiments, the target cell is a B cell. In some embodiments, the target cell is a T cell. In some embodiments, the target cell is a naïve T cell. In some embodiments, the target cell is a memory T cell. In some embodiments, the target cell is a myeloma cell

[0538] In one embodiment, a method of delivering an immune response to a multiple myeloma cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of killing a multiple myeloma cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of depleting multiple myeloma cells in a patient comprises administering an Adapter to the patient. In another embodiment, a method of treating multiple myeloma in a patient comprises administering an Adapter to the patient. In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said multiple myeloma cell (e.g., CS1 or BCMA), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first

antigenic determinant (AD) (e.g., AFP p26 or a variant thereof), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) (e.g., AFP p26 or a variant thereof), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In the methods of killing a multiple myeloma cell in a patient comprising administering an Adapter to a patient, the Adapter can be any of the Adapters described herein (e.g., as described in Section V and Section XI) and/or the patient can have been treated with any of the cells expressing CARS described herein (e.g., as described in Section VII and Section XI). In some embodiments, the Adapter comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to AFP p26 or a variant thereof. In some embodiments of the methods of killing a multiple myeloma cell in a patient comprising administering an Adapter to a patient, the patient has previously been treated with an Adapter (in addition to the cell expressing a CAR). In some embodiments, the Adapter that is administered to the patient and the Adapter that was previously administered to the patient bind to different ADs (e.g., on the same or different multiple myeloma cells). In some embodiments, the Adapter that is administered to the patient binds to CS1 and the Adapter that was previously administered to the patient binds to BCMA. In some embodiments, the Adapter that is administered to the patient binds to BCMA and the Adapter that was previously administered to the patient binds to CS1. In the methods of killing a multiple myeloma cell in a patient comprising administering an Adapter to a patient, the Adapter can be in a pharmaceutically acceptable composition. In some embodiments, the patient has relapsed multiple myeloma. In some embodiments, the patient has multiple myeloma that relapsed following treatment with a biologic agent, for example, antibody or CAR-T cell. In some embodiments, the patient has multiple myeloma that relapsed following treatment with antibody or CAR-T cell that targeted CS1 or BCMA.

[0539] In one embodiment, a method of delivering an immune response to a multiple myeloma cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of killing a multiple myeloma cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of depleting multiple myeloma cells in a patient comprises administering an Adapter to the patient. In another embodiment, a method of treating multiple myeloma in a patient comprises administering an Adapter to the patient. In one embodiment, the patient comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first

antigenic determinant (AD) on said multiple myeloma cell (e.g., CS1 or BCMA), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In one embodiment, the patient comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first antigenic determinant (AD) (e.g., AFP p26 or a variant thereof), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In one embodiment, the patient comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) (e.g., AFP p26 or a variant thereof), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In the methods of killing a multiple myeloma cell in a patient comprising administering an Adapter to a patient, the Adapter can be any of the Adapters described herein (e.g., as described in Section V and Section XI) and/or the patient can comprise any of the cells expressing CARS described herein (e.g., as described in Section VII and Section XI). In some embodiments, the Adapter comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to AFP p26 or a variant thereof. In some embodiments of the methods of killing a multiple myeloma cell in a patient comprising administering an Adapter to a patient, the patient comprises an Adapter (in addition to the cell expressing a CAR). In some embodiments, the Adapter that is administered to the patient and the Adapter comprised by the patient bind to different ADs (e.g., on the same or different multiple myeloma cells). In some embodiments, the Adapter that is administered to the patient binds to CS1 and the Adapter comprised by the patient binds to BCMA. In some embodiments, the Adapter that is administered to the patient binds to BCMA and the Adapter comprised by the patient binds to CS1. In the methods of killing a multiple myeloma cell in a patient comprising administering an Adapter to a patient, the Adapter can be in a pharmaceutically acceptable composition. In some embodiments, the patient has relapsed multiple myeloma. In some embodiments, the patient has multiple myeloma that relapsed following treatment with a biologic agent, for example, antibody or CAR-T cell. In some embodiments, the patient has multiple myeloma that relapsed following treatment with antibody or CAR-T cell that targeted CS1 or BCMA.

[0540] In one embodiment, a method of redirecting an immune response to a multiple myeloma cell in a patient comprises administering an Adapter to the patient. In another embodiment, a method of redirecting multiple myeloma cell killing in a patient comprises administering an Adapter to the patient. In another embodiment, a method of redirecting lymphocyte depletion in a patient comprises administering an Adapter

to the patient. In another embodiment, a method of redirecting treatment of multiple myeloma comprises administering an Adapter to the patient. In certain embodiments, a method of redirecting treatment of an autoimmune disease or disorder comprises administering an Adapter to the patient. In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said multiple myeloma cell (e.g., CS1 or BCMA), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first antigenic determinant (AD) (e.g., AFP p26 or a variant thereof), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In one embodiment, the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) (e.g., AFP p26 or a variant thereof), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said multiple myeloma cell (e.g., CS1 or BCMA). In the methods of killing a multiple myeloma cell in a patient comprising administering an Adapter to a patient, the Adapter can be any of the Adapters described herein (e.g., as described in Section V and Section XI) and/or the patient can have been treated with any of the cells expressing CARS described herein (e.g., as described in Section VII and Section XI). In some embodiments, the Adapter comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to AFP p26 or a variant thereof. In some embodiments of the methods of killing a multiple myeloma cell in a patient comprising administering an Adapter to a patient, the patient has previously been treated with an Adapter (in addition to the cell expressing a CAR). In some embodiments, the Adapter that is administered to the patient and the Adapter that was previously administered to the patient bind to different ADs (e.g., on the same or different multiple myeloma cells). In some embodiments, the Adapter that is administered to the patient binds to CS1 and the Adapter that was previously administered to the patient binds to BCMA. In some embodiments, the Adapter that is administered to the patient binds to BCMA and the Adapter that was previously administered to the patient binds to CS1. In the methods of redirecting multiple myeloma cell killing in a patient comprising administering an Adapter to a patient, the Adapter can be in a pharmaceutically acceptable composition. In some embodiments, the patient has relapsed multiple myeloma. In some embodiments, the patient has multiple myeloma that relapsed following treatment with a biologic

agent, for example, antibody or CAR-T cell. In some embodiments, the patient has multiple myeloma that relapsed following treatment with antibody or CAR-T cell that targeted CS1 or BCMA.

[0541] In one embodiment, a method of delivering an immune response to a multiple myeloma cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of killing a multiple myeloma cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of depleting multiple myeloma cells in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of treating multiple myeloma in a patient comprises administering a cell expressing a CAR to the patient. In one embodiment, a first AD (e.g., BCMA) and a second AD (e.g., CS1) are present on the multiple myeloma cell, the patient has been treated with an Adapter comprising (i) said first AD and (ii) an ADBD that binds to the second AD on said multiple myeloma cell; and the CAR comprises (i) an ADBD that binds to said first AD on the multiple myeloma cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, the patient has been treated with an Adapter comprising (i) a first AD (e.g., BCMA) and (ii) an ADBD that binds to a second AD on the multiple myeloma cell (e.g., CS1); and the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the multiple myeloma cell (e.g., CS1); the patient has been treated with an Adapter comprising (i) an ADBD that binds to the first AD on said multiple myeloma cell and (ii) a second AD (e.g., BCMA); and the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the multiple myeloma cell (e.g., CS1); the patient has been treated with an Adapter comprising (i) an ADBD comprising an ASBD that binds to the first AD on the multiple myeloma cell and (ii) a second AD (e.g., BCMA); and the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In the methods of killing a multiple myeloma cell in a patient comprising administering a cell expressing a CAR to a patient, the cell expressing a CAR can be any of the cells expressing CARs described herein (e.g., as described in Section VII and Section XI) and/or the patient can have been treated with any of Adapters described herein (e.g., as described in Section V and Section XI). In some embodiments, the Adapter comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to AFP p26 or a variant thereof. In the methods of killing a multiple myeloma cell in a patient comprising administering a cell expressing a CAR to a patient, the cell expressing a CAR can be in a pharmaceutically acceptable composition. In some embodiments, the patient has relapsed multiple myeloma. In some embodiments, the patient has multiple myeloma that relapsed following treatment with a biologic agent, for

example, antibody or CAR-T cell. In some embodiments, the patient has multiple myeloma that relapsed following treatment with antibody or CAR-T cell that targeted CS1 or BCMA.

[0542] In one embodiment, a method of delivering an immune response to a multiple myeloma cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of killing a multiple myeloma cell in a patient comprises administering a cell expressing a CAR to the patient. In another embodiment, a method of treating multiple myeloma in a patient comprises administering a cell expressing a CAR to the patient. In one embodiment, a first AD (e.g., BCMA) and a second AD (e.g., CS1) are present on the multiple myeloma cell, the patient comprises an Adapter comprising (i) said first AD and (ii) an ADBD that binds to the second AD on said multiple myeloma cell; and the CAR comprises (i) an ADBD that binds to said first AD on the multiple myeloma cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, the patient comprises an Adapter comprising (i) a first AD (e.g., BCMA) and (ii) an ADBD that binds to a second AD (e.g., CS1) on the multiple myeloma cell; and the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the multiple myeloma cell (e.g., CS1); the patient comprises an Adapter comprising (i) an ADBD that binds to the first AD on said multiple myeloma cell and (ii) a second AD (e.g., BCMA); and the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the multiple myeloma cell (e.g., CS1); the patient comprises an Adapter comprising (i) an ADBD comprising an ASBD that binds to the first AD on the multiple myeloma cell and (ii) a second AD (e.g., BCMA or AFP p26 or a variant thereof); and the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In the methods of killing a multiple myeloma cell in a patient comprising administering a cell expressing a CAR to a patient, the cell expressing a CAR can be any of the cells expressing CARs described herein (e.g., as described in Section VII and Section XI) and/or the patient can comprise any of Adapters described herein (e.g., as described in Section V and Section XI). In some embodiments, the Adapter comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to AFP p26 or a variant thereof. In the methods of killing a multiple myeloma cell in a patient comprising administering a cell expressing a CAR to a patient, the cell expressing a CAR can be in a pharmaceutically acceptable composition. In some embodiments, the patient has relapsed multiple myeloma. In some embodiments, the patient has multiple myeloma that relapsed following treatment with a biologic agent, for example, antibody or CAR-T cell. In some embodiments, the patient has multiple myeloma that relapsed following treatment with antibody or CAR-T cell that targeted CS1 or BCMA.

[0543] In one embodiment, a method of delivering an immune response to a multiple myeloma cell in a patient comprises administering a cell expressing a CAR and an Adapter to the patient. In another embodiment, a method of killing a multiple myeloma cell in a patient comprises administering a cell expressing a CAR and an Adapter to the patient. In another embodiment, a method of depleting multiple myeloma cells in a patient comprises administering a cell expressing a CAR and an Adapter to the patient. In another embodiment, a method of treating multiple myeloma in a patient comprises administering a cell expressing a CAR and an Adapter to the patient. In one embodiment, a first AD (e.g., BCMA) and a second AD (e.g., CS1) are present on the multiple myeloma cell, the Adapter comprises (i) said first AD and (ii) an ADBD that binds to the second AD on said multiple myeloma cell; and the CAR comprises (i) an ADBD that binds to said first AD on the multiple myeloma cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, the Adapter comprises (i) a first AD (e.g., BCMA) and (ii) an ADBD that binds to a second AD on the multiple myeloma cell (e.g., CS1); and the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD (e.g., CS1) is present on the multiple myeloma cell; the Adapter comprises (i) an ADBD that binds to the first AD on said multiple myeloma cell and (ii) a second AD (e.g., BCMA); and the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In one embodiment, a first AD is present on the multiple myeloma cell (e.g., CS1); the Adapter comprises (i) an ADBD comprising an ASBD that binds to the first AD on the multiple myeloma cell and (ii) a second AD (e.g., BCMA or AFP p26 or a variant thereof); and the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain. In the methods of killing a multiple myeloma cell in a patient comprising administering a cell expressing a CAR and an Adapter to a patient, the cell expressing a CAR can be any of the cells expressing CARs described herein (e.g., as described in Section VII and Section XI) and the Adapter can be any of the Adapters described herein (e.g., as described in Section V and Section XI). In some embodiments, the Adapter comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to CS1, BCMA, or CS1 and BCMA. In some embodiments, the CAR comprises an ADBD (e.g., D domain) that binds to AFP p26 or a variant thereof. In the methods of killing a multiple myeloma cell in a patient comprising administering a cell expressing a CAR and an Adapter to a patient, the cell expressing a CAR and the Adapter can be in a pharmaceutically acceptable composition. In some embodiments, the cell expressing a CAR and the Adapter are in a single pharmaceutically acceptable composition. In some embodiments, the cell expressing a CAR and the Adapter are in separate pharmaceutically acceptable compositions. In some embodiments, the patient has relapsed multiple myeloma. In some embodiments, the patient has multiple myeloma that relapsed following treatment with a biologic agent, for example, antibody or CAR-T cell. In some embodiments, he

patient has multiple myeloma that relapsed following treatment with antibody or CAR-T cell that targeted CS1 or BCMA.

[0544] In one embodiment, the methods described herein are useful for inhibiting tumor growth, reducing neovascularization, reducing angiogenesis, inducing differentiation, reducing tumor volume, and/or reducing the tumorigenicity of a tumor.

[0545] In one embodiment of the methods of killing a target cell in a patient or the methods of redirecting target cell killing in a patient, the patient has been diagnosed with a disease or disorder of the immune system and the target cell is a cell of the immune system. Thus in some embodiments, the methods provided herein treat a disease or disorder of the immune system.

[0546] In some embodiments, the disease or disorder of the immune system is an autoimmune disease or disorder. In some embodiments, the autoimmune disease or disorder is Type I diabetes, systemic sclerosis, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, or alopecia areata. In some embodiments, the autoimmune disease or disorder is Type I diabetes. In some embodiments, the autoimmune disease or disorder is systemic sclerosis. In some embodiments, the autoimmune disease or disorder is multiple sclerosis. In some embodiments, the autoimmune disease or disorder is rheumatoid arthritis. In some embodiments, the autoimmune disease or disorder is inflammatory bowel disease (IBD). In some embodiments, the autoimmune disease or disorder is Crohn's disease. In some embodiments, the autoimmune disease or disorder is ulcerative colitis.

[0547] In one embodiment of the methods of killing, a target cell in a patient or the methods of redirecting target cell killing in a patient, the target cell is a cell of the immune system. In some embodiments, the target cell is a B cell. In some embodiments, the target cell is a T cell. In some embodiments, the target cell is a naïve T cell. In some embodiments, the target cell is a memory T cell.

[0548] In one embodiment of the methods of killing, a target cell in a patient or the methods of redirecting target cell killing in a patient, the patient has been diagnosed with an autoimmune disease or disorder and the target cell is a cell of the immune system expressing a CD45 AD. In some embodiments, the target cell is a B cell. In some embodiments, the target cell is a T cell. In some embodiments, the target cell is a memory T cell. In some embodiments, the target cell expresses CD45. In some embodiments, the target cell expresses CD45RO.

[0549] In one embodiment of the methods of killing a target cell in a patient or the methods of redirecting target cell killing in a patient, the patient has an infection, and the target cell is a bacterial cell (*e.g.*, tuberculosis, smallpox, and anthrax), a cell of a parasite (*e.g.*, malaria or leishmaniasis) a fungal cell, a mold, a mycoplasma, or a cell infected with a virus (*e.g.*, HIV, hepatitis b, rabies, Nipah virus, west Nile virus, a meningitis virus, or CMV). Thus in some embodiments, the methods provided herein treat an infection.

[0550] In one embodiment, the methods described herein are useful for preparing or conditioning a patient for bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT). Thus in some embodiments, the methods of killing a target cell in a patient or the methods of redirecting target cell killing in a patient provided herein condition a subject for BMT or HSCT. In some embodiments, the methods provided herein condition a subject for HSCT. In some embodiments, the HSCT is autologous HSCT. In some embodiments, the methods for conditioning a patient disclosed herein does not comprise high dose chemotherapy or total body irradiation (TBI). In some embodiments, the methods for conditioning disclosed herein comprise reduced intensity chemotherapy. In some embodiments, the methods for conditioning disclosed herein comprise total body irradiation. In some embodiments, the patient is more than 65 years old. In some embodiments, the patient has cancer. In some embodiments, the patient has a hematologic cancer. In some embodiments, the patient has a relapsed hematologic cancer. In some embodiments, the hematologic cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), or multiple myeloma (MM). In some embodiments, the patient has an autoimmune disease or disorder. In some embodiments, the autoimmune disease or disorder is Type I diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease (IBD), Crohn's disease, or ulcerative.

[0551] In several embodiments, the administration of the Adapter and/or chimeric antigen receptor cells is intravenous, though other routes, such as intra-arterial, intramuscular, local, or other acceptable route can be used for a given treatment scenario.

[0552] Also provided are therapeutic compositions useful for practicing therapeutic methods described herein. In one embodiment, therapeutic compositions provided herein contain a physiologically tolerable carrier together with at least one species of Adapter as described herein, dissolved or dispersed therein as an active ingredient. In another embodiment, therapeutic compositions provided herein contain a physiologically tolerable carrier together with at least one species of a CAR cell as described herein, dissolved or dispersed therein as an active ingredient. In a preferred embodiment, therapeutic composition is not immunogenic when administered to a human patient for therapeutic purposes.

[0553] The preparation of a pharmacological composition that contains active ingredients dissolved or dispersed therein is well understood in the art. Typically such compositions are prepared as sterile injectables either as liquid solutions or suspensions, aqueous or non-aqueous. However, solid forms suitable for solution, or suspensions, in liquid prior to use can also be prepared. The preparation can also be emulsified. Thus, an Adapter-containing composition can take the form of solutions, suspensions, tablets, capsules, sustained release formulations or powders, or other compositional forms. In some embodiments, the Adapter compositions are formulated to ensure or optimize distribution in vivo. For example, the blood-brain barrier (BBB) excludes many highly hydrophilic compounds and if so desired, the compositions are prepared so as to increase transfer across the BBB, by for example, formulation in liposomes. For methods of manufacturing

liposomes, *see, e.g.*, U.S. Pat. Nos. 4,522,811, 5,374,548, and 5,399,331. The liposomes can comprise one or more moieties that are selectively transported into specific cells or organs, thus enhance targeted drug delivery (*see, e.g.*, Ranade, Clin. Pharmacol. 29: 685 (1989)).

[0554] The Adapter (and/or CAR cell) can be mixed other active ingredients and/or excipients that are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in therapeutic methods described herein. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents and other auxiliary substances known in the art, which enhance the effectiveness of the active ingredient.

[0555] Therapeutic Adapter formulations can include pharmaceutically acceptable salts of the components therein. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the polypeptide) that are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, tartaric, mandelic and other pharmaceutically acceptable salts known in the art. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine and other salts derived from inorganic bases known in the art.

[0556] Physiologically tolerable carriers are known in the art. Exemplary of liquid carriers are sterile aqueous solutions that contain no materials in addition to the active ingredients and water, or contain a buffer such as sodium phosphate at physiological pH value, physiological saline or both, such as phosphate-buffered saline. Still further, aqueous carriers can contain more than one buffer salt, as well as salts such as sodium and potassium chlorides, dextrose, propylene glycol, polyethylene glycol, and other solutes.

[0557] Liquid compositions can also contain liquid phases in addition to, and to the exclusion of water. Exemplary of such additional liquid phases are glycerin, vegetable oils such as cottonseed oil, organic esters such as ethyl oleate, and water-oil emulsions.

[0558] In one embodiment, a therapeutic composition contains an Adapter, typically in an amount of at least 0.1 weight percent of Adapter per weight of total therapeutic composition. A weight percent is a ratio by weight of Adapter per total composition. Thus, for example, 0.1 weight percent is 0.1 grams of Adapter per 100 grams of total composition.

[0559] Adapter-containing therapeutic compositions typically contains about 10 micrograms (μg) per milliliter (ml) to about 100 milligrams (mg) per ml of Adapter as active ingredient per volume of composition, and more preferably contains about 1 mg/ml to about 10 mg/ml (*i.e.*, about 0.1 to 1 weight percent).

[0560] The dosage ranges for the administration of the Adapter are those large enough to produce the desired effect in which the disease symptoms mediated by the target molecule are ameliorated. The dosage should not be so large as to cause adverse side effects, such as hyperviscosity syndromes, pulmonary edema, congestive heart failure, and other adverse side effects known in the art. Generally, the dosage will vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art. The dosage can be adjusted by the individual physician in the event of any complication.

[0561] The Adapter can be administered parenterally by injection or by gradual infusion over time. Although the target molecule can typically be accessed in the body by systemic administration and therefore most often treated by intravenous administration of therapeutic compositions, other tissues and delivery means are contemplated where there is a likelihood that the tissue targeted contains the target molecule. Thus, Adapter can be administered intravenously, intraperitoneally, intramuscularly, subcutaneously, intracavity, transdermally, and can be delivered by peristaltic means. Adapter can also be delivered by aerosol to airways and lungs.

[0562] Therapeutic compositions containing an Adapter can be conventionally administered intravenously, as by injection of a unit dose, for example. The term "unit dose" when used in reference to a therapeutic composition provided herein refers to physically discrete units suitable as unitary dosage for the subject, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required diluent; *e.g.*, carrier, or vehicle. In a specific embodiment, therapeutic compositions containing an Adapter are administered subcutaneously.

[0563] In some embodiments, the Adapter is administered in a manner compatible with the dosage formulation, and in a therapeutically effective amount. The quantity to be administered depends on the subject to be treated, capacity of the subject's system to utilize the active ingredient, and degree of therapeutic effect desired. Precise amounts of active ingredient required to be administered depend on the judgment of the practitioner and are peculiar to each individual. However, suitable dosage ranges for systemic application are disclosed herein and depend on the route of administration. Suitable regimes for administration are also variable, but are typified by an initial administration followed by repeated doses at one or more hour intervals by a subsequent injection or other administration. Alternatively, continuous intravenous infusion sufficient to maintain concentrations in the blood in the ranges specified for *in vivo* therapies are contemplated.

[0564] The Adapter compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The dosage ranges for the administration of the Adapter are those large enough to produce the desired effect in which the disease symptoms mediated by the target molecule are

ameliorated. The dosage should not be so large as to cause adverse side effects, such as, hyperviscosity syndromes, pulmonary edema, congestive heart failure, and other adverse side effects known in the art. Generally, the dosage will vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art. The dosage can be adjusted by the individual physician in the event of any complication.

[0565] The dosage schedule and amounts effective for therapeutic and prophylactic uses, *i.e.*, the "dosing regimen," will depend upon a variety of factors, including the cause, stage and severity of the disease or disorder, the health, physical status, age of the mammal being treated, and the site and mode of the delivery of the Adapter. Therapeutic efficacy and toxicity of the complex and formation can be determined by standard pharmaceutical, pharmacological, and toxicological procedures in cell cultures or experimental animals. Data obtained from these procedures can likewise be used in formulating a range of dosages for human use. Moreover, therapeutic index (*i.e.*, the dose therapeutically effective in 50 percent of the population divided by the dose lethal to 50 percent of the population (ED50/LD50)) can readily be determined using known procedures. The dosage is preferably within a range of concentrations that includes the ED50 with little or no toxicity, and may vary within this range depending on the dosage form employed, sensitivity of the patient, and the route of administration.

[0566] The dosage regimen also takes into consideration pharmacokinetics parameters known in the art, such as, drug absorption rate, bioavailability, metabolism and clearance (*see, e.g.*, Hidalgo-Aragones, J. Steroid Biochem. Mol. Biol. 58: 611-617 (1996); Groning *et al.*, Pharmazie 51: 337-341 (1996); Fotherby, Contraception 54: 59-69 (1996); and Johnson *et al.*, J. Pharm. Sci. 84: 1144-1146 (1995)). It is well within the state of the art for the clinician to determine the dosage regimen for each subject being treated. Moreover, single or multiple administrations of Adapter compositions can be administered depending on the dosage and frequency as required and tolerated by the subject. The duration of prophylactic and therapeutic treatment will vary depending on the particular disease or condition being treated. Some diseases are amenable to acute treatment whereas others require long-term, chronic therapy. Adapter can be administered serially, or simultaneously with the additional therapeutic agent.

[0567] In some embodiments, the Adapter is administered at about 1 mg/kg to about 50 mg/kg, about 1 mg/kg to about 25 mg/kg, about 1 mg/kg to about 20 mg/kg, about 1 mg/kg to about 15 mg/kg, about 1 mg/kg to about 10 mg/kg, or about 1 mg/kg to about 5 mg/kg.

[0568] In another embodiment, an Adapter is administered in combination with more one or more additional therapeutics.

[0569] A therapeutically effective amount of an Adapter, such as an Adapter fusion protein, can be an amount such that when administered in a physiologically tolerable composition is sufficient to achieve a plasma concentration of from about 0.1 microgram (μg) per milliliter (ml) to about 100 $\mu\text{g/ml}$, preferably

from about 1 µg/ml to about 5 µg/ml, and usually about 5 µg/ml. Stated differently, the dosage can vary from about 0.1 mg/kg to about 300 mg/kg, preferably from about 0.2 mg/kg to about 200 mg/kg, most preferably from about 0.5 mg/kg to about 20 mg/kg, in one or more dose administrations daily, for one or several days.

[0570] In one embodiment the disease or disorder is a disease or disorder of the immune system, such as inflammation or an autoimmune disease.

[0571] The cells expressing a CAR provided herein can be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as chemotherapeutics, antibodies, cytokines or cell populations. Compositions provided herein are preferably formulated for intravenous administration that can be administered one or more times.

[0572] The CAR-modified T cells can also serve as a type of vaccine for ex vivo immunization and/or in vivo therapy in a mammal. Preferably, the mammal is a human.

[0573] Cancers that can be treated with the Adapter or CAR cells include tumors that are not vascularized, or not yet substantially vascularized, as well as vascularized tumors. The cancers can comprise non-solid tumors (such as hematological tumors, for example, leukemias and lymphomas) or can comprise solid tumors. Types of cancers to be treated with the Adapter include, but are not limited to, carcinoma, blastoma, and sarcoma, and certain leukemia or lymphoid malignancies, benign and malignant tumors, and malignancies *e.g.*, sarcomas, carcinomas, and melanomas. Adult tumors/cancers and pediatric tumors/cancers are also included.

[0574] Examples of solid tumors, such as sarcomas and carcinomas, include fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, and other sarcomas, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, lymphoid malignancy, pancreatic cancer, breast cancer, lung cancers, ovarian cancer, prostate cancer, hepatocellular carcinoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, pheochromocytomas sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, Wilms' tumor, cervical cancer, testicular tumor, seminoma, bladder carcinoma, melanoma, and CNS tumors (such as a glioma (such as brainstem glioma and mixed gliomas), glioblastoma (also known as glioblastoma multiforme) astrocytoma, CNS lymphoma, germinoma, medulloblastoma, Schwannoma, craniopharyngioma, ependymoma, pineaioma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, retinoblastoma and brain metastases). In some embodiments, the solid tumor is breast cancer. In some embodiments, the solid tumor is ovarian cancer.

[0575] In another embodiment, the Adapters and/or CAR cells described herein are useful for treating a patient having hematological cancers. Examples of hematological (or hematogenous) cancers include leukemias, including acute leukemias (such as acute lymphocytic leukemia, acute myelocytic leukemia, acute myelogenous leukemia and myeloblasts, promyelocytic, myelomonocytic, monocytic and erythroleukemia),

chronic leukemias (such as chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia), polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (indolent and high grade forms), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia and myelodysplasia. Further examples of hematological (or hematogenous) cancers include acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the hematological (or hematogenous) cancer is AML. In some embodiments, the hematological (or hematogenous) cancer is CLL. In some embodiments, the hematological (or hematogenous) cancer is MM.

[0576] In one embodiment, the antigenic determinant binding domain portion of the Adapter and/or CAR is designed to treat a particular cancer. Cancers that can be treated include tumors that are not vascularized, or not yet substantially vascularized, as well as vascularized tumors. The cancers can comprise non-solid tumors (such as hematological tumors, for example, leukemias and lymphomas) or can comprise solid tumors. Types of cancers to be treated with the CARs include, but are not limited to, carcinoma, blastoma, and sarcoma, and certain leukemia or lymphoid malignancies, benign and malignant tumors, and malignancies *e.g.*, sarcomas, carcinomas, and melanomas. Adult tumors/cancers and pediatric tumors/cancers are also included.

[0577] Examples of hematological (or hematogenous) cancers include leukemias, including acute leukemias (such as acute lymphocytic leukemia, acute myelocytic leukemia, acute myelogenous leukemia and myeloblasts, promyelocytic, myelomonocytic, monocytic and erythroleukemia), chronic leukemias (such as chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, and chronic lymphocytic leukemia), polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma (indolent and high grade forms), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia and myelodysplasia. Further examples of hematological (or hematogenous) cancers include acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM). In some embodiments, the hematological (or hematogenous) cancer is AML. In some embodiments, the hematological (or hematogenous) cancer is CLL. In some embodiments, the hematological (or hematogenous) cancer is MM.

[0578] Examples of solid tumors, such as sarcomas and carcinomas, include fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, and other sarcomas, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, lymphoid malignancy, pancreatic cancer, breast cancer, lung cancers, ovarian cancer, prostate cancer, hepatocellular carcinoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, medullary thyroid carcinoma, papillary thyroid carcinoma, pheochromocytomas sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, Wilms' tumor, cervical cancer, testicular tumor, seminoma, bladder carcinoma, melanoma,

and CNS tumors (such as a glioma (such as brainstem glioma and mixed gliomas), glioblastoma (also known as glioblastoma multiforme) astrocytoma, CNS lymphoma, germinoma, medulloblastoma, Schwannoma, craniopharyngioma, ependymoma, pineaioma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, retinoblastoma and brain metastases).

[0579] In one embodiment, cancers and disorders can be treated using the Adapters or CAR cells that target CD19, CD20, CD22, and ROR1. In one specific embodiment, the CAR, Adapter and/or CAR/Adapter combination targets CD22 and is used to treat B-cell lymphoma. In another embodiment the CAR, Adapter and/or CAR/Adapter combination targets CD19 and is used to treat cancers and disorders including but are not limited to pre-B ALL (pediatric indication), adult ALL, mantle cell lymphoma, diffuse large B- cell lymphoma, and salvage post allogenic bone marrow transplantation. In another embodiment the CAR, Adapter and/or CAR/Adapter combination targets CS1 and is used to treat multiple myeloma. In another embodiment the CAR, Adapter and/or CAR/Adapter combination targets BCMA and is used to treat multiple myeloma. In another embodiment the CAR, Adapter and/or CAR/Adapter combination targets CS1 and BCMA, and is used to treat multiple myeloma.

[0580] "B-cell associated diseases" as used herein include B-cell immunodeficiencies, autoimmune diseases and/or excessive/uncontrolled cell proliferation associated with B-cells (including lymphomas and/or leukemias). Examples of such diseases, wherein the CARs, Adapters and/or CAR/Adapter combinations provided herein may be used for therapeutic approaches include but are not limited to: systemic lupus erythematosus (SLE), diabetes, rheumatoid arthritis (RA), reactive arthritis, multiple sclerosis (MS), pemphigus vulgaris, celiac disease, Crohn's disease, inflammatory bowel disease, ulcerative colitis, autoimmune thyroid disease, X-linked agammaglobulinemia, pre-B acute lymphoblastic leukemia, systemic lupus erythematosus, common variable immunodeficiency, chronic lymphocytic leukemia, diseases associated with selective IgA deficiency and/or IgG subclass deficiency, B lineage lymphomas (Hodgkin's lymphoma and/or non-Hodgkin's lymphoma), immunodeficiency with thymoma, transient hypogammaglobulinemia and/or hyper IgM syndrome, as well as virally-mediated B-cell diseases such as EBV mediated lymphoproliferative disease, and chronic infections in which B-cells participate in the pathophysiology.

[0581] In one embodiment, the CAR, Adapter and/or CAR/Adapter combination is designed to target mesothelin to treat mesothelioma, pancreatic cancer, ovarian cancer, and other mesothelin-expressing cancers known in the art. In one embodiment, the CAR, Adapter and/or CAR/Adapter combination is designed to target CD33/IL3Ra to treat acute myelogenous leukemia and other CD33/IL3Ra-expressing cancers known in the art. In one embodiment, the CAR, Adapter and/or CAR/Adapter combination is designed to target c-Met to treat triple negative breast cancer, non-small cell lung cancer, and other c-Met expressing cancers known in the art. In one embodiment, the CAR, Adapter and/or CAR/Adapter combination is designed to target PSMA

to treat prostate cancer and other PSMA-expressing cancers known in the art. In one embodiment, the CAR, Adapter and/or CAR/Adapter combination is designed to target Glycolipid F77 to treat prostate cancer and other Glycolipid F77-expressing cancers known in the art. In one embodiment, the CAR, Adapter and/or CAR/Adapter combination is designed to target EGFRvIII to treat glioblastoma and other EGFRvIII-expressing cancers known in the art. In one embodiment, the CAR, Adapter and/or CAR/Adapter combination is designed to target GD2 to treat neuroblastoma, melanoma, and other GD2 expressing cancers known in the art. In one embodiment, the CAR, Adapter and/or CAR/Adapter combination is designed to target NY-ESO-1 to treat myeloma, sarcoma, melanoma, and other NY-ESO-1-expressing cancers known in the art. In one embodiment, CAR, Adapter and/or CAR/Adapter combination is can be designed to target MAGEA3 to treat myeloma, sarcoma, melanoma, and other MAGEA3-expressing cancers known in the art. However, the invention should not be construed to be limited to solely to the antigen targets and diseases disclosed herein. Rather, the invention should be construed to include any antigenic target that is associated with a disease where a CAR, Adapter and/or CAR/Adapter combination can be used to treat the disease.

[0582] In a preferred embodiment, the CAR is expressed in a T cell and provides a method for treating or preventing cancer, comprising the administration of host cells expressing CAR to a cancer patient in which the cancer cell expresses a tumor antigen on its surface, and wherein the Adapter specifically binds the target antigen. Exemplary target antigenic determinants that the Adapter and CAR bind include, but are not limited to, BCMA, CS1, CD19, CD123, TSLPR, and CD267. In some embodiments, the CAR is expressed in a T cell and provides a method for treating multiple myeloma, comprising the administration of host cells expressing CAR to a multiple myeloma patient in which the tumor cell expresses BCMA and/or CS1 on its surface, and wherein the Adapter specifically binds BCMA, CS1, or BCMA and CS1.

[0583] Articles of manufacture, including kits containing the Adapter, CAR cell, and/or CAR cell/Adapter compositions, are provided herein. The article of manufacture may comprise a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials or syringes. The containers may be formed from a variety of materials such as glass or plastic. The container holds one or more Adapter, CAR cell, nucleic acids encoding Adapter, and/or vectors or host cells of the present disclosure. The label or package insert may include directions for administering the Adapter, CAR cell, and/or CAR cell/Adapter compositions to a patient. Such kits have uses including, but not limited to, therapeutic applications of the Adapter, CAR cell, and/or CAR/Adapter compositions.

XI. Further compositions and methods using thereof

[0584] In some embodiments, the disclosure provides:

- [1.] an engineered human immune effector cell comprising

- a) a chimeric antigen receptor (CAR) comprising (1) an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and
 - b) a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell,
- wherein the engineered cell is capable of directing an immune response to a CD45 AD expressing cell in an in vitro assay, and wherein the engineered cell does not express the CD45 AD;
- [2.] the engineered cell according to [1], wherein the immune response is killing the CD45 AD expressing cell;
 - [3.] the engineered cell according to [1] or [2], wherein the CD45 AD is present in the human CD45R0 isoform but not in the human CD45RA, CD45RAB, or CD45RABC isoforms;
 - [4.] the engineered cell according to [1] or [2], wherein the CD45 AD is present in the human CD45RA isoform but not in the human CD45R0 isoform;
 - [5.] the engineered cell according to [1] or [2], wherein the CD45 AD is present in the human CD45R0 and CD45RABC isoforms;
 - [6.] the engineered cell according to any one of [1] to [5], wherein the ADBD competes with the UCHL-1, A6, or ODP4 antibody for binding to the CD45 AD in an in vitro binding assay;
 - [7.] the engineered cell according to any one of [1] to [5], wherein the ADBD competes with the 4KB5, MB1, KiB3, 2H4, or MT2 antibody for binding to the CD45 AD in an in vitro binding assay;
 - [8.] the engineered cell according to any one of [1] to [7], wherein the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding the human CD45 AD;
 - [9.] the engineered cell according to [8], wherein the genetic modification is a deletion, insertion, or substitution that eliminates expression of human CD45;
 - [10.] the engineered cell according to any one of [1] to [9], wherein the genetic modification is a substitution of a gene or fragment thereof encoding the CD45 AD with a nucleotide sequence encoding a homologue, variant, or derivative of human CD45, wherein the encoded homologue, variant, or derivative does not comprise the human CD45 AD;
 - [11.] the engineered cell according to [10], wherein the homologue is a non-human primate CD45;
 - [12.] the engineered cell according to [10], wherein the variant is naturally occurring;
 - [13.] the engineered cell according to [10] or [12], wherein the variant or derivative is capable of signaling;
 - [14.] the engineered cell according to any one of [1] to [13], wherein the ADBD comprises a single-chain variable fragment (scFv);

- [15.] the engineered cell according to any one of [1] to [13], wherein the ADBD comprises an alternative scaffold binding domain (ASBD);
- [16.] the engineered cell according to any one of [1] to [13], wherein the ADBD comprises a D domain;
- [17.] the engineered cell according to any one of [1] to [16], wherein the CAR comprises 2 or more ADBDs;
- [18.] the engineered cell according to any one of [1] to [16], wherein the CAR comprises 2 ADBDs;
- [19.] the engineered cell of [18], wherein the CAR comprises an ASBD and a scFv;
- [20.] the engineered cell of [18], wherein the CAR comprises a D domain and a scFv;
- [21.] the engineered cell of [18], wherein the CAR comprises 2 ASBDs;
- [22.] the engineered cell of [18], wherein the CAR comprises 2 D domains;
- [23.] the engineered cell of any one according to any one of [1] to [16], wherein the CAR comprises 2 scFvs;
- [24.] the engineered cell according to any one of [1] to [16], wherein the CAR comprises 2 ASBDs;
- [25.] the engineered cell according to any one of [1] to [16], wherein the CAR comprises 3, 4, or 5 ASBDs;
- [26.] the engineered cell according to any one of [1] to [16], wherein the CAR comprises 2 D domains;
- [27.] the engineered cell according to any one of [1] to [16], wherein the CAR comprises 3, 4, or 5 D domains;
- [28.] the engineered cell according to any one of [17] to [27], wherein at least one ADBD specifically binds to an antigenic determinant of AFP, BCMA, CS1, CD123, CD19, CD20, CD22, or CD137;
- [29.] the engineered cell according to any one of [17] to [27], wherein at least one ADBD specifically binds to AFP p26 or a variant thereof (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123);
- [30.] the engineered cell according to any one of [17] to [27], wherein at least one ADBD comprises a sequence selected from SEQ ID NO: 841-984;
- [31.] the engineered cell according to any one of [1] to [30], wherein the CAR intracellular domain is a signaling domain;
- [32.] the engineered cell according to any one of [1] to [31], wherein the CAR intracellular domain comprises a primary signaling domain;
- [33.] the engineered cell according to any one of [1] to [32], wherein the CAR intracellular domain comprises a CD3 ζ primary signaling domain;
- [34.] the engineered cell according to any one of [1] to [33], wherein the CAR intracellular domain further comprises a costimulatory signaling domain;

- [35.] the engineered cell according to any one of [1] to [34], wherein the CAR intracellular domain comprises a costimulatory signaling domain selected from: CD28, 41BB, CD27, and CD134;
- [36.] the engineered cell according to any one of [1] to [34], wherein the CAR intracellular domain comprises a 41BB costimulatory signaling domain;
- [37.] the engineered cell according to any one of [1] to [36], wherein the immune effector cell is a T cell;
- [38.] the engineered cell according to any one of [1] to [36], wherein the immune effector cell is an NK cell;
- [39.] a method of killing a target cell comprising contacting the engineered cell according to any one of [1] to [38] with the target cell, wherein the target cell expresses human CD45;
- [40.] the method according to [39], wherein the target cell expresses human CD45R0 or human CD45RA isoform;
- [41.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to any one of [1] to [38] with the target cell, wherein the target cell expresses human CD45;
- [42.] the method according to [41], wherein the target cell expresses human CD45R0 or human CD45RA isoform;
- [43.] the method according to any one of [39] to [42], wherein the contacting is done in vitro;
- [44.] the method according to any one of [39] to [42], wherein the contacting is done in vivo;
- [45.] the method according to any one of [39] to [42], wherein the contacting is done ex vivo;
- [46.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [1] to [38];
- [47.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [1] to [38];
- [48.] a method of depleting lymphocytes comprising administering to a subject in need thereof an effective amount of the engineered cell according to any one of [1] to [38];
- [49.] a method of depleting memory T cell comprising administering to a subject in need thereof an effective amount of the engineered cell according to any one of [1] to [38];
- [50.] the method according to [49], wherein the CD45 AD is a CD45RO specific AD;
- [51.] a method of treating an autoimmune disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [1] to [38];

- [52.] the method according to [51], wherein the CD45 AD is a CD45RO specific AD;
- [53.] the method according to [51] or [52], wherein the autoimmune disease or disorder is Type I diabetes, systemic sclerosis, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, Inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, or alopecia areata;
- [54.] a method of conditioning a subject for transplantation comprising administering to the subject in need thereof an effective amount of the engineered cell according to any one of [1] to [38];
- [55.] the method according to [54], wherein the transplantation is bone marrow transplantation (BMT);
- [56.] the method according to [54], wherein the transplantation is hematopoietic stem cell transplantation (HSCT);
- [57.] the method according to any one of [54] to [56], wherein the transplantation is autologous transplantation;
- [58.] the method according to any one of [54] to [56], wherein the transplantation is allogeneic transplantation;
- [59.] the method according to any one of [54] to [58], wherein the subject has hematological cancer;
- [60.] the method according to any one of [54] to [59], wherein the subject has relapsed hematological cancer;
- [61.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [1] to [38];
- [62.] the method according to any one of [59] to [61], wherein the hematological cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
- [63.] the method according to any one of [59] to [61], wherein the hematological cancer is AML, CLL, or multiple myeloma;
- [64.] an engineered human immune effector cell comprising
 - a) a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and
 - b) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell,
 wherein the first AD is not the at least one human CD45 AD, wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a CD45 AD expressing cell in an in vitro assay, wherein the Adapter comprises the first AD and a second

- ADBD that specifically binds to the at least one human CD45 AD, and wherein the engineered cell does not express the at least one human CD45 AD;
- [65.] the engineered cell according to [64], wherein the immune response is killing the CD45 AD expressing cell;
 - [66.] the engineered cell according to [64] or [65], wherein the at least one CD45 AD is present in the human CD45R0 isoform but not in the human CD45RA, CD45RAB, or CD45RABC isoforms;
 - [67.] the engineered cell according to [64] or [65], wherein the at least one CD45 AD is present in the human CD45RA isoform but not in the human CD45R0 isoform;
 - [68.] the engineered cell according to [64] or [65], wherein the at least one CD45 AD is present in the human CD45R0 and CD45RABC isoforms;
 - [69.] the engineered cell according to any one of [64] to [68], wherein the second ADBD competes with the UCHL-1, A6, or ODP4 antibody for binding to the CD45 AD in an in vitro binding assay;
 - [70.] the engineered cell according to any one of [64] to [68], wherein the second ADBD competes with the 4KB5, MB1, KiB3, 2H4, or MT2 antibody for binding to the CD45 AD in an in vitro binding assay;
 - [71.] the engineered cell according to any one of [64] to [70], wherein the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding the human CD45 AD;
 - [72.] the engineered cell according to [71], wherein the genetic modification is a deletion, insertion, or substitution that eliminates expression of human CD45;
 - [73.] the engineered cell according to any one of [64] to [72], wherein the genetic modification is a substitution of a gene or fragment thereof encoding the CD45 AD with a nucleotide sequence encoding a homologue, variant, or derivative of human CD45, wherein the encoded homologue, variant, or derivative does not comprise the human CD45 AD;
 - [74.] the engineered cell according to [73], wherein the homologue is a non-human primate CD45;
 - [75.] the engineered cell according to [73], wherein the variant is naturally occurring;
 - [76.] the engineered cell according to [73] or [75], wherein the variant or derivative is capable of signaling;
 - [77.] the engineered cell according to any one of [64] to [76], wherein the ADBD comprises a single-chain variable fragment (scFv);
 - [78.] the engineered cell according to any one of [64] to [76], wherein the ADBD comprises an alternative scaffold binding domain (ASBD);
 - [79.] the engineered cell according to any one of [64] to [76], wherein the ADBD comprises a D domain;

- [80.] the engineered cell according to any one of [64] to [79], wherein the first ADBD specifically binds to an antigenic determinant of AFP, BCMA, CS1, CD123, CD19, CD20, CD22, or CD137;
- [81.] the engineered cell according to any one of [64] to [79], wherein the first ADBD specifically binds to AFP p26 or a variant thereof (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123),
- [82.] the engineered cell according to any one of [64] to [79], wherein the first ADBD comprises a sequence selected from SEQ ID NO: 841-984;
- [83.] the engineered cell according to any one of [64] to [82], wherein the CAR comprises 2 or more ADBDs;
- [84.] the engineered cell according to any one of [64] to [82], wherein the CAR comprises 2 ADBDs;
- [85.] the engineered cell of [84], wherein the CAR comprises an ASBD and a scFv;
- [86.] the engineered cell of [84], wherein the CAR comprises a D domain and a scFv
- [87.] the engineered cell of [84], wherein the CAR comprises 2 ASBDs;
- [88.] the engineered cell of [84], wherein the CAR comprises 2 D domains;
- [89.] the engineered cell of any one according to any one of [64] to [82], wherein the CAR comprises 2 scFvs;
- [90.] the engineered cell of any one according to any one of [64] to [82], wherein the CAR comprises 2 ASBDs;
- [91.] the engineered cell of any one according to any one of [64] to [82], wherein the CAR comprises 3, 4, or 5 ASBDs;
- [92.] the engineered cell of any one according to any one of [64] to [82], wherein the CAR comprises 2 D domains;
- [93.] the engineered cell of any one according to any one of [64] to [82], wherein the CAR comprises 3, 4, or 5 D domains;
- [94.] the engineered cell according to any one of [64] to [93], wherein the CAR intracellular domain is a signaling domain;
- [95.] the engineered cell according to any one of [64] to [94], wherein the CAR intracellular domain comprises a primary signaling domain;
- [96.] the engineered cell according to any one of [64] to [95], wherein the CAR intracellular domain comprises a CD3 ζ primary signaling domain;
- [97.] the engineered cell according to any one of [64] to [96], wherein the CAR intracellular domain further comprises a costimulatory signaling domain;
- [98.] the engineered cell according to any one of [64] to [97], wherein the CAR intracellular domain comprises a costimulatory signaling domain selected from: CD28, 41BB, CD27, and CD134;

- [99.] the engineered cell according to any one of [64] to [97], wherein the CAR intracellular domain comprises a 41BB costimulatory signaling domain;
- [100.] the engineered cell according to any one of [64] to [99], wherein the immune effector cell is a T cell;
- [101.] the engineered cell according to any one of [64] to [99], wherein the immune effector cell is an NK cell;
- [102.] a method of killing a target cell comprising contacting the engineered cell according to any one of [64] to [101] with an Adapter and the target cell, wherein the target cell expresses CD45, and wherein the Adapter comprises the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [103.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to any one of [64] to [101] with an Adapter and the target cell, wherein the target cell expresses CD45, and wherein the Adapter comprises the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [104.] the method according to [102] or [103], wherein the target cell expresses human CD45R0 or human CD45RA isoform;
- [105.] a method of treating hematological cancer comprising contacting the engineered cell according to any one of [64] to [101] with an Adapter and a cancer cell, wherein the cancer cell expresses CD45, and wherein the Adapter comprises the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [106.] the method according to any one of [102] to [106], wherein the contacting is done in vitro;
- [107.] the method according to any one of [102] to [106], wherein the contacting is done in vivo;
- [108.] the method according to any one of [102] to [106], wherein the contacting is done ex vivo;
- [109.] a method of directing an immune response to a target cell in a subject comprising
 - a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [110.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [111.] a method of directing an immune response to a target cell in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first

- AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];
- [112.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising
- a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [113.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [114.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];
- [115.] a method of depleting lymphocytes comprising
- a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [116.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [117.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];
- [118.] a method of depleting memory T cell comprising
- a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101]; and

- b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [119.] a method of depleting memory T cell comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];
- [120.] a method of depleting memory T cell comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];
- [121.] the method according to any one of [118] to [120], wherein the human CD45 AD is a CD45RO specific AD;
- [122.] a method of treating an autoimmune disease or disorder comprising
 - a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [123.] a method of treating an autoimmune disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];
- [124.] a method of treating an autoimmune disease or disorder comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];
- [125.] the method according to any one of [122] to [124], wherein the human CD45 AD is a CD45RO specific AD;
- [126.] the method according to any one of [124] to [125], wherein the autoimmune disease or disorder is Type I diabetes, systemic sclerosis, multiple sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, Inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, or alopecia areata;
- [127.] a method of conditioning a subject for transplantation comprising
 - a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101]; and

- b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [128.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [129.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];
- [130.] the method according to any one of [127] to [129], wherein the transplantation is bone marrow transplantation (BMT);
- [131.] the method according to any one of [127] to [129], wherein the transplantation is hematopoietic stem cell transplantation (HSCT);
- [132.] the method according to any one of [127] to [131], wherein the transplantation is autologous transplantation;
- [133.] the method according to any one of [127] to [131], wherein the transplantation is allogeneic transplantation;
- [134.] the method according to any one of [127] to [133], wherein the subject has hematological cancer;
- [135.] the method according to any one of [127] to [133], wherein the subject has relapsed hematological cancer;
- [136.] a method of treating a hematological cancer comprising
 - a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [137.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [64] to [101], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- [138.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to any one of [64] to [101];

- [139.] the method according to any one of [127] to [139], wherein the hematological cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
- [140.] the method according to any one of [127] to [139], wherein the hematological cancer is AML, CLL, or multiple myeloma;
- [141.] the method according to any one of [64] to [140], wherein the CD45 AD is present in the human CD45R0 isoform but not in the human CD45RA, CD45RAB, or CD45RABC isoforms;
- [142.] the method according to any one of [64] to [140], wherein the CD45 AD is present in the human CD45RA isoform but not in the human CD45R0 isoform;
- [143.] the method according to any one of [64] to [140], wherein the CD45 AD is present in the human CD45R0 and CD45RABC isoforms;
- [144.] the method according to any one of [64] to [143], wherein the second ADBD competes with the UCHL-1, A6, or ODP4 antibody for binding to the CD45 AD in an in vitro binding assay;
- [145.] the method according to any one of [64] to [143], wherein the second ADBD competes with the 4KB5, MB1, KiB3, 2H4, or MT2 antibody for binding to the CD45 AD in an in vitro binding assay;
- [146.] an engineered human immune effector cell comprising:
- a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that bind to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - b) a genetic modification that eliminates the expression of the first AD on the engineered cell, wherein the engineered cell does not express the first AD;
- [147.] the engineered cell according to [146], wherein the first AD is a human CD45 AD;
- [148.] the engineered cell according to [146] or [147], wherein the CD45 AD is present in the human CD45R0 isoform but not in the human CD45RA, CD45RAB, or CD45RABC isoforms;
- [149.] the engineered cell according to [146] or [147], wherein the CD45 AD is present in the human CD45RA isoform but not in the human CD45R0 isoform;
- [150.] the engineered cell according to [146] or [147], wherein the CD45 AD is present in the human CD45R0 and CD45RABC isoforms;
- [151.] the engineered cell according to [146], wherein the first AD is a human CD26, CD30, CD33, or CD38 AD;
- [152.] the engineered cell according to any one of [146] to [151], wherein the two or more ADBDs bind to ADs expressed on the same target cell;

- [153.] the engineered cell according to any one of [146] to [151], wherein the two or more ADBDs bind to ADs expressed on different target cells;
- [154.] the engineered cell according to any one of [146] to [153], wherein the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding a polypeptide comprising the first AD;
- [155.] the engineered cell according to any one of [146] to [154], wherein the genetic modification is a substitution of a gene or fragment thereof encoding a polypeptide comprising the first AD with a nucleotide sequence encoding a homologue, variant, or derivative of the polypeptide comprising the first AD, wherein the encoded homologue, variant, or derivative does not comprise the first AD;
- [156.] the engineered cell according to [155], wherein the homologue is a non-human primate homologue;
- [157.] the engineered cell according to [155], wherein the variant is naturally occurring;
- [158.] the engineered cell according to [155] or [157], wherein the variant or derivative is capable of signaling;
- [159.] the engineered cell according to any one of [146] to [158], wherein the CAR comprises 2 ADBDs that bind to different targets;
- [160.] the engineered cell according to any one of [146] to [159], wherein the CAR comprises 2 ADBDs that (a) are the same, (b) bind to the same AD, (c) bind to different ADs of the same antigen, (d) bind to different ADs on the same cell, or (e) bind to different ADs on different cells;
- [161.] the engineered cell according to any one of [146] to [160], wherein the first ADBD specifically binds to an antigenic determinant of AFP, BCMA, CS1, CD123, CD19, CD20, CD22, or CD137;
- [162.] the engineered cell according to any one of [146] to [160], wherein the first ADBD specifically binds to AFP p26, or a variant thereof (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123);
- [163.] the engineered cell according to any one of [146] to [160], wherein the first ADBD comprises a sequence selected from SEQ ID NO: 841-984;
- [164.] the engineered cell according to any one of [146] to [163], wherein the CAR specifically binds to an antigen selected from: CD19, CD22, CD123, CS1, HER2, BCMA, TACI, BAFFR, and PDL1;
- [165.] the engineered cell according to any one of [146] to [163], wherein the CAR specifically binds to BCMA, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 44-338, and 339;

- [166.] the engineered cell according to any one of [146] to [163], wherein the CAR specifically binds to CD123, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 340-772 and 773;
- [167.] the engineered cell according to any one of [146] to [163], wherein the CAR specifically binds to CD19, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 1030-1058, and 1059;
- [168.] the engineered cell according to any one of [146] to [163], wherein the CAR specifically binds to CD22, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 1060-1068, and 1069;
- [169.] the engineered cell according to any one of [146] to [163], wherein the CAR specifically binds to CS1, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 780-794, and 796;
- [170.] the engineered cell according to any one of [146] to [163], wherein the CAR specifically binds to PDL1, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 1010-1016, 1074-1078, and 1079;
- [171.] the engineered cell according to any one of [146] to [170], wherein the CAR comprises 2 ASBDs;
- [172.] the engineered cell of [171], wherein the CAR comprises an ASBD and a scFv;
- [173.] the engineered cell of [171], wherein the CAR comprises a D domain and a scFv
- [174.] the engineered cell of [171], wherein the CAR comprises 2 ASBDs;
- [175.] the engineered cell of [171], wherein the CAR comprises 2 D domains;
- [176.] the engineered cell of any one according to any one of [146] to [170], wherein the CAR comprises 2 scFvs;
- [177.] the engineered cell of any one according to any one of [146] to [170], wherein the CAR comprises 2 ASBDs;
- [178.] the engineered cell of any one according to any one of [146] to [170], wherein the CAR comprises 3, 4, or 5 ASBDs;
- [179.] the engineered cell of any one according to any one of [146] to [170], wherein the CAR comprises 2 D domains;
- [180.] the engineered cell of any one according to any one of [146] to [170], wherein the CAR comprises 3, 4, or 5 D domains;
- [181.] the engineered cell according to any one of [146] to [180], wherein the CAR intracellular domain is a signaling domain;

- [182.] the engineered cell according to any one of [146] to [181], wherein the CAR intracellular domain comprises a primary signaling domain;
- [183.] the engineered cell according to any one of [146] to [182], wherein the CAR intracellular domain comprises a CD3 ζ primary signaling domain;
- [184.] the engineered cell according to any one of [146] to [183], wherein the CAR intracellular domain further comprises a costimulatory signaling domain;
- [185.] the engineered cell according to any one of [146] to [184], wherein the CAR intracellular domain comprises a costimulatory signaling domain selected from: CD28, 41BB, CD27, and CD134;
- [186.] the engineered cell according to any one of [146] to [184], wherein the CAR intracellular domain comprises a 41BB costimulatory signaling domain;
- [187.] the engineered cell according to any one of [146] to [186], wherein the immune effector cell is a T cell;
- [188.] the engineered cell according to any one of [146] to [186], wherein the immune effector cell is an NK cell;
- [189.] a method of killing a target cell comprising contacting the engineered cell according to any one of [146] to [188] with the target cell;
- [190.] the method according to [189], wherein the target cell expresses human CD45;
- [191.] the method according to [189], wherein the target cell expresses human CD45R0 or human CD45RA isoform;
- [192.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to any one of [146] to [188] with the target cell;
- [193.] the method according to [192], wherein the target cell expresses human CD45;
- [194.] the method according to [192], wherein the target cell expresses human CD45R0 or human CD45RA isoform;
- [195.] the method according to any one of [189] to [194], wherein the contacting is done in vitro;
- [196.] the method according to any one of [189] to [194], wherein the contacting is done in vivo;
- [197.] the method according to any one of [189] to [194], wherein the contacting is done ex vivo;
- [198.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188];
- [199.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188];

- [200.] a method of depleting lymphocytes comprising administering to a subject in need thereof an effective amount of the engineered cell according to any one of [146] to [188];
- [201.] a method of conditioning a subject for transplantation comprising administering to the subject in need thereof an effective amount of the engineered cell according to any one of [146] to [188];
- [202.] the method according to [201], wherein the transplantation is bone marrow transplantation (BMT);
- [203.] the method according to [201], wherein the transplantation is hematopoietic stem cell transplantation (HSCT);
- [204.] the method according to any one of [201] to [203], wherein the transplantation is autologous transplantation;
- [205.] the method according to any one of [201] to [203], wherein the transplantation is allogeneic transplantation;
- [206.] the method according to any one of [201] to [205], wherein the subject has hematological cancer;
- [207.] the method according to any one of [201] to [205], wherein the subject has relapsed hematological cancer;
- [208.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188];
- [209.] the method according to any one of [206] to [208], wherein the hematological cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
- [210.] the method according to any one of [206] to [208], wherein the hematological cancer is AML, CLL, or multiple myeloma;
- [211.] a method of killing a target cell comprising contacting the engineered cell according to any one of [146] to [188] with an Adapter and the target cell, wherein the Adapter comprises an AD recognized by the CAR and a second ADBD;
- [212.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to any one of [146] to [188] with an Adapter and the target cell, and wherein the Adapter comprises an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell;
- [213.] a method of treating hematological cancer comprising contacting the engineered cell according to any one of [146] to [188] with an Adapter and a cancer cell, wherein the Adapter comprises an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the cancer cell;

- [214.] the method according to any one of [211] to [213], wherein the contacting is done in vitro;
- [215.] the method according to any one of [211] to [213], wherein the contacting is done in vivo;
- [216.] the method according to any one of [211] to [213], wherein the contacting is done ex vivo;
- [217.] a method of directing an immune response to a target cell in a subject comprising
- a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell;
- [218.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell;
- [219.] a method of directing an immune response to a target cell in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell, wherein the subject has been administered the engineered cell according to any one of [146] to [188];
- [220.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising
- a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [221.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [222.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD

that is capable of binding a second AD on a target cell, wherein the subject has been administered the engineered cell according to any one of [146] to [188];

- [223.] a method of depleting lymphocytes comprising
- a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [224.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [225.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell, wherein the subject has been administered the engineered cell according to any one of [146] to [188];
- [226.] a method of conditioning a subject for transplantation comprising
- a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [227.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [228.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell, wherein the subject has been administered the engineered cell according to any one of [146] to [188];
- [229.] the method according to any one of [226] to [228], wherein the transplantation is bone marrow transplantation (BMT);

- [230.] the method according to any one of [226] to [228], wherein the transplantation is hematopoietic stem cell transplantation (HSCT);
- [231.] the method according to any one of [226] to [230], wherein the transplantation is autologous transplantation;
- [232.] the method according to any one of [226] to [230], wherein the transplantation is allogeneic transplantation;
- [233.] the method according to any one of [226] to [232], wherein the subject has hematological cancer;
- [234.] the method according to any one of [226] to [232], wherein the subject has relapsed hematological cancer;
- [235.] a method of treating a hematological cancer comprising
 - a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [236.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [146] to [188], wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell;
- [237.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on a target cell, wherein the subject has been administered the engineered cell according to any one of [146] to [188];
- [238.] the method according to any one of [233] to [237], wherein the hematological cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
- [239.] the method according to any one of [233] to [237], wherein the hematological cancer is AML, CLL, or multiple myeloma;
- [240.] an engineered human immune effector cell comprising:
 - a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - b) a genetic modification that eliminates the expression of a second AD on the engineered cell,

- wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a cell expressing the second AD in an in vitro assay, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the engineered cell does not express the second AD;
- [241.] the engineered cell according to [240], wherein the immune response is killing the cell expressing the second AD;
- [242.] the engineered cell according to [240] or [241], wherein the second AD is a human CD45 AD;
- [243.] the engineered cell according to [242], wherein the CD45 AD is present in the human CD45R0 isoform but not in the human CD45RA, CD45RAB, or CD45RABC isoforms;
- [244.] the engineered cell according to [242], wherein the CD45 AD is present in the human CD45RA isoform but not in the human CD45R0 isoform;
- [245.] the engineered cell according to [242], wherein the CD45 AD is present in the human CD45R0 and CD45RABC isoforms;
- [246.] the engineered cell according to [240] or [241], wherein the second AD is a human CD26, CD30, CD33, or CD38 AD;
- [247.] the engineered cell according to any one of [240] to [246], wherein the first AD is not expressed on a target cell and the second AD is expressed on a target cell;
- [248.] the engineered cell according to any one of [240] to [246], wherein the first AD is expressed on a target cell;
- [249.] the engineered cell according to any one of [240] to [246], wherein the first AD and the second AD are expressed on the same target cell;
- [250.] the engineered cell according to any one of [240] to [246], wherein the first AD and the second AD are expressed on different target cells;
- [251.] the engineered cell according to any one of [240] to [250], wherein the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding a polypeptide comprising the second AD;
- [252.] the engineered cell according to any one of [240] to [250], wherein the genetic modification is a substitution of a gene or fragment thereof encoding a polypeptide comprising the second AD with a nucleotide sequence encoding a homologue, variant, or derivative of the polypeptide comprising the second AD, wherein the encoded homologue, variant, or derivative does not comprise the second AD;
- [253.] the engineered cell of [252], wherein the homologue is a non-human primate homologue;
- [254.] the engineered cell of [252], wherein the variant is naturally occurring;
- [255.] the engineered cell of [252] or [254], wherein the variant or derivative is capable of signaling;

- [256.] the engineered cell according to any one of [240] to [255], wherein the first ADBD comprises a single-chain variable fragment (scFv);
- [257.] the engineered cell according to any one of [240] to [255], wherein the first ADBD comprises an alternative scaffold binding domain (ASBD);
- [258.] the engineered cell according to any one of [240] to [255], wherein the first ADBD comprises a D domain;
- [259.] the engineered cell according to any one of [240] to [258], wherein the first ADBD specifically binds to an antigenic determinant of AFP, BCMA, CS1, CD123, CD19, CD20, CD22, or CD137;
- [260.] the engineered cell according to any one of [240] to [258], wherein the first ADBD specifically binds to AFP p26, or a variant thereof (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123);
- [261.] the engineered cell according to any one of [240] to [258], wherein the first ADBD comprises a sequence selected from SEQ ID NO: 841-984;
- [262.] the engineered cell according to any one of [240] to [261], wherein the CAR comprises 2 or more ADBDs;
- [263.] the engineered cell according to any one of [240] to [261], wherein the CAR comprises 2 ADBDs;
- [264.] the engineered cell of [263], wherein the CAR comprises an ASBD and a scFv;
- [265.] the engineered cell of [263], wherein the CAR comprises a D domain and a scFv;
- [266.] the engineered cell of [263], wherein the CAR comprises 2 ASBDs;
- [267.] the engineered cell of [263], wherein the CAR comprises 2 D domains;
- [268.] the engineered cell of any one according to any one of [240] to [261], wherein the CAR comprises 2 scFvs;
- [269.] the engineered cell of any one according to any one of [240] to [261], wherein the CAR comprises 2 ASBDs;
- [270.] the engineered cell of any one according to any one of [240] to [261], wherein the CAR comprises 3, 4, or 5 ASBDs;
- [271.] the engineered cell of any one according to any one of [240] to [261], wherein the CAR comprises 2 D domains;
- [272.] the engineered cell of any one according to any one of [240] to [261], wherein the CAR comprises 3, 4, or 5 D domains;
- [273.] an engineered human immune effector cell comprising:
 - a) a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that specifically binds to a

first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and

b) a genetic modification that eliminates the expression of a second AD on the engineered cell, wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a cell expressing the second AD in an in vitro assay, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the engineered cell does not express the second AD;

[274.] the engineered cell according to [273], wherein the immune response is killing the cell expressing the second AD;

[275.] the engineered cell according to [273] or [274], wherein the second AD is a human CD45 AD;

[276.] the engineered cell according to [275], wherein the CD45 AD is present in the human CD45R0 isoform but not in the human CD45RA, CD45RAB, or CD45RABC isoforms;

[277.] the engineered cell according to [275], wherein the CD45 AD is present in the human CD45RA isoform but not in the human CD45R0 isoform;

[278.] the engineered cell according to [275], wherein the CD45 AD is present in the human CD45R0 and CD45RABC isoforms;

[279.] the engineered cell according to [273] or [274], wherein the second AD is a human CD26, CD30, CD33, or CD38 AD;

[280.] the engineered cell according to any one of [273] to [279], wherein the first AD is expressed on a target cell;

[281.] the engineered cell according to any one of [273] to [279], wherein the first AD and the second AD are expressed on the same target cell;

[282.] the engineered cell according to any one of [273] to [279], wherein the first AD and the second AD are expressed on different target cells;

[283.] the engineered cell according to any one of [273] to [282], wherein the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding a polypeptide comprising the second AD;

[284.] the engineered cell according to any one of [273] to [282], wherein the genetic modification is a substitution of a gene or fragment thereof encoding a polypeptide comprising the second AD with a nucleotide sequence encoding a homologue, variant, or derivative of the polypeptide comprising the second AD, wherein the encoded homologue, variant, or derivative does not comprise the second AD;

[285.] the engineered cell of [284], wherein the homologue is a non-human primate homologue;

[286.] the engineered cell of [284], wherein the variant is naturally occurring;

- [287.] the engineered cell of [284] or [286], wherein the variant or derivative is capable of signaling;
- [288.] the engineered cell according to any one of [273] to [287], wherein the first ADBD comprises a single-chain variable fragment (scFv);
- [289.] the engineered cell according to any one of [273] to [287], wherein the first ADBD comprises an alternative scaffold binding domain (ASBD);
- [290.] the engineered cell according to any one of [273] to [287], wherein the first ADBD comprises a D domain;
- [291.] the engineered cell according to any one of [273] to [287], wherein the CAR comprises 2 ADBDs;
- [292.] the engineered cell of [291], wherein the CAR comprises an ASBD and a scFv;
- [293.] the engineered cell of [291], wherein the CAR comprises a D domain and a scFv
- [294.] the engineered cell of [291], wherein the CAR comprises 2 ASBDs;
- [295.] the engineered cell of [291], wherein the CAR comprises 2 D domains;
- [296.] the engineered cell of any one according to any one of [273] to [287], wherein the CAR comprises 2 scFvs;
- [297.] the engineered cell of any one according to any one of [273] to [287], wherein the CAR comprises 2 ASBDs;
- [298.] the engineered cell of any one according to any one of [273] to [287], wherein the CAR comprises 3, 4, or 5 ASBDs;
- [299.] the engineered cell of any one according to any one of [273] to [287], wherein the CAR comprises 2 D domains;
- [300.] the engineered cell of any one according to any one of [273] to [287], wherein the CAR comprises 3, 4, or 5 D domains;
- [301.] the engineered cell according to any one of [273] to [300], wherein the first ADBD specifically binds to an antigenic determinant of AFP, BCMA, CS1, CD123, CD19, CD20, CD22, or CD137;
- [302.] the engineered cell according to any one of [273] to [300], wherein the first ADBD specifically binds to AFP p26, or a variant thereof (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123),
- [303.] the engineered cell according to any one of [273] to [300], wherein the first ADBD comprises a sequence selected from SEQ ID NO: 841-984;
- [304.] the engineered cell according to any one of [273] to [303], wherein the CAR comprises 2 ADBDs that bind to different targets;

- [305.] the engineered cell according to any one of [273] to [303], wherein the CAR comprises 2 ADBDs that (a) are the same, (b) bind to the same AD, (c) bind to different ADs of the same antigen, (d) bind to different ADs on the same cell, or (e) bind to different ADs on different cells;
- [306.] the engineered cell according to any one of [273] to [305], wherein the CAR specifically binds to an antigen selected from: CD19, CD22, CD123, BCMA, CS1, TACI, BAFFR, and PDL1;
- [307.] the engineered cell according to any one of [273] to [305], wherein the CAR specifically binds to BCMA, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: SEQ ID NO: 44-338, and 339; or the engineered cell according to any one of [273] to [305], wherein the CAR specifically binds to CS1;
- [308.] the engineered cell according to any one of [273] to [305], wherein the CAR specifically binds to CD123, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 340-772 and 773;
- [309.] the engineered cell according to any one of [273] to [305], wherein the CAR specifically binds to CD19, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 1030-1058, and 1059;
- [310.] the engineered cell according to any one of [273] to [305], wherein the CAR specifically binds to CD22, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 1060-1068, and 1069;
- [311.] the engineered cell according to any one of [273] to [305], wherein the CAR specifically binds to CS1, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 780-794, and 795;
- [312.] the engineered cell according to any one of [273] to [305], wherein the CAR specifically binds to PDL1, and optionally wherein the CAR comprises a sequence selected from SEQ ID NO: 1010-1016, 1074-1078, and 1079;
- [313.] the engineered cell according to any one of [240] to [312], wherein the CAR intracellular domain is a signaling domain;
- [314.] the engineered cell according to any one of [240] to [313], wherein the CAR intracellular domain comprises a primary signaling domain;
- [315.] the engineered cell according to any one of [240] to [314], wherein the CAR intracellular domain comprises a CD3 ζ primary signaling domain;
- [316.] the engineered cell according to any one of [240] to [315], wherein the CAR intracellular domain further comprises a costimulatory signaling domain;
- [317.] the engineered cell according to any one of [240] to [316], wherein the CAR intracellular domain comprises a costimulatory signaling domain selected from: CD28, 41BB, CD27, and CD134;

- [318.] the engineered cell according to any one of [240] to [316], wherein the CAR intracellular domain comprises a 41BB costimulatory signaling domain;
- [319.] the engineered cell according to any one of [240] to [318], wherein the immune effector cell is a T cell;
- [320.] the engineered cell according to any one of [240] to [318], wherein the immune effector cell is an NK cell;
- [321.] a method of killing a target cell comprising contacting the engineered cell according to any one of [240] to [320] with the target cell;
- [322.] the method according to [321], wherein the target cell expresses human CD45;
- [323.] the method according to [321], wherein the target cell expresses human CD45R0 or human CD45RA isoform;
- [324.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to any one of [240] to [320] with the target cell;
- [325.] the method according to [324], wherein the target cell expresses human CD45;
- [326.] the method according to [324], wherein the target cell expresses human CD45R0 or human CD45RA isoform;
- [327.] the method according to any one of [321] to [326], wherein the contacting is done in vitro;
- [328.] the method according to any one of [321] to [326], wherein the contacting is done in vivo;
- [329.] the method according to any one of [321] to [326], wherein the contacting is done ex vivo;
- [330.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320];
- [331.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320];
- [332.] a method of depleting lymphocytes comprising administering to a subject in need thereof an effective amount of the engineered cell according to any one of [240] to [320];
- [333.] a method of conditioning a subject for transplantation comprising administering to the subject in need thereof an effective amount of the engineered cell according to any one of [240] to [320];
- [334.] the method according to [333], wherein the transplantation is bone marrow transplantation (BMT);
- [335.] the method according to [333], wherein the transplantation is hematopoietic stem cell transplantation (HSCT);

- [336.] the method according to any one of [333] to [335], wherein the transplantation is autologous transplantation;
- [337.] the method according to any one of [333] to [335], wherein the transplantation is allogeneic transplantation;
- [338.] the method according to any one of [333] to [337], wherein the subject has hematological cancer;
- [339.] the method according to any one of [333] to [337], wherein the subject has relapsed hematological cancer;
- [340.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320];
- [341.] the method according to any one of [338] to [340], wherein the hematological cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
- [342.] the method according to any one of [338] to [340], wherein the hematological cancer is AML, CLL, or multiple myeloma;
- [343.] a method of killing a target cell comprising contacting the engineered cell according to any one of [240] to [320] with an Adapter and the target cell, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the target cell;
- [344.] a method of delivering an immune response to a target cell comprising contacting the engineered cell according to any one of [240] to [320] with an Adapter and the target cell, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the target cell;
- [345.] a method of treating hematological cancer comprising contacting the engineered cell according to any one of [240] to [320] with an Adapter and a cancer cell, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the cancer cell;
- [346.] the method according to any one of [343] to [345], wherein the contacting is done in vitro;
- [347.] the method according to any one of [343] to [345], wherein the contacting is done in vivo;
- [348.] the method according to any one of [343] to [345], wherein the contacting is done ex vivo;
- [349.] a method of directing an immune response to a target cell in a subject comprising
 - a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320]; and

- b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the second AD is expressed on the target cell;
- [350.] a method of directing an immune response to a target cell in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the target cell;
- [351.] a method of directing an immune response to a target cell in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the subject has been administered the engineered cell according to any one of [240] to [320], and wherein the second AD is expressed on the target cell;
- [352.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising
- a) administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the second AD is expressed on a target cell associated with the proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection;
- [353.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on a target cell associated with the proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection;
- [354.] a method of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection in a subject comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the subject has been administered the engineered cell according to any one of [240] to [320], and wherein the second AD is expressed on a target cell associated with the proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection;

- [355.] a method of depleting lymphocytes comprising
- a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the second AD is expressed on a lymphocyte target cell;
- [356.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on a lymphocyte target cell;
- [357.] a method of depleting lymphocytes comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the subject has been administered the engineered cell according to any one of [240] to [320], and wherein the second AD is expressed on a lymphocyte target cell;
- [358.] a method of conditioning a subject for transplantation comprising
- a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the second AD is expressed on a target cell associated with the transplantation;
- [359.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on a target cell associated with the transplantation;
- [360.] a method of conditioning a subject for transplantation comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the subject has been administered the engineered cell according to any one of [240] to [320], and wherein the second AD is expressed on a target cell associated with the transplantation;
- [361.] the method according to any one of [358] to [360], wherein the transplantation is bone marrow transplantation (BMT);

- [362.] the method according to any one of [358] to [360], wherein the transplantation is hematopoietic stem cell transplantation (HSCT);
- [363.] the method according to any one of [358] to [362], wherein the transplantation is autologous transplantation;
- [364.] the method according to any one of [358] to [362], wherein the transplantation is allogeneic transplantation;
- [365.] the method according to any one of [358] to [364], wherein the subject has hematological cancer;
- [366.] the method according to any one of [358] to [364], wherein the subject has relapsed hematological cancer;
- [367.] a method of treating a hematological cancer comprising
 - a) administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320]; and
 - b) administering to the subject a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the second AD is expressed on a target cell associated with the hematological cancer;
- [368.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of the engineered cell according to any one of [240] to [320], wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on a target cell associated with the hematological cancer;
- [369.] a method of treating a hematological cancer comprising administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the subject has been administered the engineered cell according to any one of [240] to [320], and wherein the second AD is expressed on a target cell associated with the hematological cancer;
- [370.] the method according to any one of [358] to [369], wherein the hematological cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
- [371.] the method according to any one of [358] to [369], wherein the hematological cancer is AML, CLL, or multiple myeloma;
- [372.] an isolated Adapter polypeptide comprising (a) an antigenic determinant (AD) and (b) one or more antigenic determinant binding domain (ADBD), wherein at least one ADBD specifically binds to a human CD45 AD, and wherein contacting the Adaptor with a CD45 AD expressing

target cell in the presence of an engineered cell according to [64] is capable of directing an immune response by the engineered cell to the target cell in an in vitro assay;

[373.] the Adapter polypeptide according to [372], wherein the immune response is killing the CD45 AD expressing cell;

[374.] the Adapter polypeptide according to [372] or [373], wherein the CD45 AD is present in the human CD45R0 isoform but not in the human CD45RA, CD45RAB, or CD45RABC isoforms;

[375.] the Adapter polypeptide according to [372] or [373], wherein the CD45 AD is present in the human CD45RA isoform but not in the human CD45R0 isoform;

[376.] the Adapter polypeptide according to [372] or [373], wherein the CD45 AD is present in the human CD45R0 and CD45RABC isoforms;

[377.] the Adapter polypeptide according to [372] or [373], which competes with the UCHL-1, A6, or ODP4 antibody for binding to the CD45 AD in an in vitro binding assay; or

[378.] the Adapter polypeptide according to [372] or [373], which competes with the 4KB5, MB1, KiB3, 2H4, or MT2 antibody for binding to the CD45 AD in an in vitro binding assay.

[0585] The term "CD45" as used herein refers to protein tyrosine phosphatase, receptor type C (PTPRC), also known as Leukocyte Common Antigen (LCA), LY5, B220, L-CA, T200, CD45R, GP180. The term "CD45" includes variants, isoforms, homologues, orthologs and paralogs. CD45 is a glycosylated type I transmembrane protein, various isoforms of which are expressed on the surface of all hematopoietic cells, except erythrocytes and plasma cells. CD45 is also expressed in lymphomas, B-cell chronic lymphocytic leukemia, hairy cell leukemia, and acute nonlymphocytic leukemia. CD45 is expressed in multiple isoforms as a result of alternative splicing of variable CD45 exons. The CD45 gene comprises 34 exons, of which exon 4 encoding peptide A, exon 5 encoding peptide B, and exon 6 encoding peptide C are alternatively spliced to generate different isoforms. The CD45R isoform, comprising peptides A, B, and C, is the longest. The CD45RO isoform, which lacks peptides A, B, and C, is the shortest. Isoforms CD45RA, CD45RB, CD45RC, CD45RAB, CD45RAC, and CD45RBC comprise the corresponding combinations of peptides A, B, and C. In some embodiments, the amino acid sequence of human CD45RABC, comprising a 25 amino acid residue N-terminal signal sequence (MTMYLWLKLLAFGFAFLDTEVFVTG, SEQ ID NO: 1101), has Genbank Accession No. NP_002829.3 (SEQ ID NO: 1102). Peptides A, B, and C correspond to residues 34-99, 100-146, and 147-194 of SEQ ID NO: 1102, respectively. In some embodiments, the amino acid sequence of human CD45RO, comprising the 25 amino acid residue N-terminal signal sequence of SEQ ID NO: 1101, has Genbank Accession No. NP_563578.2 (SEQ ID NO: 1103).

[0586] Only the CD45RA, CD45RO, CD45RB, CD45RAB, CD45RBC and CD45RABC isoforms are traditionally identified in humans. CD45RA is expressed on naïve T cells. The CD45RO isoform is expressed on activated and memory T cells, some B cell subsets, activated monocytes/macrophages, and granulocytes.

CD45RB is a 220 kD glycoprotein expressed on peripheral B cells, naïve T cells, thymocytes, weakly on macrophages, and dendritic cells. As T cells become activated and progress from naïve to memory cells, CD45RB expression is downregulated. Additionally, functionally distinct CD4⁺ T cell subsets, which secrete differing cytokine profiles, can be separated by CD45RB intensity.

[0587] The extracellular domain of the different CD45 isoforms comprise overlapping sets of antigenic determinants. CD45 reactive monoclonal antibodies have been categorized based on their specificity towards the different isoforms. An anti-CD45 antibody, as used herein refers to an antibody that specifically binds to CD45RO, CD45RB, CD45RAB, CD45RBC and CD45RABC isoforms. An anti-CD45RA antibody, as used herein refers to an antibody that specifically binds to CD45RA, CD45RAB, or CD45RABC isoforms, but does not bind to CD45RB or CD45RO. Anti-CD45RA antibodies include, but are not limited to, 4KB5, MB1, KiB3, MT2. An anti-CD45RB antibody, as used herein refers to an antibody that specifically binds to CD45RB, CD45RAB, CD45RBC, or CD45RABC, but does not bind to CD45RA, and CD45RO. An anti-CD45RO antibody, as used herein refers to an antibody that specifically binds to CD45RO, but does not bind to the other isoforms. CD45RO specific antibodies include, but are not limited to, UCHL1, A6, OPD4. In some embodiments, a CD45 specific antigenic determinant binding domain (ADBD) disclosed herein specifically binds to CD45RO, but does not bind to the other CD45 isoforms. In some embodiments, a CD45 specific ADBD disclosed herein specifically binds to CD45RA, CD45RAB, and CD45RABC, but does not bind to the other CD45 isoforms. In some embodiments, a CD45 specific ADBD disclosed herein specifically binds to all CD45 isoforms. Cell type specific glycosylation of CD45 contributes to the formation of human CD45 antigenic determinants. For example, differential expression of the antigenic determinant bound by the CD45RB^{MEM55} antibody is regulated by cell type specific O-linked glycosylation during B cell development. Koethe et al., Journal of Leukocyte Biology, 90(1): 5-19. Expression of the antigenic determinant bound by the UCHL1 and A6 antibodies are also dependent on the glycosylation of the CD45RO isoform. In some embodiments, a CD45 specific ADBD disclosed herein specifically binds to a glycosylation dependent antigenic determinant of human CD45. In some embodiments, a CD45 specific ADBD disclosed herein specifically binds to a glycosylation dependent antigenic determinant of human CD45RB. In some embodiments, a CD45 specific ADBD disclosed herein specifically binds to a glycosylation dependent antigenic determinant of human CD45RO.

[0588] The term "non-human primate CD45" as used herein refers to a primate ortholog of human CD45. In some embodiments, the non-human primate CD45 is a rhesus CD45. In some embodiments, the amino acid sequence of rhesus (*Macaca mulatta*) CD45RABC, comprising an N-terminal signal sequence, has Genbank Accession No. XP_014976209 (SEQ ID NO: 1104). In some embodiments, the non-human primate CD45 is a cynomolgus CD45. In some embodiments, the amino acid sequence of cynomolgus (*Macaca fascicularis*) CD45RABC, comprising an N-terminal signal sequence, has Genbank Accession No. XP_005540386 (SEQ

ID NO: 1105). Due to differences in their primary amino acid sequence, human CD45 and non-human primate CD45s comprise different sets of antigenic determinants. In some embodiments, a human CD45 specific ADBD disclosed herein specifically binds to an antigenic determinant that is also present in a non-human primate CD45. In some embodiments, a human CD45 specific ADBD disclosed herein specifically binds to an antigenic determinant that is not present in a non-human primate CD45. In some embodiments, a human CD45 specific ADBD disclosed herein specifically binds to an antigenic determinant that is not present in a rhesus CD45. In some embodiments, a human CD45 specific ADBD disclosed herein specifically binds to an antigenic determinant that is not present in a cynomolgus CD45.

[0589] In some embodiments, the AD (*e.g.*, in an Adapter and/or on a target cell) is an epitope of human CD45. In some embodiments, the AD is an epitope of the extracellular domain (ECD) of human CD45. In some embodiments, the AD is an epitope of the ECD of human CD45RA. In some embodiments, the AD is an epitope of the ECD of human CD45RB. In some embodiments, the AD is an epitope of the ECD of human CD45RAB. In some embodiments, the AD is an epitope of the ECD of human CD45RBC. In some embodiments, the AD is an epitope of the ECD of human CD45RAC. In some embodiments, the AD is an epitope of the ECD of human CD45RABC. In some embodiments, the AD is an epitope of the ECD of human CD45RO. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1106. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1107. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1108. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1109. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1110. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1111. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1112.

[0590] In some embodiments, the AD is a glycosylation dependent epitope of human CD45.

[0591] In some embodiments, the AD is an epitope of human CD45 that is not present in a non-human primate CD45. In some embodiments, the AD is an epitope of human CD45 that is not present in a rhesus CD45. In some embodiments, the AD is an epitope of human CD45 that is not present in a cynomolgus CD45.

[0592] In some embodiments, the AD is an epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the AD is an epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0593] In some embodiments, the AD is an epitope of CD26. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 29-766 of SEQ ID NO: 1113.

[0594] In some embodiments, the AD is an epitope of CD30. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 19-379 of SEQ ID NO: 1114.

[0595] In some embodiments, the AD is an epitope of CD33. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 18-259 of SEQ ID NO: 1115.

[0596] In some embodiments, the AD is an epitope of CD38. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 43-300 of SEQ ID NO: 1116.

[0597] In some embodiments of the compositions and methods disclosed herein, the ADBD has the ability to bind to an antigenic determinant expressed on the surface of an immune effector cells. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45R, CD45RA, CD45RB, or CD45RO. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45RA. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45RB. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45RO. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45, but does not have the ability to bind to a non-human primate homologue of CD45. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45, but does not have the ability to bind to rhesus or cynomolgus CD45. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45R, CD45RA, CD45RB, or CD45RO, but does not have the ability to bind to a non-human primate homologue of CD45. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45R, CD45RA, CD45RB, or CD45RO, but does not have the ability to bind to rhesus or cynomolgus CD45. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45RO, but does not have the ability to bind to a non-human primate homologue of CD45. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD45RO, but does not have the ability to bind to rhesus or cynomolgus CD45. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD26, CD30, CD33, or CD38. In

some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD26, CD30, CD33, or CD38, but does not have the ability to bind to a non-human primate homologue of CD26, CD30, CD33, or CD38, respectively. In some embodiments, the ADBD has the ability to bind to an antigenic determinant of human CD26, CD30, CD33, or CD38, but does not have the ability to bind to rhesus or cynomolgus CD26, CD30, CD33, or CD38, respectively.

[0598] In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45R, CD45RA, CD45RB, or CD45RO. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45RO. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45RA. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45RB. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45, but does not have the ability to bind to a non-human primate homologue of CD45. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45, but does not have the ability to bind to rhesus or cynomolgus CD45. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45R, CD45RA, CD45RB, or CD45RO, but does not have the ability to bind to a non-human primate homologue of CD45. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45R, CD45RA, CD45RB, or CD45RO, but does not have the ability to bind to rhesus or cynomolgus CD45. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45RO, but does not have the ability to bind to a non-human primate homologue of CD45. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD45RO, but does not have the ability to bind to rhesus or cynomolgus CD45. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD26, CD30, CD33, or CD38. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD26, CD30, CD33, or CD38, but does not have the ability to bind to a non-human primate homologue of CD26, CD30, CD33, or CD38, respectively. In some embodiments, the ADBD is a D domain-based polypeptide that has the ability to bind to an antigenic determinant of human CD26, CD30, CD33, or CD38, but does not have the ability to bind to rhesus or cynomolgus CD26, CD30, CD33, or CD38, respectively.

[0599] In some embodiments, the ADBD (*e.g.*, of an Adapter and/or CAR) specifically binds to an AD of human CD45. In some embodiments, the ADBD specifically binds to an AD of the extracellular domain

(ECD) of human CD45. In some embodiments, the ADBD specifically binds to an AD of the ECD of human CD45RA. In some embodiments, the ADBD specifically binds to an AD of the ECD of human CD45RB. In some embodiments, the ADBD specifically binds to an AD of the ECD of human CD45RAB. In some embodiments, the ADBD specifically binds to an AD of the ECD of human CD45RBC. In some embodiments, the ADBD specifically binds to an AD of the ECD of human CD45RAC. In some embodiments, the ADBD specifically binds to an AD of the ECD of human CD45RABC. In some embodiments, the ADBD specifically binds to an AD of the ECD of human CD45RO. In some embodiments, the ADBD specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1106. In some embodiments, the ADBD specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1107. In some embodiments, the ADBD specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1108. In some embodiments, the ADBD specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1109. In some embodiments, the ADBD specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1110. In some embodiments, the ADBD specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1111. In some embodiments, the ADBD specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1112.

[0600] In some embodiments, the ADBD specifically binds to a glycosylation dependent epitope of human CD45.

[0601] In some embodiments, the ADBD specifically binds to an epitope of human CD45 that is not present in a non-human primate CD45. In some embodiments, the ADBD specifically binds to an epitope of human CD45 that is not present in a rhesus CD45. In some embodiments, the ADBD specifically binds to of human CD45 that is not present in a cynomolgus CD45.

[0602] In some embodiments, the ADBD specifically binds to the same epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD specifically binds to the same epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0603] In some embodiments, the ADBD specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD specifically

binds to an epitope of human CD45 that overlaps with the epitope bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0604] In some embodiments, the ADBD competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is UCHL-1, A6, or ODP4. In some embodiments, the ADBD competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is 4KB5, MB1, KiB3, 2H4, or MT2.

[0605] In some embodiments, the ADBD specifically binds to an AD of CD26. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 29-766 of SEQ ID NO: 1113.

[0606] In some embodiments, the ADBD specifically binds to an AD of CD30. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 19-379 of SEQ ID NO: 1114.

[0607] In some embodiments, the ADBD specifically binds to an AD of CD33. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 18-259 of SEQ ID NO: 1115.

[0608] In some embodiments, the ADBD specifically binds to an AD of CD38. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 43-300 of SEQ ID NO: 1116.

[0609] In some embodiments, the ADBD specifically binds to an AD of human CD45. In some embodiments, the ADBD specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0610] In some embodiments, the ADBD comprises a fragment of an antibody that is sufficient to confer recognition and specific binding to an AD of human CD45. In some embodiments, the ADBD comprises a fragment of an antibody that is sufficient to confer recognition and specific binding to an AD of human CD26, CD30, CD33, or CD38.

[0611] In some embodiments, the ADBD is a scFv that (*e.g.*, of an Adapter and/or CAR) specifically binds to an AD of human CD45. In some embodiments, the ADBD is a scFv that specifically binds to an AD of the extracellular domain (ECD) of human CD45. In some embodiments, the ADBD is a scFv that specifically binds to an AD of the ECD of human CD45RA. In some embodiments, the ADBD is a scFv that specifically binds to an AD of the ECD of human CD45RB. In some embodiments, the ADBD is a scFv that specifically binds to an AD of the ECD of human CD45RAB. In some embodiments, the ADBD is a scFv that specifically binds to an AD of the ECD of human CD45RBC. In some embodiments, the ADBD is a scFv that specifically binds to an AD of the ECD of human CD45RAC. In some embodiments, the ADBD is a scFv that specifically binds to an AD of the ECD of human CD45RABC. In some embodiments, the ADBD is a scFv that specifically binds to an AD of the ECD of human CD45RO. In some embodiments, the ADBD is a scFv that

specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1106. In some embodiments, the ADBD is a scFv that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1107. In some embodiments, the ADBD is a scFv that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1108. In some embodiments, the ADBD is a scFv that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1109. In some embodiments, the ADBD is a scFv that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1110. In some embodiments, the ADBD is a scFv that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1111. In some embodiments, the ADBD is a scFv that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1112.

[0612] In some embodiments, the ADBD is a scFv that specifically binds to a glycosylation dependent epitope of human CD45.

[0613] In some embodiments, the ADBD is a scFv that specifically binds to an epitope of human CD45 that is not present in a non-human primate CD45. In some embodiments, the ADBD is a scFv that specifically binds to an epitope of human CD45 that is not present in a rhesus CD45. In some embodiments, the ADBD is a scFv that specifically binds to of human CD45 that is not present in a cynomolgus CD45.

[0614] In some embodiments, the ADBD is a scFv that specifically binds to the same epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD is a scFv that specifically binds to the same epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0615] In some embodiments, the ADBD is a scFv that specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD is a scFv that specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0616] In some embodiments, the ADBD is a scFv that competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is UCHL-1, A6, or ODP4. In some embodiments, the ADBD is a scFv that competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is 4KB5, MB1, KiB3, 2H4, or MT2.

[0617] In some embodiments, the ADBD is an scFv that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0618] In some embodiments, the ADBD is a SDAB that specifically binds to an AD of human CD45. In some embodiments, the ADBD is a SDAB that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0619] In some embodiments, the ADBD comprises a human antibody or a fragment thereof that specifically binds to an AD of human CD45. In some embodiments, the ADBD comprises a human antibody or a fragment thereof that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0620] In some embodiments, the ADBD comprises a humanized antibody or a fragment thereof that specifically binds to an AD of human CD45. In some embodiments, the ADBD comprises a humanized antibody or a fragment thereof that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0621] In some embodiments, the ADBD is an ASBD that specifically binds to an AD of human CD45. In some embodiments, the ADBD is an ASBD that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0622] In some embodiments, the ASBD specifically binds to an AD of human CD45. In some embodiments, the ASBD specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0623] In some embodiments, the ASBD specifically binds to an AD of human CD45. In some embodiments, the ASBD specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0624] In some embodiments, the ADBD is a D domain that (*e.g.*, of an Adapter and/or CAR) specifically binds to an AD of human CD45. In some embodiments, the ADBD is a D domain that specifically binds to an AD of the extracellular domain (ECD) of human CD45. In some embodiments, the ADBD is a D domain that specifically binds to an AD of the ECD of human CD45RA. In some embodiments, the ADBD is a D domain that specifically binds to an AD of the ECD of human CD45RB. In some embodiments, the ADBD is a D domain that specifically binds to an AD of the ECD of human CD45RAB. In some embodiments, the ADBD is a D domain that specifically binds to an AD of the ECD of human CD45RBC. In some embodiments, the ADBD is a D domain that specifically binds to an AD of the ECD of human CD45RAC. In some embodiments, the ADBD is a D domain that specifically binds to an AD of the ECD of human CD45RABC. In some embodiments, the ADBD is a D domain that specifically binds to an AD of the ECD of human CD45RO. In some embodiments, the ADBD is a D domain that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1106. In some embodiments, the ADBD is a D domain that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1107. In some embodiments, the ADBD is a D domain that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino

acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1108. In some embodiments, the ADBD is a D domain that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1109. In some embodiments, the ADBD is a D domain that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1110. In some embodiments, the ADBD is a D domain that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1111. In some embodiments, the ADBD is a D domain that specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1112.

[0625] In some embodiments, the ADBD is a D domain that specifically binds to a glycosylation dependent epitope of human CD45.

[0626] In some embodiments, the ADBD is a D domain that specifically binds to an epitope of human CD45 that is not present in a non-human primate CD45. In some embodiments, the ADBD is a D domain that specifically binds to an epitope of human CD45 that is not present in a rhesus CD45. In some embodiments, the ADBD is a D domain that specifically binds to of human CD45 that is not present in a cynomolgus CD45.

[0627] In some embodiments, the ADBD is a D domain that specifically binds to the same epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD is a D domain that specifically binds to the same epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0628] In some embodiments, the ADBD is a D domain that specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD is a D domain that specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0629] In some embodiments, the ADBD is a D domain that competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is UCHL-1, A6, or ODP4. In some embodiments, the ADBD is a D domain that competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is 4KB5, MB1, KiB3, 2H4, or MT2.

[0630] In some embodiments, the ASBD is a D-domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0631] In some embodiments, the ASBD is a Z-domain scaffold-based binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is a Z-domain scaffold-based binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0632] In some embodiments, the ASBD is a DARPIn-based AD binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is a DARPIn-based AD binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0633] In some embodiments, the ASBD is an adnectin-based AD binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is an adnectin-based AD binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0634] In some embodiments, the ASBD is a lipocalin-, affilin-, or anticalin-based AD binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is a lipocalin-, affilin-, or anticalin-based AD binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0635] In some embodiments, the ASBD is an Avimer scaffold-based AD binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is an Avimer scaffold-based AD binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0636] In some embodiments, the ASBD is a fynomer scaffold-based AD binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is a fynomer scaffold-based AD binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0637] In some embodiments, the ASBD is a knottin scaffold-based AD binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is a fynomer scaffold-based AD binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0638] In some embodiments, the ASBD is a Kunitz scaffold-based AD binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is a Kunitz scaffold-based AD binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0639] In some embodiments, the ASBD is a WW domain-based AD binding domain that specifically binds to an AD of human CD45. In some embodiments, the ASBD is a WW domain-based AD binding domain that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0640] Provided herein are multi-domain soluble Adapter proteins. The Adapter comprises an antigenic determinant (AD) (*e.g.*, as described in Section II) and an antigenic determinant binding domain (ADBD) (*e.g.*, as described in Section III). The Adapter can further comprise additional ADs, additional ADBDs, and/or other additional domains (*e.g.*, as described in Section V). In some embodiments, the Adapter comprises an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 AD. In some embodiments, the Adapter comprises an antigenic determinant binding domain (ADBD) that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0641] In some embodiments, the Adapter comprises an AD that is a human CD45 AD. In some embodiments, the Adapter comprises an AD that is an AD of human CD26, CD30, CD33, or CD38.

[0642] In some embodiments, The AD in the Adapter is an epitope of human CD45. In some embodiments, The AD in the Adapter is an epitope of the extracellular domain (ECD) of human CD45. In some embodiments, The AD in the Adapter is an epitope of the ECD of human CD45RA. In some embodiments, The AD in the Adapter is an epitope of the ECD of human CD45RB. In some embodiments, The AD in the Adapter is an epitope of the ECD of human CD45RAB. In some embodiments, The AD in the Adapter is an epitope of the ECD of human CD45RBC. In some embodiments, The AD in the Adapter is an epitope of the ECD of human CD45RAC. In some embodiments, The AD in the Adapter is an epitope of the ECD of human CD45RABC. In some embodiments, The AD in the Adapter is an epitope of the ECD of human CD45RO. In further embodiments, The AD in the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1106. In further embodiments, The AD in the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1107. In further embodiments, The AD in the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1108. In further embodiments, The AD in the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1109. In further embodiments, The AD in the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1110. In further embodiments, The AD in the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1111. In further embodiments, The AD in the Adapter comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1112.

[0643] In some embodiments, The AD in the Adapter is a glycosylation dependent epitope of human CD45.

[0644] In some embodiments, The AD in the Adapter is an epitope of human CD45 that is not present in a non-human primate CD45. In some embodiments, The AD in the Adapter is an epitope of human CD45 that is not present in a rhesus CD45. In some embodiments, The AD in the Adapter is an epitope of human CD45 that is not present in a cynomolgus CD45.

[0645] In some embodiments, The AD in the Adapter is an epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, The AD in the Adapter is an epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0646] In some embodiments, The AD in the Adapter is an epitope of human CD26, CD30, CD33, or CD38.

[0647] In some embodiments, the ADBD in the Adapter specifically binds to an AD of human CD45. In some embodiments, the ADBD in the Adapter specifically binds to an AD of the extracellular domain (ECD) of human CD45. In some embodiments, the ADBD in the Adapter specifically binds to an AD of the ECD of

human CD45RA. In some embodiments, the ADBD in the Adapter specifically binds to an AD of the ECD of human CD45RB. In some embodiments, the ADBD in the Adapter specifically binds to an AD of the ECD of human CD45RAB. In some embodiments, the ADBD in the Adapter specifically binds to an AD of the ECD of human CD45RBC. In some embodiments, the ADBD in the Adapter specifically binds to an AD of the ECD of human CD45RAC. In some embodiments, the ADBD in the Adapter specifically binds to an AD of the ECD of human CD45RABC. In some embodiments, the ADBD in the Adapter specifically binds to an AD of the ECD of human CD45RO. In some embodiments, the ADBD in the Adapter specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1106. In some embodiments, the ADBD in the Adapter specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1107. In some embodiments, the ADBD in the Adapter specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1108. In some embodiments, the ADBD in the Adapter specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1109. In some embodiments, the ADBD in the Adapter specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1110. In some embodiments, the ADBD in the Adapter specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1111. In some embodiments, the ADBD in the Adapter specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1112.

[0648] In some embodiments, the ADBD in the Adapter specifically binds to a glycosylation dependent epitope of human CD45.

[0649] In some embodiments, the ADBD in the Adapter specifically binds to an epitope of human CD45 that is not present in a non-human primate CD45. In some embodiments, the ADBD in the Adapter specifically binds to an epitope of human CD45 that is not present in a rhesus CD45. In some embodiments, the ADBD in the Adapter specifically binds to of human CD45 that is not present in a cynomolgus CD45.

[0650] In some embodiments, the ADBD in the Adapter specifically binds to the same epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD in the Adapter specifically binds to the same epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0651] In some embodiments, the ADBD in the Adapter specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD in the Adapter specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0652] In some embodiments, the ADBD in the Adapter competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is UCHL-1, A6, or ODP4. In some embodiments, the ADBD in the Adapter competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is 4KB5, MB1, KiB3, 2H4, or MT2.

[0653] In some embodiments, the ADBD in the Adapter specifically binds to an epitope of human CD26, CD30, CD33, or CD38.

[0654] In some embodiments, an ADBD in the Adapter can be an antibody, an antigen-binding fragment thereof, a ScFv, an alternative scaffold binding domain, a D domain, a T cell receptor, or an antigen-binding fragment thereof that specifically binds to a human CD45 AD. In some embodiments, an ADBD in the Adapter can be an antibody, an antigen-binding fragment thereof, a ScFv, an alternative scaffold binding domain, a D domain, a T cell receptor, or an antigen-binding fragment thereof that specifically binds to an AD of human CD26, CD30, CD33, or CD38.

[0655] In some embodiments, the Adapter is bispecific. In some embodiments, the Adapter comprises an ADBD that binds to a CD45 AD and an ADBD that binds to a second AD. In some embodiments, the Adapter comprises an ADBD that binds to a first CD45 AD and an ADBD that binds to a second CD45 AD.

[0656] As provided herein, chimeric antigen receptors (CARs) are multi-domain proteins that comprise an extracellular domain comprising an ADBD, a transmembrane domain, and an intracellular signaling domain (*e.g.*, as described in Section VI).

[0657] In some embodiments, the ADBD in the CAR specifically binds to an AD of human CD45. In some embodiments, the ADBD in the CAR specifically binds to an AD of the extracellular domain (ECD) of human CD45. In some embodiments, the ADBD in the CAR specifically binds to an AD of the ECD of human CD45RA. In some embodiments, the ADBD in the CAR specifically binds to an AD of the ECD of human CD45RB. In some embodiments, the ADBD in the CAR specifically binds to an AD of the ECD of human CD45RAB. In some embodiments, the ADBD in the CAR specifically binds to an AD of the ECD of human CD45RBC. In some embodiments, the ADBD in the CAR specifically binds to an AD of the ECD of human CD45RAC. In some embodiments, the ADBD in the CAR specifically binds to an AD of the ECD of human CD45RABC. In some embodiments, the ADBD in the CAR specifically binds to an AD of the ECD of human CD45RO. In some embodiments, the ADBD in the CAR specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1106. In some embodiments, the ADBD in the CAR specifically binds to

an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1107. In some embodiments, the ADBD in the CAR specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1108. In some embodiments, the ADBD in the CAR specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1109. In some embodiments, the ADBD in the CAR specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1110. In some embodiments, the ADBD in the CAR specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1111. In some embodiments, the ADBD in the CAR specifically binds to an AD of comprising 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1112.

[0658] In some embodiments, the ADBD in the CAR specifically binds to a glycosylation dependent epitope of human CD45.

[0659] In some embodiments, the ADBD in the CAR specifically binds to an epitope of human CD45 that is not present in a non-human primate CD45. In some embodiments, the ADBD in the CAR specifically binds to an epitope of human CD45 that is not present in a rhesus CD45. In some embodiments, the ADBD in the CAR specifically binds to of human CD45 that is not present in a cynomolgus CD45.

[0660] In some embodiments, the ADBD in the CAR specifically binds to the same epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD in the CAR specifically binds to the same epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0661] In some embodiments, the ADBD in the CAR specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the ADBD in the CAR specifically binds to an epitope of human CD45 that overlaps with the epitope bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0662] In some embodiments, the ADBD in the CAR competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is UCHL-1, A6, or ODP4. In some embodiments, the ADBD in the CAR competes with a reference antibody for binding to human CD45 in an in vitro binding assay, wherein the reference antibody is 4KB5, MB1, KiB3, 2H4, or MT2.

[0663] In some embodiments, the ADBD in the CAR specifically binds to an AD of CD26. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 29-766 of SEQ ID NO: 1113.

[0664] In some embodiments, the ADBD in the CAR specifically binds to an AD of CD30. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 19-379 of SEQ ID NO: 1114.

[0665] In some embodiments, the ADBD in the CAR specifically binds to an AD of CD33. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 18-259 of SEQ ID NO: 1115.

[0666] In some embodiments, the ADBD in the CAR specifically binds to an AD of CD38. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of residues 43-300 of SEQ ID NO: 1116.

[0667] In some embodiments, a CAR provided herein comprises an ABDB that specifically binds to an AD of human CD45. In some embodiments, a CAR provided herein comprises an ABDB that specifically binds to an AD of human CD26, CD30, CD33, or CD38. In some embodiments, a CAR provided herein comprises an ABDB that specifically binds to AFP p26, or a variant thereof (*e.g.*, a polypeptide comprising the amino acid sequence of SEQ ID NO: 16, 1117, 1118, 1119, 1120, 1121, 1122, or 1123).

[0668] To avoid or reduce the possibility that CAR cells disclosed herein target an immune response (*e.g.*, kill) to themselves, a CAR cell can be genetically modified to reduce or eliminate the expression of one or more AD targeted by the CAR cell directly by a CAR described herein or indirectly through an Adaptor described herein. For example, a CAR cell disclosed herein with an ADBD that specifically binds to an AD of human CD45 or a CAR cell disclosed herein suited to be used in combination with an Adapter comprising an ADBD that specifically binds to an AD of human CD45 can be engineered to reduce or eliminate the expression of the human CD45 AD recognized by the ADBD. In some embodiments, the CAR cell is a human immune effector cell.

[0669] In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of one AD bound by a CAR or Adapter disclosed herein. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of more than one AD bound by a CAR or Adapter disclosed herein. In some embodiments, the CAR cell comprises more than one genetic modification that reduces or eliminates the expression of more than one AD bound by a CAR or Adapter disclosed herein. In some embodiments, the more than one AD is comprised by a single antigen. In some embodiments, the AD is a human CD45 AD. In some embodiments, the CAR cell is a human immune effector cell.

[0670] In some embodiments, the genetic modification reduces expression of the AD by about 50%, about 60%, about 70%, about 80%, about 90%, about 95% compared to a reference cell without the genetic modification. In some embodiments, the genetic modification eliminates expression of the AD.

[0671] In some embodiments, the genetic modification reduces expression of the polypeptide comprising the AD by about 50%, about 60%, about 70%, about 80%, about 90%, about 95% compared to a reference cell without the genetic modification. In some embodiments, the genetic modification eliminates expression of the polypeptide comprising the AD. In some embodiments, the AD is a human CD45 AD.

[0672] In some embodiments, the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding the AD. In some embodiments, the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding the AD that eliminates expression of the AD. In some embodiments, the AD is a human CD45 AD.

[0673] In some embodiments, the genetic modification is a substitution of a gene or fragment thereof encoding a polypeptide comprising the AD with a nucleotide sequence encoding a homologue, variant, or derivative of the polypeptide comprising the AD, wherein the encoded homologue, variant, or derivative does not comprise the AD. In some embodiments, the homologue is a non-human primate homologue. In some embodiments, the homologue is derived from rhesus macaque. In some embodiments, the homologue is derived from cynomolgus monkey. In some embodiments, the variant is a naturally occurring variant. In some embodiments, the variant is a splice variant. In some embodiments, the variant has altered glycosylation pattern. In some embodiments, the variant or derivative is capable of signaling. In some embodiments, the AD is a human CD45 AD.

[0674] The genetic modification can reduce or eliminate the expression of any AD for which it is desirable for a CAR or an Adapter to bind, *e.g.*, any of the ADs described in Section IIa.

[0675] In some embodiments, the genetic modification reduces or eliminates the expression of a human CD45 AD. In some embodiments, the AD is an epitope of the extracellular domain (ECD) of human CD45. In some embodiments, the AD is an epitope of the ECD of human CD45RA. In some embodiments, the AD is an epitope of the ECD of human CD45RB. In some embodiments, the AD is an epitope of the ECD of human CD45RAB. In some embodiments, the AD is an epitope of the ECD of human CD45RBC. In some embodiments, the AD is an epitope of the ECD of human CD45RAC. In some embodiments, the AD is an epitope of the ECD of human CD45RABC. In some embodiments, the AD is an epitope of the ECD of human CD45RO. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1106. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1107. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1108. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1109. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or

5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1110. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1111. In further embodiments, the AD comprises 5-25, 5-50, 5-75, 5-100, 5-125, or 5-150 amino acid residues, more than 150 amino acid residues, or all of the amino acid residues of SEQ ID NO: 1112.

[0676] In some embodiments, the genetic modification reduces or eliminates the expression of a human CD45 AD that is a glycosylation dependent epitope of human CD45.

[0677] In some embodiments, the genetic modification reduces or eliminates the expression of a human CD45 AD. In some embodiments, the AD is an epitope of human CD45 that is not present in a non-human primate CD45. In some embodiments, the AD is an epitope of human CD45 that is not present in a rhesus CD45. In some embodiments, the AD is an epitope of human CD45 that is not present in a cynomolgus CD45.

[0678] In some embodiments, the genetic modification reduces or eliminates the expression of a human CD45 AD. In some embodiments, the AD is an epitope of human CD45 that is bound by the UCHL-1, A6, or ODP4 antibody. In some embodiments, the AD is an epitope of human CD45 that is bound by the 4KB5, MB1, KiB3, 2H4, or MT2 antibody.

[0679] In some embodiments, the genetic modification reduces or eliminates the expression of a human CD45 AD. In some embodiments, the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding human CD45. In some embodiments, the genetic modification is a deletion, insertion, or substitution in a gene or fragment thereof encoding human CD45 that eliminates expression of the CD45 AD.

[0680] In some embodiments, the genetic modification reduces or eliminates the expression of a human CD45 AD. In some embodiments, the genetic modification is a substitution of a gene or fragment thereof encoding human CD45 with a nucleotide sequence encoding a homologue, variant, or derivative of human CD45, wherein the encoded homologue, variant, or derivative does not comprise the human CD45 AD. In some embodiments, the homologue is a non-human primate homologue. In some embodiments, the homologue is rhesus macaque CD45. In some embodiments, the homologue is cynomolgus CD45. In some embodiments, the variant is a naturally occurring variant of human CD45. In some embodiments, the CD45 variant is a splice variant. In some embodiments, the CD45 variant has altered glycosylation pattern. In some embodiments, the variant or derivative is capable of signaling.

[0681] In some embodiments, the genetic modification reduces or eliminates the expression of a human CD26, CD30, CD33, or CD38, AD. In some embodiments, the genetic modification reduces or eliminates the expression of human CD26, CD30, CD33, or CD38. In some embodiments, the genetic modification eliminates the expression of human CD26, CD30, CD33, or CD38. In some embodiments, the genetic

modification is a substitution of a gene or fragment thereof encoding human CD26, CD30, CD33, or CD38 with a nucleotide sequence encoding a homologue, variant, or derivative of CD26, CD30, CD33, or CD38, wherein the homologue, variant, or derivative does not comprise the AD targeted by a CAR or Adapter described herein.

[0682] The production of CAR cells comprising a genetic modification, useful in practicing the provided methods, may be carried out using a variety of standard techniques for recombinant DNA methodologies, genetic manipulation, and genome editing known in the art. Genetically modified CAR cells described herein that lack expression of an AD can routinely be obtained using any suitable means known in the art, including for example, siRNA, shRNA, CRISPR, TALEN, and/or ZFN. Methods for genetic manipulation of CAR cells is described, for example, in U.S. Patent Appl. Pub. 20170204372, which is incorporated herein by reference in its entirety.

[0683] Described herein are methods of use comprising contacting a target cell with a CAR cell (*e.g.*, as described above in Section VII) and an Adapter (*e.g.*, as described above in Section V) or a composition (*e.g.*, as described above in Section VIII). In some embodiments, the target cell expresses CD45. In some embodiments the CAR or Adapter comprises an ADBD that specifically binds to a CD45 AD. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD described herein. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of a human CD45 AD.

[0684] For example, in one embodiment, a method of delivering an immune response to a target cell comprises contacting the target cell with any of the compositions described herein (*e.g.*, as described in Section VIII). In another embodiment, a method of killing a target cell comprises contacting the target cell with any of the compositions described herein (*e.g.*, as described in Section VIII). As used herein, "contacting" can refer to contacting a target cell in vitro (*e.g.*, in a cell culture) or contacting a target cell in vivo (*e.g.*, in a patient). In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD described herein. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of a human CD45 AD. In some embodiments, the target cell expresses CD45.

[0685] In the methods of killing a target cell provided herein, the target cell can be a cell of the immune system. In some embodiments, the target cell is a B cell. In some embodiments, the target cell is a T cell. In some embodiments, the target cell is a naïve T cell. In some embodiments, the target cell is a memory T cell. In some embodiments, the target cell is a memory T cell expressing CD45RO.

[0686] In some embodiments, the target cell expresses CD45. In some embodiments, the target cell expresses CD45RO. In some embodiments, the target cell expresses CD45RA. In some embodiments, the target cell expresses CD45RAB. In some embodiments, the target cell expresses CD45RAC. In some embodiments, the

target cell expresses CD45RBC. In some embodiments, the target cell expresses CD45RABC. In some embodiments, the CD45 is human CD45.

[0687] In some embodiments of the compositions and methods disclosed herein, the target is an antigenic determinant of human CD45. In some embodiments, the target is an antigenic determinant of human CD45R, CD45RA, CD45RB, or CD45RO. In some embodiments, the target is an antigenic determinant of human CD45 that is not present in a non-human primate homologue of CD45. In some embodiments, the target is an antigenic determinant of human CD45R, CD45RA, CD45RB, or CD45RO that is not present in a non-human primate homologue of CD45. In some embodiments, the target is an antigenic determinant of human CD45 that is not present in rhesus or cynomolgus CD45. In some embodiments, the target is an antigenic determinant of human CD26, CD30, CD33, or CD38. In some embodiments, the target is an antigenic determinant of human CD26, CD30, CD33, or CD38 that is not present in a non-human primate homologue of CD26, CD30, CD33, or CD38, respectively. In some embodiments, the target is an antigenic determinant of human CD26, CD30, CD33, or CD38 that is not present in rhesus or cynomolgus CD26, CD30, CD33, or CD38, respectively.

[0688] In some embodiments of the compositions and methods disclosed herein, the target cell can be a cell expressing CD45. In some embodiments, a target cell can be a cell expressing CD45R, CD45RA, CD45RB, or CD45RO. In some embodiments, a target cell can be a cell expressing CD26, CD30, CD33, or CD38.

[0689] Described herein are methods of delivering an immune response to a target cell in a patient and/or killing a target cell in a patient comprising administering an Adapter (as described herein (*e.g.*, as described in Section V above)) and/or a CAR cell described herein (*e.g.*, as described in Section VII) to the patient. Also described herein are methods of treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection comprising administering an Adapter described herein (*e.g.*, as described in Section V) and/or a CAR cell described herein (*e.g.*, as described in Section VII) to the patient. In particular embodiments, provided herein are methods of treating hematological cancer or autoimmune disease comprising administering an Adapter described herein (*e.g.*, as described in Section V) and/or a CAR cell described herein (*e.g.*, as described in Section VII) to the patient. In some embodiments, the target cell expresses CD45. In some embodiments the CAR or Adapter comprises an ADBD that specifically binds to a CD45 AD. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of an AD described herein. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of a CD45 AD.

[0690] In one embodiment of the methods of killing a target cell in a patient or the methods of redirecting target cell killing in a patient, the target cell is a cell of the immune system. In some embodiments, the target cell is a B cell. In some embodiments, the target cell is a T cell. In some embodiments, the target cell is a

naïve T cell. In some embodiments, the target cell is a memory T cell. In some embodiments, the target cell is a memory T cell expressing CD45RO.

[0691] In some embodiments, the target cell expresses CD45. In some embodiments, the target cell expresses CD45RO. In some embodiments, the target cell expresses CD45RA. In some embodiments, the target cell expresses CD45RAB. In some embodiments, the target cell expresses CD45RAC. In some embodiments, the target cell expresses CD45RBC. In some embodiments, the target cell expresses CD45RABC. In some embodiments, the CD45 is human CD45.

[0692] In one embodiment of the methods of killing a target cell in a patient or the methods of redirecting target cell killing in a patient, the patient has been diagnosed with an autoimmune disease or disorder and the target cell is a cell of the immune system expressing a CD45 AD. In some embodiments, the target cell is a B cell. In some embodiments, the target cell is a T cell. In some embodiments, the target cell is a memory T cell. In some embodiments, the target cell expresses CD45. In some embodiments, the target cell expresses CD45RO.

[0693] In one embodiment, the methods described herein are useful for preparing or conditioning a patient for bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT). Thus in some embodiments, the methods of killing a target cell in a patient or the methods of redirecting target cell killing in a patient provided herein condition a subject for BMT or HSCT. In some embodiments, the methods provided herein condition a subject for HSCT. In some embodiments, the HSCT is autologous HSCT. In some embodiments, the methods for conditioning a patient disclosed herein does not comprise high dose chemotherapy or total body irradiation (TBI). In some embodiments, the methods for conditioning disclosed herein comprise reduced intensity chemotherapy. In some embodiments, the methods for conditioning disclosed herein comprise total body irradiation. In some embodiments, the patient is more than 65 years old. In some embodiments, the patient has cancer. In some embodiments, the patient has a hematologic cancer. In some embodiments, the patient has a relapsed hematologic cancer. In some embodiments, the hematologic cancer is acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), or multiple myeloma (MM). In some embodiments, the patient has an autoimmune disease or disorder. In some embodiments, the autoimmune disease or disorder is Type I diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease (IBD), Crohn's disease, or ulcerative.

[0694] In one embodiment of the methods of conditioning a patient for HSCT the patient has been diagnosed with a hematologic cancer and the target cell is a cell expressing a CD45 AD. In some embodiments, the patient is administered an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising (1) an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and (ii) a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell. In some

embodiments, the patient is administered an engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising an antigenic determinant binding domain (ADBD) that specifically binds to a human CD45 antigenic determinant (AD; and (ii) a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell. In some embodiments, the patient is administered an (a) engineered human immune effector cell comprising (i) a chimeric antigen receptor (CAR) comprising a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), and (ii) a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell and (b) an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD.

[0695] Articles of manufacture, including kits containing the Adapter, CAR cell, and/or CAR cell/Adapter compositions, are provided herein. The article of manufacture may comprise a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials or syringes. The containers may be formed from a variety of materials such as glass or plastic. The container holds one or more Adapter, CAR cell, nucleic acids encoding Adapter, and/or vectors or host cells of the present disclosure. The label or package insert may include directions for administering the Adapter, CAR cell, and/or CAR cell/Adapter compositions to a patient. Such kits have uses including, but not limited to, therapeutic applications of the Adapter, CAR cell, and/or CAR/Adapter compositions. In some embodiments, the CAR comprises an ADBD that specifically binds to a CD45 AD. In some embodiments, the Adapter comprises an ADBD that specifically binds to a CD45 AD. In some embodiments, the CAR cell comprises a genetic modification that reduces or eliminates the expression of a CD45 AD.

[0696] Various embodiments of the invention will now be illustrated through the description of experiments in accordance therewith. The examples that follow are provided to facilitate the practice of the disclosed embodiments, and are not to be construed as limiting in any way the remainder of the disclosure. In the examples, reference is made to the appended figures.

Examples

Example 1. Exemplary D domains and ADs

Table 3. Exemplary D-domains

SEQ ID NO:	D-Domain Sequence	Target	ELISA_avg
44	MGSWYEF ^{SWRLQ} AIHQRLNALGGSEAE ^{LAAFEKEIAAFESE} LQAYKGKGNP EVEELRAYAAGIRGALQAYRHN	BCMA	9.4868
45	MGSWHEFTWRLIAIQQRLEALGGSEAE ^{LAAFEKEIAAFESE} LQAYKGKGNP EVEELRAYAAGIRHHLQAYRHN	BCMA	17.125
46	MGSWREFAWRLVAINSRKALGGSEAE ^{LAAFEKEIAAFESE} LQAYKGKGNP EVEELRH ^{YAA} SIRDGLQAYRHN	BCMA	9.66

47	MGSWHEFAWRLQAINQRLNALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRHYYAHHIRNGLQAYRHN	BCMA	13.14
48	MGSWNEFAWRLTAIEQRLMALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRHYYAAGIRDNLQAYRHN	BCMA	18.28
49	MGSWTEFAWRLQAIHQRLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRVYAAKIRISLQAYRHN	BCMA	18.71
50	MGSWIEFAWRLQAIHQRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLREYAAANIRDSLQAYRHN	BCMA	18.97
51	MGSWHEFTWRLVAIQQLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRKFAAKIRYELQAYRHN	BCMA	19.51
52	MGSWHEFTWRLTAIRERLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELREYAAASIRNMLQAYRHN	BCMA	12.99
53	MGSWIEFSWRLEAIRQRLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRSYAAAIRQELQAYRHN	BCMA	9.92
54	MGSWVEFSWRLEAIRQRLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRSYAAAIRQELQAYRHN	BCMA	19.14
55	MGSWVEFSWRLEAIRQRLTALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRKYAARIRGELQAYRHN	BCMA	21.3
56	MGSWVEFAWRLTAIDQRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRFYAAKIRSHLQAYRHN	BCMA	8.43
57	MGSWVEFAWRLTAIKQRLTALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRLYAAKIRRVLQAYRHN	BCMA	8.9
58	MGSWVEFAWRLTAIHTRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRKYAAKIRKQLQAYRHN	BCMA	6.08
59	MGSWTEFAWRLTAIDQRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRAYAAKIRTRLQAYRHN	BCMA	15.148
60	MGSWSEFAWRLTAIHQRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRLFAAQIRENLQAYRHN	BCMA	18.04
61	MGSWNEFAWRLTAIDQRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRHFAANIRNDLQAYRHN	BCMA	11.53
62	MGSWTEFAWRLTAIDQRLMALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEILRELAEEIRFHLQAYRHN	BCMA	8.55
63	MGSWSEFMNRLDAITYRLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRHYAAQIRDSLQAYRHN	BCMA	12.9
64	MGSWTEFMERLDAISYRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRDYAAIIRNSLQAYRHN	BCMA	9.87
65	MGSWAEFMDRLDAITYRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRGYAAIIRSELQAYRHN	BCMA	10.83
66	MGSWIEFQERLDAIFYRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRDAAATIRRLQAYRHN	BCMA	18.58
67	MGSWIEFQQLRDAIFYRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRDMAAIIRKQLQAYRHN	BCMA	20.02
68	MGSWYEFQSRDLDAIFYRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREAAASIRTQLQAYRHN	BCMA	14.08
69	MGSWSEFIDRLDAITYRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRWYAGVIREQLQAYRHN	BCMA	10.18
70	MGSWSEFYDRLYAINQRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRWYAAFIraqLQAYRHN	BCMA	5.98
71	MGSWYEFYDRLDAIVHRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRWYAAAMIRVRLQAYRHN	BCMA	14.68
72	MGSWVEFQDRLEAITDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAAMIRVILQAYRHN	BCMA	8.8783
73	MGSWVEFQERLMAISDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRWQAAMIRYTLQAYRHN	BCMA	6.7
74	MGSWVEFQHRLEAISMRHLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRWQAAYIRVVLQAYRHN	BCMA	4.05

75	MGSWVEFQSRLEAIATRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRWQAAMIRFMLQAYRHN	BCMA	18.008
76	MGSWEEFYRLGAIARLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRWQAAMIRFMLQAYRHN	BCMA	3.11
77	MGSWVEFYRLQAIISWRLKALGGSEAEALAAFEKEIAAFESSELQAYKGKGNH EVEELRIQAALIRVMLQAYRHN	BCMA	14.23
78	MGSWVEFRSRLEAISNRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRTTAALIRVYLQAYRHN	BCMA	3.04
79	MGSWVEFKARLEAISRRLTALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRVYLQAYRHN	BCMA	8.7071
80	MGSWSEFYTRLAINNRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYTAALIRIYLQAYRHN	BCMA	3.66
81	MGSWAEFYHRLDAISRRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYTAALIRIYLQAYRHN	BCMA	4.31
82	MGSWTEFASRLVAIRQLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRVMLQAYRHN	BCMA	7.99
83	MGSWSEFDQRLAAIYQRLNALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRVMLQAYRHN	BCMA	7.72
84	MGSWVEFHNRLSAISDRLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRVMLQAYRHN	BCMA	7.36
85	MGSWNEFEDRLSAISARLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRVMLQAYRHN	BCMA	4.09
86	MGSWVEFEYRLVAIFDRLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYQAALIRVMLQAYRHN	BCMA	7.63
87	MGSWVEFQGRLGAIHERLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRVFLQAYRHN	BCMA	3.8343
88	MGSWYEFMSRLSAIWRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYQAALIRFYLQAYRHN	BCMA	7.12
89	MGSWTEFSQRLGAISERLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRFMLQAYRHN	BCMA	4.15
90	MGSWTEFHDRLEAITHRLNALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALLRVFLQAYRHN	BCMA	5.79
91	MGSWTEFEHRLAIAIARLNALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRFWLQAYRHN	BCMA	6.34
92	MGSWTEFANRLEAIIARLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFSAAALIRVYLQAYRHN	BCMA	6.42
93	MGSWEEFDRRLYAIARRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYQAALIRVWLQAYRHN	BCMA	8.85
94	MGSWIEFHQRLAIIIVTRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYQAALIRVFLQAYRHN	BCMA	8
95	MGSWSEFYDRLEAIIADRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRTEAAALIRVYLQAYRHN	BCMA	8.215
96	MGSWVEFEDRLSAIMERLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYRAALIRVYLQAYRHN	BCMA	10.39
97	MGSWVEFEERLAAIATRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRWRAALIRVYLQAYRHN	BCMA	16.29
98	MGSWSEFRGRQLAIHSLNALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYSAALIRIYLQAYRHN	BCMA	7.585
99	MGSWTEFRDRLGAIYHRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYQAALIRVYLQAYRHN	BCMA	6.7
100	MGSWVEFYHRLAIIIRYRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYVAIVIRYRLQAYRHN	BCMA	7.8
101	MGSWVEFYDRLEAIIIRYRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYIAAVIRYRLQAYRHN	BCMA	5.636
102	MGSWVEFYDRLEAIIIRKRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFRAALIRIWLQAYRHN	BCMA	9.76

103	MGSWEFSEERLEAISIRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRVSAALIRVWLQAYRHN	BCMA	11.26
104	MGSWSEFSDRLHAISDRQLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRIQAAIRVWLQAYRHN	BCMA	6.3725
105	MGSWIEFSEHRLAIVDRLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRNTAAIRVYLQAYRHN	BCMA	18.67
106	MGSWEFSDRLAAILRRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRFAAAIIRVQLQAYRHN	BCMA	9.08
107	MGSWMEFSDRLDAIHERLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRFAAAIIRVQLQAYRHN	BCMA	6.3
108	MGSWSEFQQLRLHAIRTRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFEEAIIRVMLQAYRHN	BCMA	11.615
109	MGSWYEFQNLGAINRRLNALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFEEAIIRVMLQAYRHN	BCMA	4.68
110	MGSWQEFQTRLHAIRHRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFEEAIIRVWLQAYRHN	BCMA	3.315
111	MGSWTEFDHRLGAIWERLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFHAAIIRIFLQAYRHN	BCMA	9.54
112	MGSWTEFHVRLSAIWDRLLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFHAAIIRIVLQAYRHN	BCMA	23.62
113	MGSWNEFDNRLQAIWDRLLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFHAAIIRITLQAYRHN	BCMA	9.87
114	MGSWTEFHERLQAIWFRLLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFHAAIIRILYLQAYRHN	BCMA	12.066
115	MGSWNEFSGRLTAIKDRLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRFHAAIIRILWLQAYRHN	BCMA	3.39
116	MGSWVEFDERLVAIWFRLLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRARAAYIRIWLQAYRHN	BCMA	8.96
117	MGSWSEFGQLRLSAIWDRLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRADAIFIRIWLQAYRHN	BCMA	14.01
118	MGSWYEFEDRLVAIWIRLLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYNAAFIRGALQAYRHN	BCMA	4.93
119	MGSWYEFQDLRLSAIWDRLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRTAAEIRITLQAYRHN	BCMA	8.895
120	MGSWHEFYRLEAIEQRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRFDAALIRIYLQAYRHN	BCMA	3.73
121	MGSWSEFEERLAAIGSRLFLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRFDAALIRIYLQAYRHN	BCMA	4.85
122	MGSWLEFHYRLHAIQFRLLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRHIAALIRNQLQAYRHN	BCMA	12.749
123	MGSWQEFYNRLAIAHMLRFLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEGLRSDAAPIRDVLQAYRHN	BCMA	6.47
124	MGSWNEFHRLWAIIFDRLLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLKMAAGIRGGLQAYRHN	BCMA	3.88
125	MGSWYEFHYRLKAIINDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRYSAAMIRHKLQAYRHN	BCMA	6.04
126	MGSWTEFHQLGAIHARLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRFSAAFIRLKLQAYRHN	BCMA	8.87
127	MGSWFEFQYRLEAIFYRLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRVRAALIRHLLQAYRHN	BCMA	17.31
128	MGSWVEFHARLDIYTRLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRLVLAHIRISLQAYRHN	BCMA	3.8
129	MGSWVEFGTRLISAIYNRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRFEEAIIRIMLQAYRHN	BCMA	15.425
130	MGSWVEFTHRLDAIYIRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRHEAAVIREELQAYRHN	BCMA	13.917

131	MGSWVEFHGRLLAIYVRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRYHAAMIRRLQAYRHN	BCMA	4
132	MGSWVEFDRRLVAIYIRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRDDAALIRLLQAYRHN	BCMA	8.93
133	MGSWVEFDRRLVAIYIRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRDYDAATIRETLQAYRHN	BCMA	8
134	MGSWLEFDRRLTAIYIRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALREDAAMIRDMLQAYRHN	BCMA	9.82
135	MGSWIEFDRRLIAIHVRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRADAAMIRMLQAYRHN	BCMA	13.72
136	MGSWIEFDRRLIAIYIRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRSDAADIRQLQAYRHN	BCMA	9.45
137	MGSWVEFDRRLIAIYIRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRSDAAMIREHLQAYRHN	BCMA	5.77
138	MGSWYEFHTRLIAIYVRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRGDAAKIRGYLQAYRHN	BCMA	4.06
139	MGSWSEFSTRLSAIYVRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRNKAASIRKTLQAYRHN	BCMA	5.35
140	MGSWVEFRLGAIYHRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRDRAATIRRLQAYRHN	BCMA	10.81
141	MGSWNEFRNLGAIDSRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRAHAAIIRSVLQAYRHN	BCMA	4.6967
142	MGSWHEFRNLGAIDSRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRARAAMIRSVLQAYRHN	BCMA	3.4936
143	MGSWTEFYQRLEAIFRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRDKAALIRLMLQAYRHN	BCMA	6.955
144	MGSWNEFYNRHLAINRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRHAAIIRQALQAYRHN	BCMA	3.004
145	MGSWEEFYGRLSAIQDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRMHAAVIRRALQAYRHN	BCMA	3.28
146	MGSWGEFNLRLVAIHVRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRSQAANIRAQLQAYRHN	BCMA	12.81
147	MGSWGEFSDRLEAIFRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRWQAIFIRANLQAYRHN	BCMA	4.26
148	MGSWMEFQGRLPAILARLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRDKAAYIRWMLQAYRHN	BCMA	8.32
149	MGSWMEFEGRLPAIILARLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRDKAAYIRWMLQAYRHN	BCMA	3.93
150	MGSWFEFQNRQLAILFRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRDKAAYIRLMLQAYRHN	BCMA	5.3933
151	MGSWVEFDMRLQAILERLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRDSAAYIRLMLQAYRHN	BCMA	23.525
152	MGSWVEFNARLDAILFRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRDKAAYIRLMLQAYRHN	BCMA	13.52
153	MGSWMEFNVRLRAILDRHLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRDKAAYIRFMLQAYRHN	BCMA	15.59
154	MGSWIEFDTRLAAIVHRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRDKAAYIRYMLQAYRHN	BCMA	13.948
155	MGSWIEFDYRLKAILHRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEGLRDKAAYIRFLQAYRHN	BCMA	11.877
156	MGSWYEFDRLLAIKVRRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRDQAAYIRFMLQAYRHN	BCMA	17.613
157	MGSWYEFQDRLSAITRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRDKAAYIRFMLQAYRHN	BCMA	10.085
158	MGSWEEFDDRLNAIVYRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLRDKAAYIRLMLQAYRHN	BCMA	18.64

159	MGSWVEFEQRLHAIIVRLRALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVENLRDQAAAYIRFMLQAYRHN	BCMA	17.747
160	MGSWVEFEWRLAIVVRLRALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEHLRDKAAYIRYMLQAYRHN	BCMA	14.95
161	MGSWYEFHRLKAIIVSRLGALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEHLRDKAAYIRYMLQAYRHN	BCMA	4.55
162	MGSWMEFKHRLAAITFRLRALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVELLRDKAAYIRLLQAYRHN	BCMA	6.06
163	MGSWMEFEGRLHAIKRRLRALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEVLRDQAAAYIRLLQAYRHN	BCMA	7.335
164	MGSWSEFVFRDLTIKSRLRALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVETLRDQAAAYIRMLQAYRHN	BCMA	19.86
165	MGSWYEFDERLSAIKRLRALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEVLRQAAYIRAILQAYRHN	BCMA	16.94
166	MGSWMEFDERLWAIKKRLRALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEFLRHQAAYIRMLQAYRHN	BCMA	9.526
167	MGSWHEFDGRLSAIKRRLWALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEHLRDKAAYIRYMLQAYRHN	BCMA	5.4
168	MGSWYEFDGRLQAIIRLRLALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEHLRFRAAYIRWILQAYRHN	BCMA	3.29
169	MGSWFEFDKRLYAIIRLRLALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEKLRKYAAIIRLYLQAYRHN	BCMA	11.82
170	MGSWVEFDNRLYAIVDRRLALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEHLRQKAAYIRLILQAYRHN	BCMA	11.717
171	MGSWIEFHQRLNAIFNRLRALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEWLRHHAAYIREMLQAYRHN	BCMA	7.3417
172	MGSWNEFRLRLWAITERLRLALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVECLRAEAAWIRTMLQAYRHN	BCMA	3.8718
173	MGSWYEFWRLRLSAISYRLQALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEWLRKEAAEIRSWLQAYRHN	BCMA	14.465
174	MGSWYEFQLRLWAIHWRLIALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEWLRMAAEIRNELQAYRHN	BCMA	20.59
175	MGSWYEFahrLEAIEWRLIALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEELRQYAAAIRNYLQAYRHN	BCMA	9.48
176	MGSWYEFDTRLGAIARNRLGALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEWLRFOAAAYIRFLQAYRHN	BCMA	13.934
177	MGSWYEFWVRLTAIRWRLEALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEWLRQAASIRWVLQAYRHN	BCMA	5.72
178	MGSWFEFDRLKAIIDRLMALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEWLRMQAAIIRNYLQAYRHN	BCMA	6.1625
179	MGSWVEFWERLDAIDNRLGALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEWLRWHAAYIRGYLQAYRHN	BCMA	11.42
180	MGSWAEFWDRDLAIDSRNLALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEYLREWAAYIRGYLQAYRHN	BCMA	18.22
181	MGSWAEFDLRLRAIAKRLVALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEMLRLDAAYIRGVLQAYRHN	BCMA	4.09
182	MGSWSEFWDRLYAIRIRLDALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEKLRSAVAIRIRNLQAYRHN	BCMA	12.52
183	MGSWSEFWFRLGAIARNRLDALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEKLRDVAHIRHWLQAYRHN	BCMA	14.93
184	MGSWSEFNDRLDAIRWRDLALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEWLRQVAATIRYRLQAYRHN	BCMA	13.59
185	MGSWVEFWDRLGAIERLQALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEKLRYTAAAIRHYLQAYRHN	BCMA	5.22
186	MGSWAEFWDRLGAIERLQALGGSEAEALAAFEKEIAAFESSELQAYKGGGNP EVEKLRYTAAAIRHYLQAYRHN	BCMA	

187	MGSWTEFWDRLGAI RERLQALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYTAAAIRHYLQAYRHN	BCMA	
188	MGSWVEFWDRLGAI RERLQALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLKYTAAAIRHYLQAYRHN	BCMA	
189	MGSWVEFWDRLGAI RERLQALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLQYTAAAIRHYLQAYRHN	BCMA	
190	MGSWVEFWDRLGAI RERLQALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYTAAAIKHYLQAYRHN	BCMA	
191	MGSWAEFWDRLGAI RERLQALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLQYTAAAIKHYLQAYRHN	BCMA	
192	MGSWTEFWDRLGAI RERLQALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLQYTAAAIKHYLQAYRHN	BCMA	
193	MGSWVEFWDRLGAI RERLEALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYVAAVIRHRLQAYRHN	BCMA	4.18
194	MGSWVEFWDRLGAI RERLQALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEELRASAAAIRIALQAYRHN	BCMA	3.07
195	MGSWVEFWDRLGAI RDRLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEELRNTAAYIRTLQAYRHN	BCMA	16.034
196	MGSWSEFWVR LGAI RDRLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEALRVTAQIRHYLQAYRHN	BCMA	23.5
197	MGSWSEFWVR LGAI RERLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYTAATIRRFQAYRHN	BCMA	7.5567
198	MGSWSEFWAR LGAI RERLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYTAATIRRFQAYRHN	BCMA	
199	MGSWSEFWVR LGAI RERLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYTAGTIRRFQAYRHN	BCMA	
200	MGSWSEFWVR LGAI RERLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYTAATIKRFLQAYRHN	BCMA	
201	MGSWSEFWAR LGAI RERLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYTAGTIKRFLQAYRHN	BCMA	
202	MGSWSEFWDR LTAIRVRLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRYTAAHIRKFLQAYRHN	BCMA	16.14
203	MGSWTEFWTRLNAIYERLDALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRTAASIRMYLQAYRHN	BCMA	8.43
204	MGSWFEFWDR LAAIRDRLEALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEDLRYVAAKIRVRLQAYRHN	BCMA	12.78
205	MGSWTEFWVR LNAIRDRLEALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEDLRHTAAIIRNYLQAYRHN	BCMA	12.53
206	MGSWVEFWHRLGAIYDRLEALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEELRRTAALIRQTLQAYRHN	BCMA	19.904
207	MGSWVEFWNR LGAIYDRLEALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRTAAVIRLYLQAYRHN	BCMA	14.55
208	MGSWSEFWERLEAIYDRLYALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEELRRTAATIRSFLQAYRHN	BCMA	18.78
209	MGSWEEFDNRLEAIFDRLEALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEELREFAATIRITLQAYRHN	BCMA	3.93
210	MGSWMEFWDR LYAIEFRLFALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRRVAATIRNELQAYRHN	BCMA	11.693
211	MGSWTEFWERLYAIEYRLFALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRSVAATIRYELQAYRHN	BCMA	12.7
212	MGSWNEFWERLYAIELRLFALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEKLRTAAYIRNELQAYRHN	BCMA	9.945
213	MGSWYEFWKRLYAIEYRLFALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEALRKVAAKIREQLQAYRHN	BCMA	14.785
214	MGSWTEFWARLYAIEMLRLFALGGSEAE LA AFEKEIA AFESELQAYKGKGNP EVEHLRRAALIREQLQAYRHN	BCMA	12.46

215	MGSWHEFWDRLYAIEFRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRQVAAKIRWHLQAYRHN	BCMA	7.3
216	MGSWDEFEFRLGALRWRLIALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRFGAAHIRHILQAYRHN	BCMA	9.2
217	MGSWTEFYHRLYAIRERLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRFGAAHIRHLLQAYRHN	BCMA	9.6275
218	MGSWVEFETRLDAIRMRLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRFGAAHIRALLQAYRHN	BCMA	14.072
219	MGSWGEFQVRLFAIRERLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRGYAAQIRSFLLQAYRHN	BCMA	7.3533
220	MGSWVEFDERLSAIRERLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRLYAAQIRVFLQAYRHN	BCMA	5.61
221	MGSWSEFDGRLGAIWDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRDRAAQIREFLQAYRHN	BCMA	10.031
222	MGSWGEFEGRRLHAIRSRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRGYAAWIRALLQAYRHN	BCMA	6.17
223	MGSWGEFNGRLGAIRERLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRAYAASIRAVLQAYRHN	BCMA	4.9533
224	MGSWWEFTFRLAAIEFRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRAIAAEIRKSLQAYRHN	BCMA	5.75
225	MGSWDEFQFRLAAIGFRLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRRAQAARIRHLLQAYRHN	BCMA	6.155
226	MGSWYEFVTRLHAIDHRLKALGGSEADLAAFEKEIAAFESSELQAYKGKGNP EVEWLRFYAAGIRMNLLQAYRHN	BCMA	4.12
227	MGSWSIEFWRLAIAIKFRLIALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRVEAAAIRRVLLQAYRHN	BCMA	8.43
228	MGSWGEFEHRLDPSTCVWLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRRGAAVIRHWLQAYRHN	BCMA	4.05
229	MGSWIEFAMRLEAIENRLTALGGSEAEALAFESMIAHFELLQNYKGKGNP EVEALTHEAFAIHKELWAYRHN	BCMA	10.73
230	MGSWNEFYQRLAIAENRLQALGGSEAEALAMFEVRIALFEDMLQGYKGKGNP EVEALKQEAIAILRELIAYRHN	BCMA	6.01
231	MGSWNEFYDRLRAIAKKRLYALGGSEAEALADFEEDIAQFEVDLQDYKGKGNP EVEALHREAHAIHETLWAYRHN	BCMA	12.36
232	MGSWGEFKHRLALIKWYLEALGGSEAEALAHFEDWIAVFEVQLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	17.09
233	MGSWYEFKHRLAIAIKWYLEALGGSEAEALAKFEAWIAEFEMILQRYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	5.505
234	MGSWYEFKHRLAIAIKWYLEALGGSEAEALAHFEQYIADFEGTLQKYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	14.833
235	MGSWYNFKHRLAIAIKWYLEALGGSEAEALARFENFIANFETQLQLYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	6.7615
236	MGSWQFQKHRLAIAIKWQLEALGGSEAEALAWFEQWIADFEHQLEHYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	10.39
237	MGSWYNFKHRLAIAIKWFLEALGGSEAEALAVFEVWIADFEHQLEHYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	16.38
238	MGSWDAFKHRLALIKWYLEALGGSEAEALAHFEYIAEFESNLQSYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	12.98
239	MGSWDGFKHRLALIKWYLEALGGSEAEALANFENWIAEFQRLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	23.62
240	MGSWNGFKHRLAIAIKWYLEALGGSEAEALASFESYIAEFESGLQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	16.53
241	MGSWNSFKHRLALIKWYLEALGGSEAEALATFEWYIASFESLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	10.34
242	MGSWSDFKYRLAVIKFYLEALGGSEAEALASFESFIAHFEDDLQKYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	13.04

243	MGWSWGFKYRLAVIKFYLEALGGSEAEALASFELFIAKFEDLQNYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	13.066
244	MGSWYGFKYRLAVIKWYLEALGGSEAEALASFKEYIAHFEHDLQAYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	9.05
245	MGSWYGFKYRLAVIKWYLEALGGSEAEALASFKEYIAQFEHDLQAYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	7.6333
246	MGSWYGFKYRLALIKWYLEALGGSEAEALASFETYIADFEDLLQAYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	13.03
247	MGSWSTFKYHLAVIKWYLEALGGSEAEALASFEDYIAQFETDLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	11.65
248	MGSWHEFKYRLALIKWYLEALGGSEAEALATFEHHIAQFEWDLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	16.19
249	MGSWNMFKYRLAHIKWYLEALGGSEAEALATFEAYIADFEDVLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	16.33
250	MGSWHGFKYRLAI IKWWLEALGGSEAEALAFEEWIASFERDLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	6.025
251	MGSWHGFKYRLAVIKWYLEALGGSEAEALAMFEGWIAQFEITLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	5.99
252	MGSWQGFKYRLAVIKWLEALGGSEAEALAFENWIAEFETKLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	7.75
253	MGWSWGFKYRLAVIKWYLEALGGSEAEALATFEEWIAEFETELQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	13.975
254	MGSWGYFKYRLAMIKWYLEALGGSEAEALASFESWIAEFEGSLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	13.018
255	MGSWHAFKYRLAMIKWYLEALGGSEAEALAHFEEWIAEFELQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	11.63
256	MGSWQHFKYRLAI IKWYLEALGGSEAEALAFESFIAKFEDLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	8.91
257	MGSWNDFKYRLAI IKYYLEALGGSEAEALAHFESYIASFEHDLQNYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	15.123
258	MGSWGAFKYRLAI IKFYLEALGGSEAEALARFEEFTIANFEHDLQNYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	12.88
259	MGSWYNFKYRLAI IKFYLEALGGSEAEALAQFEIWIAEFEHDLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	19.91
260	MGSEWQFKYRLAI IKYMLEALGGSEAEALAFESWIANFESDLQHYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	11.01
261	MGSWQQFKYRLAI IKYYLEALGGSEAEALAGFETYIAKFEEVLQSYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	15.12
262	MGSWAGFKYRLAVIKYYLEALGGSEAEALAHFEQWIAHFEGMLQDYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	12.68
263	MGSWTAFKYRLAI IKFYLEALGGSEAEALAHFESYIAHFEDMLQHYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	7.43
264	MGSWAHFKYRLAI IKFWLEALGGSEAEALANFEEYIAEFESTLQVYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	13.12
265	MGSWANFKYRLALIKWHLEALGGSEAEALASFEEIWIADFESLQWYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	14.288
266	MGSWATFKYRLALIKWHLEALGGSEAEALADFEEYIAGFEEGLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	15.07
267	MGSWTHFKYRLALIKWWLEALGGSEAEALAGFEVHIADFEALQMYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	7.3669
268	MGSWNTFKYHLAVIKFMLEALGGSEAEALAFEEQWIAEFETLQSYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	10.601
269	MGSWTQFKYHLAVIKWYLEALGGSEAEALAGFEQWIAEFETLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	21.118
270	MGSWNQFKYRLAVIKFYLEALGGSEAEALAHFETWIAAFEEQLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	BCMA	12.85

271	MGSWNEFKYHLAVIKFYLEALGGSEAEALAHFETWIAEFYELQKYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	13.68
272	MGSWVQFKYHLAVIKFYLEALGGSEAEALAHFETWIAEFVALQGYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	12.696
273	MGSWVDFKYHLAVIKFWLEALGGSEAEALANFETWIANFEQELQMYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	13.22
274	MGSWVDFKYHLAVIKWYLEALGGSEAEALADFENWIAHFESILQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	10.43
275	MGSWVEFKYHLAVIKFTLEALGGSEAEALADFEETIARFEMI LQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	6.92
276	MGSWSHFKYHLALIKWYLEALGGSEAEALAKFEFWIAEFHNLQMYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	7.93
277	MGSWYHFKYHLALIKWYLEALGGSEAEALAHFEHWIAEFWTLQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	8.85
278	MGSWQGFKYHLALIKFYLEALGGSEAEALAHFEHWLAEFHDLQTYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	21.2
279	MGSWLSFKHHLALIKWYLEALGGSEAEALASFEAWIALFEHQ LQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	6.305
280	MGSWSEFKYKLALIKWYLEALGGSEAEALAHFEGWIANFETTLQKYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	11.288
281	MGSWIEFKYKLAI IKFYLEALGGSEAEALAHFEHWIADFEFVLQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	14.88
282	MGSWQNFKYHLAMIKWYLEALGGSEAEALANFEETIAQFEINLQHYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	9.55
283	MGSWYNFKYHLAI IKWWLEALGGSEAEALADFEHYIADFERNLQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	8.6264
284	MGSWYQFKYHLAI IKWYLEALGGSEAEALAGFENYIATFEQELQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	18.41
285	MGSWSHFKYHLAI IKFYLEALGGSEAEALAGFEIWIAKFEDELQMYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	9.34
286	MGSWVGFKHLAI IKWYLEALGGSEAEALAGFEI FIADFEALLQMYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	9.71
287	MGSWVNFKYKLAI IKYMLEALGGSEAEALAFFEDWIAEFERTLQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	7.3895
288	MGSWSNFKYRLAVIKYMLEALGGSEAEALAFFEDWIADFELHLQVYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	9.34
289	MGSWTNFKYKLAVIKFMLEALGGSEAEALAFFEDWIAQFEIDLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	11.408
290	MGSWTGFKYRLAI IKFMLEALGGSEAEALAFFEQWIADFENELQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	13.89
291	MGSWHNFKYRLAI IKFMLEALGGSEAEALAFENWIAADFEDSLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	13.59
292	MGSWFAFKHRLAVIKYMLEALGGSEAEALAFFEHWIAQFEHDLQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	11.985
293	MGSWYEFKHRLAVIKYMLEALGGSEAEALAFFENWIAQFEHELQTYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	3.71
294	MGSWYKFHKLAVIKYMLEALGGSEAEALAFEEWIAEFVTLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	4.54
295	MGSWFYFKQLAFIKWYLEALGGSEAEALANFEIYIAEFVMLQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	7.23
296	MGSWFSFKHHLAVIKWNLEALGGSEAEALASFEEQIAEFESVLQAYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	6.45
297	MGSWGNFKYRLAI IKFHLEALGSSEAEALATFEAWIANFESMLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	22.7
298	MGSWSYFKYGLAI IKIRLEALGGSEAEALADFERWIAAFEHDLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	13.33

299	MGSWSYFKFGLAHIKLRLEALGGSEAEADFEQWIASFEEQLQTYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	18.354
300	MGSWSYFKWGLAHIKLRLEALGGSEAEADFEFWIAEFEGLLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	17.64
301	MGSWIYFKYGLAHIKTRLEALGGSEAEADFEQWIAEFKMLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	21.12
302	MGSWGIFYKYGLATIKHRLEALGGSEAEADFEWIAKFEEQLQVYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	14.01
303	MGSWEYFKYGLATIKMHLEALGGSEAEADFEHWIAHFEHLQOMYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	18.403
304	MGSWSYFKYGLATIKEKLEALGGSEAEADFEWIAFMFEKLQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	18.15
305	MGSWHYFKNGLAIKEKLEALGGSEAEADFEIWIAMFEMELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	19.85
306	MGSWQYFKYGLAIKIKLEALGGSEAEADFEAWIATFEKLQOHYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	10.28
307	MGSWVYFKHGLAVIKMRLEALGGSEAEADFEWIAQFEMTLQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	21.45
308	MGSWVYFKYGLAVIKEKLEALGGSEAEADFEWIAEFEGFLQOYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	17.58
309	MGSWYIFKYGLAVIKGKLEALGGSEAEADFEWIAKFENHLQSYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	3.84
310	MGSWTYFKYGLALIKYRLEALGGSEAEADFEWIAQFEVSLQHYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	15.21
311	MGSWDYFKYGLALIKIKLEALGGSEAEADFEVWIAQFEMALQVYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	15.76
312	MGSWTYFKFGLAHIKDSLEALGGSEAEADFEQWIAFMFEQLQVYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	17.01
313	MGSWGIFYKHGLAHIKSSLEALGGSEAEADFEVWIAAFENELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	18.505
314	MGSWGIFYKTGLAIKKAQLEALGGSEAEADFEWIAQFEETLQFYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	12.75
315	MGSWAYFKYGLAVIKLHLEALGGSEAEADFEWYIAEFYELQAYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	13.44
316	MGSWLDKFKEGLADIKRSLEALGGSEAEADFEVWIAFVIALFEWKLQTYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	3.03
317	MGSWEVFKHELAVIKDYLEALGGSEAEADFEWGIWFEWFLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	9.33
318	MGSWIVFKQSLAWIKHLEALGGSEAEADFEWYIANFEHTLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	10.57
319	MGSWIYFKDSLAYIKKYLEALGGSEAEADFEWYIANFEHELQYKKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	3.2
320	MGSWDHFKYNLAWIKKYLEALGGSEAEADFEWYIANFEKRLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	9.81
321	MGSWFTFKQNLAWIKLHLEALGGSEAEADFEWYIADFENKLQLYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	14.204
322	MGSWREFKYGLAHIKRVLEALGGSEAEADFEWYIAKFEQELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	14.7
323	MGSWIQFKYGLAHIKRTLEALGGSEAEADFEWYIADFEEQLQGYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	8.3567
324	MGSWVEFKHNLAWIKVTLLEALGGSEAEADFEWYIAQFEEQLQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	15.83
325	MGSWISFKDNLAMIKEFLEALGGSEAEADFEWYIATFEVELQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	7.16
326	MGSWHIFKDNLATIKAFLEALGGSEAEADFEWYIAKFEEELQGYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	3.47

327	MGSWTSFKHGLAGIKRVLEALGGSEAEALATFEWYIAQFERHLQAYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	9.765
328	MGSWQSFKHALADIKINLEALGGSEAEALQFEYAIQVFEYRLQAYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	13.719
329	MGSWHTFKEALQIKGELEALGGSEAEALQFEYAIQVFEYRLQMYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	6.76
330	MGSWTDFKTSADIKAELEALGGSEAEALQFEYIYIAI FEYRLQYKKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	18.76
331	MGSWTNFKEGLAIEIKRDLEALGGSEAEALQFEYVIAVFEFRLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	12.327
332	MGSWHTFKDGLAEIKSELEALGGSEAEALQFEYVIAI FEYRLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	10.65
333	MGSWQFFKEHLASIKFWLEALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	10.58
334	MGSWTYFKHLASIKFWLEALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	6.5951
335	MGSWIIFKGYLAHIKHHLEALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	5.18
336	MGSWYLFQSHLAHIKHHLEALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	7.69
337	MGSWYSFKWTLARIKLELEALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	4.05
338	MGSWTTLKWRLAHIKQHLEALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	17.82
339	MGSWYGFQWYLAHIKQHLEALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	BCMA	10.65
340	MGSWIEFNMRVLAIEDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.2
341	MGSWIEFHERLWAIEDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.4
342	MGSWFEFYERLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	6
343	MGSWFEFWDRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.9
344	MGSWHEFWSRLDAIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.8
345	MGSWYEFWIRLEAIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	10.4
346	MGSWHEFWDRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	10.6
347	MGSWEEFWDRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.1
348	MGSWWFEFDDRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.5
349	MGSWTEFHDRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	5.8
350	MGSWAEFEDRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	6.2
351	MGSWVEFWFRLEAIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.2
352	MGSWVEFWQRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	7.7
353	MGSWSEFWQRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.7
354	MGSWSEFITRLWAIIDRLWALGGSEAEALQFEYVIAIADFEYHLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.3

355	MGSWYEFETRLEAIYDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRVEAAETREDLQAYRHN	CD123	3.2
356	MGSWTEFYRLEAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRVEAANIRDMLQAYRHN	CD123	7.5
357	MGSWYEFVIRLEAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRWYAADIRHELQAYRHN	CD123	6.4
358	MGSWTEFSIRLEAIYDRLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRTYAANIRHELQAYRHN	CD123	11.9
359	MGSWTEFSIRLEAIYDRLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRTYAAFIRHELQAYRHN	CD123	10.2
360	MGSWTEFVWRLEAIWDRDLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLREDAAVIRHFLQAYRHN	CD123	3.6
361	MGSWVEFHERLEAIEDRLMALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLREDAAFIRQLLQAYRHN	CD123	3.7
362	MGSWVEFHDRLAIEDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLREDAAYIRSILQAYRHN	CD123	4.6
363	MGSWIEFYDRLEAIYDRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLREDAAFIRSWLQAYRHN	CD123	7.5
364	MGSWVEFDQRLEAIYDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLREDAQIRKWLQAYRHN	CD123	5.1
365	MGSWVEFHDRLAIEDRLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLREYAAGIRWFLQAYRHN	CD123	3.3
366	MGSWEEFAQRLYAIEWRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRVYAAQIRYHLQAYRHN	CD123	16.9
367	MGSWDEFARWLDVIFARLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRKNAQIRDGLQAYRHN	CD123	4.6
368	MGSWDEFYRLEAIEMLRGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRHYAAQIRHMLQAYRHN	CD123	7.2
369	MGSWEEFYDRLEAIYNRLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLREYAADIREMLQAYRHN	CD123	18.6
370	MGSWDEFGRRLYAIEWQLYALGGEEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRKEAAVIRENLQAYRHN	CD123	
371	MGSWDEFGRRLYAIEWQLYALGGTEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRKEAAVIRENLQAYRHN	CD123	
372	MGSWDEFGRRLYAIEQLYALGGEEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRENLQAYRHN	CD123	
373	MGSWDEFGRRLYAIEWQLYALGGEEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRENLQAYRHN	CD123	
374	MGSWDEFGRRLYAIKWQLYALGGEEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRENLQAYRHN	CD123	
375	MGSWDEFGRRLYAIEWQLYALGGEEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRENLQAYRHN	CD123	
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378	MGSWDEFGRRLYAIEWQLYALGGGEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRSNIQAYRHN	CD123	
379	MGSWDEFGRRLYAIEWQLYALGGTEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRSNIQAYRHN	CD123	
380	MGSWDEFGRRLYAIEWQLYALGGEEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRSNIQAYRHN	CD123	
381	MGSWDEFGRRLAIAIEWQLYALGGEEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRENLQAYRHN	CD123	
382	MGSWDEFGRRLYAIEWQLYALGGEEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALREIAAVIRENLQAYRHN	CD123	

383	MGSWDEFGRRLYAIEWQLYALGGEEAELAAFEKEIAAFESSELQAYKGKGNP EVEKLREEAAVIRENLQAYRHN	CD123	
384	MGSWDEFGRRLYAIEWRLYALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRSNLQAYRHN	CD123	
385	MGSWDEFGRRLYAIEWRLYALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRSNLQAYRHN	CD123	5.8
386	MGSWDEFGRRLYAIEWRLYALGGEEAELAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRSNLQAYRHN	CD123	
387	MGSWDEFGRRLYAIEWQLYALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRSNLQAYRHN	CD123	
388	MGSWDEFGRRLYAIEWRLYALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRSNLQAYRHN	CD123	
389	MGSWDEFGRRLYAIEWRLYALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRENLQAYRHN	CD123	
390	MGSWDEFGRRLAAIKTQLAALGGEEAELAAFEKEIAAFESSELQAYKGKGNP EVEKLREIAAVIRENLQAYRHN	CD123	
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392	MGSWDEFGRRLAAIKTQLAALGGEEAELAAFEKEIAAFESSELQAYKGKGNP EVEALRKEAAVIRENLQAYRHN	CD123	
393	MGSWDEFGRRLAAIKTQLAALGGTEAEELAAFEKEIAAFESSELQAYKGKGNP EVEALRKEAAVIRENLQAYRHN	CD123	
394	MGSWDEFQRLIAIEERLFAALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEWLREEAAVIRKYLQAYRHN	CD123	5.9
395	MGSWVEFDQRLGAIWDRVLALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEHLRQGAIVIRDDLQAYRHN	CD123	5.3
396	MGSWVEFDMRLSAIWERLIALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEWLREDAAEIREFLQAYRHN	CD123	3.3
397	MGSWVEFDQRLDAIYERLYALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEWLREDAAEIREHLQAYRHN	CD123	10.5
398	MGSWHEFDQRLWAIERLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVETLRLYAALIRHDLQAYRHN	CD123	3.3
399	MGSWVEFDRLDAIEGRLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEDLRWLAAEIRADLQAYRHN	CD123	3.5
400	MGSWVEFYRLDAIEDRLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEWLRIAAASIREDLQAYRHN	CD123	9.4
401	MGSWVEFYRLDAIEERLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEVLRDWAAWIREDLQAYRHN	CD123	8.4
402	MGSWVEFDRLDAIENRLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEVLRDNAAWIREILQAYRHN	CD123	4.2
403	MGSWVEFDRLDALEDRLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEYLRLDAAFIREELQAYRHN	CD123	9.7
404	MGSWMEFVDRDLAIESRLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEWLRIEAAFIREEQLQAYRHN	CD123	5.8
405	MGSWVEFVDRDLWAIERLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEELRIQAAIIREALQAYRHN	CD123	6
406	MGSWVEFNYRLGAIEDRLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEMLRQIAAEIREFLQAYRHN	CD123	6.9
407	MGSWVEFFTRDLAINERLEALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEMLRYEAAEIRHMLQAYRHN	CD123	3.9
408	MGSWVEFNRDLAIGERLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEILRHQAAEIRWFLQAYRHN	CD123	3.9
409	MGSWVEFWGRDLAIEERLWALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEMLREDAAEIRGQLQAYRHN	CD123	5.4
410	MGSWVEFWDRDLWAIIDYRLFALGGSEAEELAAFEKEIAAFESSELQAYKGKGNP EVEALRDEAAWIREELQAYRHN	CD123	3.6

411	MGSWVEFVDRLWAIDERLDAALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRTWAAWIREDLQAYRHN	CD123	3.2
412	MGSWFEFWDRLLEAIWERLDAALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRREAAI IREDLQAYRHN	CD123	10.3
413	MGSWFEFEDRLLEAIYQRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDEAAWIRSDLQAYRHN	CD123	5.5
414	MGSWFEFHDLRLWAIDERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEILREEAADIRDLQAYRHN	CD123	3.5
415	MGSWYEFEDRLWAIDNRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRVHAADIRDDLQAYRHN	CD123	4.9
416	MGSWFEFQDRLWAIDNRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRDHAAMIRWELQAYRHN	CD123	3.2
417	MGSWDEFEERLFAIDERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRYLAADIREELQAYRHN	CD123	5
418	MGSWEEFWERLDAIDTRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRNDAADIREPLQAYRHN	CD123	6.8
419	MGSWMEFWERLEAIDMRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRDDAAVIRDDLQAYRHN	CD123	4.2
420	MGSWLEFMWRDLAIDERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLREMAAAIRDDLQAYRHN	CD123	5.1
421	MGSWTEFYNRDLDAIDQRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLREYAADIRTDLQAYRHN	CD123	3.3
422	MGSWWEFIWRLEAIEQRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRRAADIRTDLQAYRHN	CD123	4
423	MGSWSEFYDRLWAIEERLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRYYAAEIREELQAYRHN	CD123	17
424	MGSWSEFEDRLWAIDQRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRAYAADIRWELQAYRHN	CD123	4.2
425	MGSWTEFWERLNAIDERLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRLYAAEIRSELQAYRHN	CD123	4
426	MGSWWEFEERLWAIDYRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLRSWAAEIRALLQAYRHN	CD123	4.1
427	MGSWWEFENRLWAIEERLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLRNYAAEIRWELQAYRHN	CD123	5.6
428	MGSWVEFEERLWAIDERLGAALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDWAADIRWWLQAYRHN	CD123	4.1
429	MGSWVEFEERLEAIEERLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDDAANIRHWLQAYRHN	CD123	3.8
430	MGSWMEFEERLWAIDSRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRSEAAWIRMELQAYRHN	CD123	3.2
431	MGSWSEFEHRLEAIESRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRSEAAWIREQLQAYRHN	CD123	7.6
432	MGSWFEFWERLDAIEWRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRSTAADIRRYLQAYRHN	CD123	3.4
433	MGSWFEFWGRLEAIESRLKALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELREHAAWIRAYLQAYRHN	CD123	4.9
434	MGSWQEFTMRDLAIYNRLETGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRQSAANIRSELQAYRHN	CD123	13.7
435	MGSWSEFNMRDLAIYERLTALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRHSAARIRLELQAYRHN	CD123	13.7
436	MGSWSEFNMRDLAIYERLTALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRHSAALIRLELQAYRHN	CD123	11.4
437	MGSWIEFNMRDLAIYERLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRKVAANIRLELQAYRHN	CD123	11.4
438	MGSWYEFHHRDLAIYERLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRSSAANIRKELQAYRHN	CD123	11.9

439	MGSWYEFKRLDAIYERLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRSSAANIREELQAYRHN	CD123	15.3
440	MGSWTEFYVRLDAIYERLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRMVAANIRTELQAYRHN	CD123	16
441	MGSWVEFYTRLDAIYGRDLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRQVAANIRMELOQAYRHN	CD123	14.4
442	MGSWVEFHMRLDAIYERLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRATAANIRVELQAYRHN	CD123	9.1
443	MGSWYEFKRLDAIYERLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRVVAANIRTELQAYRHN	CD123	25.5
444	MGSWNEFVIRLDAIYERLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRMAAANIRMELOQAYRHN	CD123	16.6
445	MGSWSEFYVRVDAIYARLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRVVAANIRHELOQAYRHN	CD123	14.7
446	MGSWSEFHVRLDAIYARLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVERLREWAANIRRELOQAYRHN	CD123	14.4
447	MGSWVEFHLRLDAIYGRMLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRVVAANIRNELQAYRHN	CD123	17.5
448	MGSWVEFEMRLDAIVGRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRRAAANIRSELQAYRHN	CD123	25.3
449	MGSWVEFNIRLDAIYERLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRHWAASIRRELOQAYRHN	CD123	13.4
450	MGSWHEFGVRLDAIYDRMLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRQAAANIRSELQAYRHN	CD123	15.6
451	MGSWTEFNRLDAIYDRMLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRASAAAIRVELQAYRHN	CD123	14.4
452	MGSWTEFNRLDAIYGRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRAAAANIRVELQAYRHN	CD123	19.3
453	MGSWVEFNWRLDAIYDRLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRVSAAKIRGELQAYRHN	CD123	9.3
454	MGSWNEFAWRLDAIYSRLAALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRVAAANIRYELQAYRHN	CD123	17.7
455	MGSWTEFAWRLDAIYDRLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRHVAANIRRELOQAYRHN	CD123	16.1
456	MGSWVEFSIRLDAIYTRLVALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLRKGAANIRKELQAYRHN	CD123	15.1
457	MGSWVEFYIRLDAIYVRLMALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRSYAANIRQELQAYRHN	CD123	16.1
458	MGSWYEFMSRLDAIYDRMLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEQLRGYAANIRNELQAYRHN	CD123	13
459	MGSWVEFYIRLDAIYDRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRRYAANIRNELQAYRHN	CD123	17
460	MGSWIEFEVRLDAIYNRLAALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVERLRRYAANIRHELOQAYRHN	CD123	20.8
461	MGSWFEFYDRLDAIYMRLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRRYAANIRAELOQAYRHN	CD123	13.6
462	MGSWFEFYMRLDAIYDRLTALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVERLRTFAANIRKELQAYRHN	CD123	13.1
463	MGSWYEFDYRLDAIYDRLAALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVERLRKWAANIREELQAYRHN	CD123	24.9
464	MGSWSEFYLRDLDAIYDRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRKTAANIREELQAYRHN	CD123	15.7
465	MGSWFEFYERLDAINWRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRGEAAAIREDLOQAYRHN	CD123	3
466	MGSWNEFEDRLDAIWWRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRVEAAFI RTMLQAYRHN	CD123	5.1

467	MGSWFYFKDDLADINYMLEALGGSEAEALAMFEDDIAGFELTLLKYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.7
468	MGSWHFFKDDLAWIKNELEALGGSEAEALAMFEDDIAMFETMLQSYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.2
469	MGSWHWFKTDLADIKKELEALGGSEAEALAMFEDDIAEFEEFLQMYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.5
470	MGSWWLFKDDLAEIKYWLEALGGSEAEALAFFEDDIAEFERGLQIYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.3
471	MGSWYEFKDDLAEIKEWLEALGGSEAEALAFFELDIADFEWLLQLYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.8
472	MGSWQWFKDDLAYIKETLEALGGSEAEALAFEDMIADFEFELQWYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	6.3
473	MGSWILFKDDLAWIKETLEALGGSEAEALAFFEDNIADFEELQGYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	6
474	MGSWIVFKDDLADIKRWLEALGGSEAEALAMFEDEIADFEWQLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.9
475	MGSWGHHFKQDLAWIKDTLEALGGSEAEALAFFEDDIAMFEMELQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.9
476	MGSWGIFYKDDLAWIKGELEALGGSEAEALAEFEWFIIVFEEDLQVYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.5
477	MGSWYWFKDDLAEIKGLLEALGGSEAEALAEFEDEIIVFEQELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	10.4
478	MGSWMFFKEDLADIKWALEALGGSEAEALAFFEEIALLFEQHLQYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.2
479	MGSWTFFKEDLAGIKWELEALGGSEAEALAWFEDEIALFEEELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	7
480	MGSWVFFKDDLADIKDELEALGGSEAEALAFFEIALALFEWELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	8.8
481	MGSWTFFKNDLAEIKDWLEALGGSEAEALADFEWDIAEFEYSLQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.9
482	MGSWTYFKDDLADIKQWLEALGGSEAEALAFFEIEIAEFEEELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.6
483	MGSWTVFKYDLADIKWWLEALGGSEAEALADFEEEIAEFEEELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.9
484	MGSWYWFKQDLAHIKSMLEALGGSEAEALAWFEEDIADFESELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.3
485	MGSWTFFKDWLADIKANLEALGGSEAEALAWFEEDLAGFEALQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.8
486	MGSWSFKEELANIQVYLEALGGSEAEALAWFEEDIADFEEDLQHYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.8
487	MGSEWFFKYELADIKDELEALGGSEAEALAWFEEDIATFEEWLQGYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.4
488	MGSWQTFKDELAKIKWELEALGGSEAEALAWFEWDIANFEELQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	5.5
489	MGSWYWFKEELAFIKWELEALGGSEAEALALFEEDIAYFEEMLQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	9.4
490	MGSWNSFKDELAIEIKAELEALGGSEAEALAFFEEDIWFEELQYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.3
491	MGSWDLFKWELAEIKGLLEALGGSEAEALAEFEYDIAWFEEDLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.4
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493	MGSWHLFKWTLAEIKYLEALGGSEAEALAWFEDDIATFEELQWYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4
494	MGSWVTFKDELADIKDFLEALGGSEAEALAFFEVDIAEFELQFYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	7.6

495	MGSWVYFKDELADIKDFLEALGGSEAEAEFEEDIATFEYDLQWYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.6
496	MGSWETFKYELAEIKDYLEALGGSEAEALWFEDDIAEFEFELQYYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.4
497	MGSWNTFKYELAEIKHFLEALGGSEAEALWFEDDIAMFEWELQEYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	5
498	MGSWVYFKDELAIEIKQFLEALGGSEAEALWFEDDIAEFETQLQHYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	9.9
499	MGSWIFFKEQLAI IKWELEALGGSEAEALWFEDDIAAFEDDLQFYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	15
500	MGSWEFFKEVLAEIKYDLEALGGSEAEALWFETDIAGFEIDLQVYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	8.2
501	MGSWVFFKEDLATIKNDLEALGGSEAEALWFEMMIADFEADLQYYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.1
502	MGSWEFFKEDLAEIKVWLEALGGSEAEALWFEMGIADFEDGLQFYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.3
503	MGSWHWFKEDLANIKDWLEALGGSEAEALWFEDNIADFEGDLQVYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.3
504	MGSWWFKEDLAFIKEDLEALGGSEAEALWFEDGIAFFEWDLQDYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	13.7
505	MGSWQWFKEDLAEIKHDLEALGGSEAEALWFEDFIAQFEDLQWYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.8
506	MGSWHWFKEDLAI IKQDLEALGGSEAEALATFEQWIAEFEWDLQEYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	5.5
507	MGSWNWFKEDLAI IKMDLEALGGSEAEALWFENIAGFEFELQGYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.1
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509	MGSWSWFKQDLADIKIQLEALGGSEAEALWFEDWIAEFEFELQDYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4
510	MGSWSWFKEDLADIKFELEALGGSEAEALWFELDIADFEQALQQYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	6.8
511	MGSWSWFKEDLASIKAVLEALGGSEAEALAFFESDIAEFELQYYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	6.9
512	MGSWWEFKEDLAEIKWFLEALGGSEAEALWFEDHIAKFEFELQYYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	5.1
513	MGSWWFKSDLASIKWELEALGGSEAEALWFEDHIAEFEDDLQWYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	5.7
514	MGSWNEFKDDLAMIKMTLEALGGSEAEALWFEDHIAEFEDDLQWYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.5
515	MGSWTFFKDDLAEIKWMLEALGGSEAEALWFESDIAYFEDELQWYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.3
516	MGSWSDFKDDLAEIKMILEALGGSEAEALAYFENDIAWFEDDLQEYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.7
517	MGSWSMFKDDLAEIKASLEALGGSEAEALWFEDDIAWFEDDLQHYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	5.2
518	MGSWQYFKDDLAEIKMVLEALGGSEAEALWFEDIAMFEDDLQIYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.6
519	MGSWSEFKDDLAEIKYFLEALGGSEAEALAMFEQTIAEFYDLQDYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	10.1
520	MGSWMEFKEELAEIKYILEALGGSEAEALWFEQSIADFEYDLQDYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	5
521	MGSWAWFKEDLAEIKVFLEALGGSEAEALAEFEVSIADFEYELQDYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	3.5
522	MGSWYEFKFDLAEIKQLEALGGSEAEALFEDDIAFFEYDLQNYKKGKGNP EVEALRKEAAAIRDELQAYRHN	CD123	4.6

523	MGSWYDFKYDLAEIKMDLEALGGSEAEALQFEFDIAFFEEELQDYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.2
524	MGSWYIFKEDLAEIKEELEALGGSEAEALAYFEEELALFEMELQWYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	11.1
525	MGSWVLFKEELAYIKFELEALGGSEAEALFENVIAIFESNLQNYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.5
526	MGSWQDFKEDLAWIKYLEALGGSEAEALAFFEYDIAIFENNLOHYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.2
527	MGSWDHFKNDLAWIKKHLEALGGSEAEALAEFEAVIAYFELYLQGYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.3
528	MGSWYDFKEDLADIKWMLEALGGSEAEALAEFENVIAIFYFENDLQEYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	8
529	MGSWYMFKEELADIKWYLEALGGSEAEALAWFEDDIAGFEWDLQAYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	7
530	MGSWYFVKDELADIKWDLEALGGSEAEALAWFEMLIAQFELDQWYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	4
531	MGSWMYFKDTLADIKWYLEALGGSEAEALAFFEDWIAEFEDDLQVYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.1
532	MGSWYQFKHDLADIKYGLEALGGSEAEALAWFEDDIADFELDLQYYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	4.7
533	MGSWYFVKDDLADIKYMLEALGGSEAEALAWFEWEIANFEDLQYYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.8
534	MGSWNFFKYDLADIMAYLEALGGSEAEALAFFEDEIANFEHDLQKYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	4.4
535	MGSWHWFKIVLADIKDGLLEALGGSEAEALAYFETTIADFEMDLQHYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	4.3
536	MGSWHWFKIVLADIKDGLLEALGGSEAEALAYFETTIADFEMDLHYYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.5
537	MGSWWMFKEELADIKDWLEALGGSEAEALASFESYIAWFEQDLQWYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	5.7
538	MGSWWMFKQELAWIKEDLEALGGSEAEALADFEWDIAEFEWDLQYYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	7.2
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540	MGSWDFKKEELAEIKHYLEALGGSEAEALAFFEFWIADFEQDLQEYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.7
541	MGSWFNFKELAVIKFQLEALGGSEAEALAFFEWVIADFEDDLQEYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	6.1
542	MGSWYQFKTELAWIKDDLEALGGSEAEALAWFEWVIADFEDDLQFYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	6.6
543	MGSWFEFKDYLADIKWDLEALGGSEAEALIFEHDIAYFEHNLQYYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.8
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545	MGSWWLFKEQLALIKYNLEALGGSEAEALADFESWIAEFEHQLQEYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	4.1
546	MGSWHVFKEELADIKFYLEALGGSEAEALAMFELWIAEFEHQLQDYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	5.4
547	MGSWIWFKDWLADIKDLLEALGGSEAEALAEFEYDIALFEDQLQAYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	7.3
548	MGSWGWFKEHAFIKADLEALGGSEAEALAWFEEELAEFEYELQFYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.3
549	MGSWTWFKDNLAWIKEDLEALGGSEAEALAWFELEIASFETALQDYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	6.9
550	MGSWTYFKNDLAGIKEDLEALGGSEAEALQFEFEIAEFEWLLQDYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.6

551	MGSWTWFKWDLADIKGDLEALGGSEAEALAFFEIEAEFEWRLQDYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	5.9
552	MGSWLYFKKEYLADIKSDLEALGGSEAEALAWFEYEIADFEEQLQYYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.7
553	MGSWHWFKEELAEIKEDLVALLGGSEAEALAWFEYDIAMFELSQNYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.1
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555	MGSWWDFKDWLAEIKHDLEALGGSEAEALAFSEIADFEEGLQWYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	4.2
556	MGSWDEFKEDLAHIKTDLEALGGSEAEALAFSEIADFEMYLQHYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	6.3
557	MGSWDFFKYDLANINWLEALGGSEAEALADFEYGIADFELWLQDYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	5.5
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559	MGSWAEFKHDLADIKRELEALGGSEAEALAWFELSIAFFFEDELQHYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.3
560	MGSWVVFQDLADINHQLEALGGSEAEALAWFEWEIADFELQHYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	3.6
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562	MGSWHWFKEDLAMITDVLEALGGSEAEALAEFESEIADFVADLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	5.2
563	MGSWSWFQWDLAGIKDHLEALGGSEAEALAEFESEIAYFEDELQWYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	12.9
564	MGSWTEFKGELAEIKWILEALGGSEAEALAFFEDEIAAFEWDLQYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	8.2
565	MGSWFEFKWTLALIKQLEALGGSEAEALADFEQIEAEFEWWLQTYKGKGNP EVEALRKEAAAIIRDELQAYRHN	CD123	4.9
566	MGSWAEFKQRLAAIKTRLEALGGSEAEALAFMDEIMAFEWELWAYKGKGNP EVEALMNEAFAIDVELYAYRHN	CD123	3.4
567	MGSWAEFKQRLAAIKTRLEALGGSEAEALAFWEIVAFFSELFAYKGKGNP EVEALRDEAIAIETELVAYRHN	CD123	3.6
568	MGSWWEFDRHRLTAIDTRLQALGGSEAEALAEFESSIAEFEWLQDYKGKGNP EVEALFAEAEAIYVELDAYRHN	CD123	4.3
569	MGSWWEFQFRLYAIDQRLALGGSEAEALAEFEQDIADFEWMLQDYKGKGNP EVEALMLEADAIEELKAYRHN	CD123	3.1
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571	MGSWYEFDMRLDAIWERLTALGGSEAEALADFEQYIAEFERQLQDYKGKGNP EVEALFDEAWAIEDELYAYRHN	CD123	13.7
572	MGSWSEFDSRLDAIAYRLFALGGSEAEALAQFEWIIADFEEQLQMYKGKGNP EVEALFSEAYAIEIELNAYRHN	CD123	4.3
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576	MGSWEEFDVRLDAIFNRLWALGGSEAEALAEFEFDIAWFEMDLQYKGKGNP EVEALFDEAEAITNELVAYRHN	CD123	4.7
577	MGSWEEFDKRLDAITRRLMALGGSEAEALAEFESTIAWFEMDLQYKGKGNP EVEALDWEAYAIDYELGAYRHN	CD123	4.5
578	MGSWYEFDRHRLDAIYDRLWALGGSEAEALAEFEFDIAADFEEWLQSYKGKGNP EVEALFDEAAAIGHHELLAYRHN	CD123	4.5

579	MGSWNEFDDRLAIWGRDLALGGSEAEALAFEEQIAGFEDELQWYKKGKGNP EVEALDQEAIEAEIKELWAYRHN	CD123	4.1
580	MGSWVEFDDRLDAIWRLDALGGSEAEALAWFEEQIAVFEHLQDYKKGKGNP EVEALNQEAEAIIDLELKAYRHN	CD123	5
581	MGSWTEFDDRLFAIYWRLDALGGSEAEALAWFEEVIAEFENDLQVYKKGKGNP EVEALDDEAHAIISIELEAYRHN	CD123	6.4
582	MGSWSEFQRLLEAIWNRLDALGGSEAEALADFEREIAFYFENQLQWYKKGKGNP EVEALNNEAFAIVDELGAYRHN	CD123	3.4
583	MGSWYEFDERLWAIWRLDALGGSEAEALAHFEWVIADFENDLQWYKKGKGNP EVEALEFEAEAIIVTELHAYRHN	CD123	3.6
584	MGSWMEFYDRLLEAIWMRLDALGGSEAEALADFESSIADFEEHLQSYKKGKGNP EVEALEWEAFAIGVELDAYRHN	CD123	3.1
585	MGSWYEFESRLEAIWRLLEALGGSEAEALAQFEQYIADFEHLQWYKKGKGNP EVEALDWEADAIWLELQAYRHN	CD123	4.4
586	MGSWEEFYMRLEAIWMRLDALGGSEAEALAVFENYIAEFEEYLQYYKKGKGNP EVEALTIADAIGTELGAIRHN	CD123	4.4
587	MGSWDEFYRRLVAITHRLHALGGSEAEALAWFEDDIAGFEWDLQTYKKGKGNP EVEALYKEAGAIGMELTAYRHN	CD123	5.4
588	MGSWEEFDTRLIAIFGRLGALGGSEAEALAFEMLIADFEEDLQNYKKGKGNP EVEALSEEAFIDHELGAIRHN	CD123	6.7
589	MGSWREFDQRLWAIWRLLEALGGSEAEALAMFEWMIATFEDDLQWYKKGKGNP EVEALYREAFIDWELDAYRHN	CD123	3.4
590	MGSWEEFHERLDAIDERLEALGGSEAEALAFEDDIASFEDWLQWYKKGKGNP EVEALSREADAINFELEAYRHN	CD123	4.3
591	MGSWNEFYERLEAIDRRFLALGGSEAEALAFEWMIADFEDDLQMYKKGKGNP EVEALINEAGAIGFELEAYRHN	CD123	5.2
592	MGSWTEFTQRLLEAIVDRFLALGGSEAEALAEFENSIADFEDWLQWYKKGKGNP EVEALNREAVAIDNELWAYRHN	CD123	3.9
593	MGSWVEFIMRLDAIYERLALGGSEAEALAEFEWHIADFEDHLQWYKKGKGNP EVEALFEEADAIWEELWAYRHN	CD123	6.4
594	MGSWNEFLRLDAIEHRLALGGSEAEALAEFEWEIADFEDDLQWYKKGKGNP EVEALVEEAIEIDVELVAYRHN	CD123	3.2
595	MGSWYEFNMRLGAIDRLQALGGSEAEALAWFEDMIAIFEDDLQIYKKGKGNP EVEALQEAAAIIHQELWAYRHN	CD123	3.8
596	MGSWEEFHWRLGAIDARLEALGGSEAEALAWFEDGIADFEAILQDYKKGKGNP EVEALDSEAVAIHHELWAYRHN	CD123	3.3
597	MGSWYEFYERLWAIIDRLWALGGSEAEALAEFEDSIATFEPQLQMYKKGKGNP EVEALVAEAWAIFDELAAYRHN	CD123	3.6
598	MGSWFEFDQRLDAITFRLWALGGSEAEALAEFEDVIALFEYHLQDYKKGKGNP EVEALEVEAWAIFHELGAIRHN	CD123	3.2
599	MGSWSEFWRLDAIEDRLWALGGSEAEALAEFEDNIALFEYSLQHYKKGKGNP EVEALVKEANAIDDELGAIRHN	CD123	4.5
600	MGSWYEFWDRDLTAIEHRLWALGGSEAEALAYFEDSIAHFEGSLQVYKKGKGNP EVEALYKEAEAIWELEAYRHN	CD123	4.4
601	MGSWYEFDDRLWAIIDRLFALGGSEAEALAFEDSIAEFEEELQHYKKGKGNP EVEALYLEAWAIIENELGAIRHN	CD123	4.7
602	MGSWNEFVERLSAIDHRLWALGGSEAEALADFEQQIAEFIEHLQEYKKGKGNP EVEALDFEADAIFDELLAYRHN	CD123	3.2
603	MGSWSEFVDRDLDAIFDRWLALGGSEAEALAWFEDTIAHFEWNLQEYKKGKGNP EVEALNGEADAITDELHAYRHN	CD123	5.3
604	MGSWAEFDSRLDAIAQRLFALGGSEAEALAHFEDFIAQFEYSLQEYKKGKGNP EVEALSNEADAIFNELKAYRHN	CD123	3.6
605	MGSWAEFDSRLIAIFDRWLALGGSEAEALAWFEDDIAQFEQHLQAYKKGKGNP EVEALRQEADAITFELKAYRHN	CD123	3.6
606	MGSWTEFEERLEAIWDRLYALGGSEAEALAEFEWDIAFYFEDGLQEYKKGKGNP EVEALFMEAEAIIRELKAYRHN	CD123	5.9

607	MGSWYEFEDRLAAIWDRNLALGGSEAEALAEFEWDIAWFEEGLQYKKGKGNP EVEALKHEASAIQTFLFAYRHN	CD123	6.4
608	MGSWLEFESRLWAIWDRDLALGGSEAEALAHFEQDIADFEMLQYKKGKGNP EVEALIREAEAIETELYAYRHN	CD123	3.4
609	MGSWMEFEDRLIAIWARLDALGGSEAEALAWFEADIADFEESLQYKKGKGNP EVEALIFEAIANKELMAYRHN	CD123	3.7
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611	MGSWYEFVSRDLAIEYRLWALGGSEAEALAWFEWDIADFEQGLQFYKKGKGNP EVEALAQEANAIGSELTAIRHN	CD123	3.2
612	MGSWEEFDYRLYAIQDRLYALGGSEAEALAFFEWEIADFEHMLQMYKKGKGNP EVEALFQEADAIDAEHLAYRHN	CD123	4.4
613	MGSWIEFFHRLDAIQDRDLALGGSEAEALAYFEWAIADFEHMLQLYKKGKGNP EVEALQFEAFIEGELYAYRHN	CD123	3.5
614	MGSWYEFSSRLNAIDRLWALGGSEAEALAYFETDIADFEESLQWYKKGKGNP EVEALNEADAIDYELYAYRHN	CD123	3.8
615	MGSWFEEFYRLDAIIDRLFALGGSEAEALAEFESMIANFEYSLQYKKGKGNP EVEALYFEADAIVDELTAIRHN	CD123	4
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618	MGSWYEFEEERLDAIEDRLIALGGSEAEALAEFEDIIAFFEQDLQYKKGKGNP EVEALEMEAEAISIELDAYRHN	CD123	4.1
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622	MGSWEEFEDRLFAIDSRLWALGGSEAEALAEFENIIASFEEVLQYKKGKGNP EVEALSVEAFIDRELGAIRHN	CD123	3.7
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624	MGSWVEFDNRFLAIDERLWALGGSEAEALAWFEEIASFEDNLQKYKKGKGNP EVEALQLEAFAIMELDAYRHN	CD123	3.3
625	MGSWFEFDDRLLEAIFDRLWALGGSEAEALAMFEFAIAEFEDALQYKKGKGNP EVEALYEEAVAIDEELYAYRHN	CD123	4.1
626	MGSWFEFDARLMAINDRLWALGGSEAEALAEFYHIALFEDQLQMYKKGKGNP EVEALTLEAVAINELWAYRHN	CD123	4
627	MGSWVEFDSRLAAIDYRLALGGSEAEALAWFEYTIANFEHTLQMYKKGKGNP EVEALVYEAHAIAITELQAYRHN	CD123	3.4
628	MGSWTEFDERLDAIDWRLEALGGSEAEALAWFEGDIALFEQYLQVYKKGKGNP EVEALMEEADAIAELDAYRHN	CD123	4.5
629	MGSWIEFDERLDAIDFRLWALGGSEAEALAWFEGWIAEFESDLQLYKKGKGNP EVEALNEEANAIFHELSAYRHN	CD123	7
630	MGSWVEFDSRLDAIDFRLWALGGSEAEALAWFEVEIADFEWLQLYKKGKGNP EVEALWHEADAIVTELYAYRHN	CD123	3.2
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633	MGSWEEFEDRLWAIDGRLYALGGSEAEALAWFEQWIATFEEDLQDYKKGKGNP EVEALEYEASAIFFEELEYRHN	CD123	9.4
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635	MGSWFENDRDLAISERLSALGGSEAEALAYFEWQIAVFETLQNYKGKGNP EVEALTEANAI FEELEAYRHN	CD123	3.9
636	MGSWVEFMDRLAIEERLSALGGSEAEALAFFEWEIAEFEEHLQVYKGKGNP EVEALEWEALAI TEELAYRHN	CD123	4
637	MGSWIEFMDRLWAIDQRLWALGGSEAEALAWFEEI AWFEELQVYKGKGNP EVEALEWEATAI SEELWAYRHN	CD123	6.5
638	MGSWEEFNWRLRAIDERL FALGGSEAEALAWFEYDIAEFEEQLQVYKGKGNP EVEALRVEAAAIAEELYAYRHN	CD123	5.4
639	MGSWWEFEIRLDAIDERLWALGGSEAEALAWFEQSI AFFENDLQVYKGKGNP EVEALRWEANAI IEELFAYRHN	CD123	3.2
640	MGSWYEFWRDLDAIDRRLWALGGSEAEALADFEEDIA DFEWMLQNYKGKGNP EVEALVDEASAI QTELWAYRHN	CD123	10
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647	MGSWVEFSNRDLAIWERLQALGGSEAEALAYFEWEIAEFEWELQSYKGKGNP EVEALNAEADAIEWELEAYRHN	CD123	5.1
648	MGSWEEFHMRLIAIDERLWALGGSEAEALAGFEESIAYFESQLQDYKGKGNP EVEALDYEAHAIWRELYAYRHN	CD123	3.9
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652	MGSWIEFWRLEAIEERLYALGGSEAEALAYFEDEIAEFEIYLQYKGKGNP EVEALKHEAAINKELMAYRHN	CD123	5.2
653	MGSWNEFVIRLFAIDRRLYALGGSEAEALAWFEDEIATFEYELQRYKGKGNP EVEALEYEAIAIVSELFAYRHN	CD123	3.5
654	MGSWYEFRLARLYAIDERLWALGGSEAEALATFEHWIADFEELQSYKGKGNP EVEALTDEAVAIGEELSAYRHN	CD123	4.5
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656	MGSWFEFETRLEAIDRLWALGGSEAEALATFEDVIAFFEDWLQFYKGKGNP EVEALKMEAWAIGEELHAYRHN	CD123	6.6
657	MGSWHEFWQRLEAIEGRWLWALGGSEAEALADFESLIADFEELQYKGKGNP EVEALMAEAEIDNELRAYRHN	CD123	7
658	MGSWYEFQRLAIEWRLLGALGGSEAEALATFEEDIA DFEELQYKGKGNP EVEALQYEAIAIEELHAYRHN	CD123	4.4
659	MGSWYEFENRIFAIEERLWALGGSEAEALAWFEYEIANFEWGLQSYKGKGNP EVEALDNEAEIDIELAAYRHN	CD123	3.3
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661	MGSWWEFEQRLDAIETRLWALGGSEAEALAYFEHIIADFEDELQIYKGKGNP EVEALGWEAFAIDGELTAYRHN	CD123	4.7
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667	MGSWHEFIWRDLAIEERLWALGGSEAEALAWFETEIATFEAQLQDYKGKGNP EVEALEWEAIAIAWELDAYRHN	CD123	3.3
668	MGSWYEFYWRLEAIEERLWALGGSEAEALAEFEKAIATFEDQLQTYKGKGNP EVEALETEALAIHAELEAYRHN	CD123	3.7
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672	MGSWWEFLDRLEAIEYRLQALGGSEAEALAVFEWEIAMFEDHLQGYKGKGNP EVEALHSEAHAIISLSAYRHN	CD123	3.1
673	MGSWAEFEDRLAAIERRLALGGSEAEALADFESSIAWFEPDLQYYKGKGNP EVEALMYEAEAFSELYAYRHN	CD123	4.2
674	MGSWWEFYDRDLTAIEARLWALGGSEAEALADFEEGIADFEYDLQDYKGKGNP EVEALHFEAWAIQSELTAYRHN	CD123	3.2
675	MGSWYEFEDRLAAIEARLWALGGSEAEALADFEEIAYFEHGLQWYKGKGNP EVEALESEAMAIIDELHAYRHN	CD123	3.8
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677	MGSWEEFFFRLEAIDDRLYALGGSEAEALAFEEVIAYFEQDLQWYKGKGNP EVEALYVEAYAIQEELEYAYRHN	CD123	3.2
678	MGSWFEFEERLNAISWRLHALGGSEAEALAYFEEDIAWFEDDLQFYKGKGNP EVEALENEAYAIWEELDAYRHN	CD123	13
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680	MGSWAEFDDRLEAIEYRLHALGGSEAEALAWFEEGIAGFEHALQSYKGKGNP EVEALETEAGAINELWAYRHN	CD123	5.8
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686	MGSWEEFYRRLHAIDNRDLWALGGSEAEALAYFEWHIADFELELQDYKGKGNP EVEALSEEATAIFEELWAYRHN	CD123	3
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702	MGSWNEFWERDLDAIEWRLFALGGSEAEALAFFELDIWFFEEELQWYKKGKGNP EVEALIFEAHAITLELDAYRHN	CD123	3
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705	MGSWDEFWDRDLDAIEDRLFALGGSEAEALADFERVIAWFFENDLQEYKKGKGNP EVEALDNEADAIIRIELHAYRHN	CD123	3.9
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707	MGSWEEFTIRLGAIYWRLLFALGGSEAEALANFEWFIAEFYELQPYKKGKGNP EVEALVIEANAIDGELQAYRHN	CD123	3.3
708	MGSWFEFEWRDLDAIENRLNALGGSEAEALAWFEYHIAAFEDSLQHYKKGKGNP EVEALEWEAHAIQSELQAYRHN	CD123	3.3
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714	MGSWEEFHDRLMAIETRLWALGGSEAEALAAFEKEIAAFESLQAYKKGKGNP EVEWLRYEAADIRDYQLAYRHN	CD123	4.3
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716	MGSWMEFIDRLDAIEHRLWALGGSEAEALAAFEKEIAAFESLQAYKKGKGNP EVEFLREEAAEIRMYQLAYRHN	CD123	4.3
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719	MGSWYEFYDRLDAIEWRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDEAAQIRDFLQAYRHN	CD123	6.2
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721	MGSWFEFVDRLTAIQVRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLREEAALIRYSLQAYRHN	CD123	5.1
722	MGSWFEFLDRLDAIEERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDEAAQIRDFLQAYRHN	CD123	12.2
723	MGSWYEFMVRDLDAIEERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLREEAASIRYHLQAYRHN	CD123	4.1
724	MGSWYEFEDRLDAIQVRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRESAANIRQLQAYRHN	CD123	6.3
725	MGSWSEFEYRLFAIENRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLREEAAMIRQLQAYRHN	CD123	3.2
726	MGSWVEFEYRLDAITERLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEILREEAAQIRDFLQAYRHN	CD123	3.9
727	MGSWVEFLDRLDAIEMRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLREEAALIRNMLQAYRHN	CD123	9
728	MGSWVEFLDRLDAIEYRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLREEAATIRIFLQAYRHN	CD123	4.9
729	MGSWVEFESRLDAIFMRLTALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLREDAAFIREFLQAYRHN	CD123	3.7
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731	MGSWYEFYNRLSAIYARLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRWYAADIRYMLQAYRHN	CD123	10.6
732	MGSWYEFYDRLSAIYARLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRWYAADIRYMLQAYRHN	CD123	5.3
733	MGSWNEFYDRLSAIYFRLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRWYAADIRMLQAYRHN	CD123	10.6
734	MGSWNEFYDRLSAIYFRLQALGGFEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRWYAADIRMLQAYRHN	CD123	9
735	MGSWVEFYDRLGAI FARLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRWYAADIRMLQAYRHN	CD123	3.9
736	MGSWVEFYDRLHAIYFRLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRWYAADIRVLQAYRHN	CD123	4.8
737	MGSWKEFDNRLYAIEDRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRWYAADIRMLQAYRHN	CD123	3.9
738	MGSWVEFWDRLWAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRHYAADIRVWLQAYRHN	CD123	4.5
739	MGSWYEFADRLWAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRYAADIIRVWLQAYRHN	CD123	4
740	MGSWYEFEEERLYAIEDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRQEAADIRLMLQAYRHN	CD123	11.5
741	MGSWTEFEWRLYAIEDRLMALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRDEAADIRQYLQAYRHN	CD123	4.2
742	MGSWIEFESRLWAIEDRLMALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRLEAADIREDLQAYRHN	CD123	8.7
743	MGSWFEFEDRLDAIWDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRMDAAMIRYILQAYRHN	CD123	5.1
744	MGSWEEFEDRLWAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEILRYDAAYIREILQAYRHN	CD123	4.1
745	MGSWIEFEDRLYAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRYEAAEIRYWLQAYRHN	CD123	4
746	MGSWYEFWDRLAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRYSAAEIRYQLQAYRHN	CD123	4.2

747	MGSWVEFESRLAAIEHRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELREYAAEIRDWLQAYRHN	CD123	3.7
748	MGSWWEFEHRLFAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRDYAAEIRDYLQAYRHN	CD123	7.6
749	MGSWYEFDSRLMAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRQEA AEIRMLQAYRHN	CD123	3.2
750	MGSWYEFWRLEAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRHEAAEIRDVLQAYRHN	CD123	3.4
751	MGSWYEFYNRLDAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRQEAADIRGQLQAYRHN	CD123	11.3
752	MGSWWEFHDRLEAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRIEAADIRRLQAYRHN	CD123	6.4
753	MGSWYEFWDRLEAIEERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRLEAADIRRLQAYRHN	CD123	4.6
754	MGSWYEFEEERLWAEIERLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRYEAAWIRDFLQAYRHN	CD123	5.4
755	MGSWYEFENRLEAIEERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLREEAAFIRDWLQAYRHN	CD123	6.1
756	MGSWYEFYRLEAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRREEAAWIRVWLQAYRHN	CD123	6.2
757	MGSWYEFENRLGAIGDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDEAA YIRAVLQAYRHN	CD123	4.8
758	MGSWYEFEHRLDAIYDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRREEAAWIRLWLQAYRHN	CD123	6.3
759	MGSWYEFWRDLDAIYDRLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDEAAEIRALLQAYRHN	CD123	6
760	MGSWVEFENRLEAIEENRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDEAAQIRMMQLQAYRHN	CD123	6.2
761	MGSWYEFEEERLEAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRQEA AFIRTMLQAYRHN	CD123	6
762	MGSWWEFEWRLEAIFDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRAEAAEIRLRLQAYRHN	CD123	6.9
763	MGSWWEFEDRLMAIYDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRAEAA LIRETLQAYRHN	CD123	15.3
764	MGSWWEFEDRLYAIEDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRWGAATIRDELQAYRHN	CD123	4.7
765	MGSWIEFWDRLEAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRDEAAWIRDSLQAYRHN	CD123	4.5
766	MGSWWEFWDRLDAIEDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRDEAAWIRGTLQAYRHN	CD123	4.9
767	MGSWEEFTDRLWAIEDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDEAA FIRKSLQAYRHN	CD123	8.9
768	MGSWVEFVDRLEAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRDQAA YIRFMLQAYRHN	CD123	4.9
769	MGSWWEFVDRLEAIEMRFLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRWRAAMIRYDLQAYRHN	CD123	7.1
770	MGSWWEFEMRLEAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRWEAA FIRDILQAYRHN	CD123	4
771	MGSWWEFEIRLEAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRDEAAEIRQVLQAYRHN	CD123	3
772	MGSWYEFYQRLAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDEAAEIRVVLQAYRHN	CD123	3
773	MGSWIEFEDRLEAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRQEA AEIRLMLQAYRHN	CD123	21.8
841	MGSWVEFYERLDAIDRRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRVHAASIRAWLQAYRHN	P26	

842	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRAHAAAIREWLQAYRHN	P26	
843	MGSWSEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRVHAAAIREWLQAYRHN	P26	
844	MGSWSEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRAHAAAIREWLQAYRHN	P26	
845	MGSWSEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLKAHAAAIREWLQAYRHN	P26	
846	MGSWSEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLQAHAAAIREWLQAYRHN	P26	
847	MGSWSEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRAHAAAGIREWLQAYRHN	P26	
848	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLREHAAHIREWLQAYRHN	P26	
849	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLREHAAAIREWLQAYRHN	P26	
850	MGSWSEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLREHAAAIREWLQAYRHN	P26	
851	MGSWHEFYDRLDAIYFRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRLLAAEIRKELQAYRHN	P26	9.6
852	MGSWHEFITRLEAIDQRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRFWAAEIRFILQAYRHN	P26	16.91
853	MGSWMEFFDRLVAIDERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRMWAEEIRFLQAYRHN	P26	18.62
854	MGSWVEFSGRLIAIDNRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRMWAEEIRYILQAYRHN	P26	5.28
855	MGSWVEFHHRLFAIDERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRMVAEEIRYILQAYRHN	P26	21.39
856	MGSWHEFMERLIAIDGRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRVAAAFIRDVLQAYRHN	P26	17.85
857	MGSWKEFIQRLDAIHRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRVAAAFIRFELQAYRHN	P26	18.41
858	MGSWSEFIFRLDAIHSRLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLRFIAAEIRLKLQAYRHN	P26	28.3
859	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRVHAAAIREWLQAYRHN	P26	5.92
860	MGSWLEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRVHAAAIREWLQAYRHN	P26	
861	MGSWFEFYHRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRVHAAAIREWLQAYRHN	P26	
862	MGSWFEFYDRLNAIDSRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRVHAAAIREWLQAYRHN	P26	
863	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRVHAAAIREWLQAYRHN	P26	
864	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRDHAAAIREWLQAYRHN	P26	
865	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLREHAAAIREWLQAYRHN	P26	
866	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRVHAAHIREWLQAYRHN	P26	
867	MGSWLEFYHRLNAIDSRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRVHAAAIREWLQAYRHN	P26	
868	MGSWLEFYHRLNAIDSRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRDHAAHIREWLQAYRHN	P26	19.23
869	MGSWFEFYHRLNAIDSRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRDHAAHIREWLQAYRHN	P26	

870	MGSWLEFYDRLNAIDSRWLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRDHAHIREWLQAYRHN	P26	
871	MGSWLEFYHRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRDHAHIREWLQAYRHN	P26	
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873	MGSWLEFYHRLNAIDSRWLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRVHAHIREWLQAYRHN	P26	
874	MGSWLEFYHRLNAIDSRWLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRDHAHIREWLQAYRHN	P26	
875	MGSWFEFYDRLNAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRDHAHIREWLQAYRHN	P26	
876	MGSWFEFYERLNAIDSRWLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRAHAASIRTWLQAYRHN	P26	27.1
877	MGSWIEFYWRLEAIDQRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRVHAHIREWLQAYRHN	P26	9.4
878	MGSWSEFVKRLDAIDQRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRVHAHIREWLQAYRHN	P26	27
879	MGSWEEFYRLEAIDARLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRVHAHIREWLQAYRHN	P26	30.3
880	MGSWVEFYHRLQAIIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRVHAHIREWLQAYRHN	P26	14.8
881	MGSWVEFVGRLEAIDARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRHAAHIREWLQAYRHN	P26	26
882	MGSWNEFMDRLNAIDNRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRKQAASIRLWLQAYRHN	P26	10
883	MGSWNEFFQRLNAIDRRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRQHAANIRWWLQAYRHN	P26	28.7
884	MGSWYEFVVRLEAIDRRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLREHAHIREWLQAYRHN	P26	18.25
885	MGSWYEFYRLDAIDHRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLREHAHIREWLQAYRHN	P26	16
886	MGSWYEFRRLLAIDRRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLREHAHIREWLQAYRHN	P26	20.9
887	MGSWTEFWHRLAIDSRWLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLREHAHIREWLQAYRHN	P26	13.19
888	MGSWTEFQNRLEAIDHRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLREHAHIREWLQAYRHN	P26	30.5
889	MGSWSEFFKRLAIDRRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELREHAHIREWLQAYRHN	P26	30.2
890	MGSWYEFQQRLEAIDTRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELREHAHIREWLQAYRHN	P26	27.3
891	MGSWTEFEKRLAIDYRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLREHAHIREWLQAYRHN	P26	17.1
892	MGSWTEFHQRLAIDRRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLREHAHIREWLQAYRHN	P26	24.4
893	MGSWLEFSQRLTAIDSRWLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLREHAHIREWLQAYRHN	P26	30.4
894	MGSWTEFVNRLAIDSRWLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEGLRTHAAHIREWLQAYRHN	P26	16.7
895	MGSWMEFVDRLEAIDRRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLREHAHIREWLQAYRHN	P26	32.1
896	MGSWVEFVSRLEAIDFRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALREHAHIREWLQAYRHN	P26	29
897	MGSWSEFHTRLAIDTRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRRHAHIREWLQAYRHN	P26	23.5

898	MGSWLEFHSRLDAIDTRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLEHAAAIRHYLQAYRHN	P26	30.8
899	MGSWTEFYQRLDAIDTRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEGLRQQAQIRAWLQAYRHN	P26	29.7
900	MGSWAEFSDRLNAIDQRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEILREHAAEIRKFLQAYRHN	P26	25.3
901	MGSWMEFNHRLQAIDGRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLREHAAAIRAFLQAYRHN	P26	33.4
902	MGSWYEFYKRLEAIDNRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLREHAAAIRHWLQAYRHN	P26	30.8
903	MGSWYEFYRLEAIDNRLIALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLREHAAKIREWLQAYRHN	P26	29.6
904	MGSWYEFVSRLEAIDDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEMLRQHAAAIRHWLQAYRHN	P26	33.1
905	MGSWYEFYSHRLEAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEPLREHAAIYIRHWLQAYRHN	P26	26
906	MGSWFEFFERLAAIEDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRVHAAAIRAFLQAYRHN	P26	20.3
907	MGSWIEFKYRLDAIEWRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRIHAAAIRTWLQAYRHN	P26	18.3
908	MGSWYEFMYRLDAIEYRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRIHAAMIREWLQAYRHN	P26	19.4
909	MGSWVEFVTRLEAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRAHAAHIRHWLQAYRHN	P26	11.7
910	MGSWYEFVIRLDAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRVHAAHIRVWLQAYRHN	P26	30.1
911	MGSWVEFVERLDAIEFRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRNHAHHSRWLQAYRHN	P26	23.8
912	MGSWSEFVHRLDAIEVRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRYHAAKIRSWLQAYRHN	P26	16.9
913	MGSWSEFYRLAAIESRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVERLREHAAHIRRWLQAYRHN	P26	30.8
914	MGSWYEFYRLSAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRVQAAHIRTWLQAYRHN	P26	27.4
915	MGSWYEFYDRDLAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRDQAAIYRTWLQAYRHN	P26	31.9
916	MGSWHEFWVRLEAIESRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRVQAAHIRSWLQAYRHN	P26	26.9
917	MGSWVEFYHRLAIEQRLMALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLREQAAAIRSWLQAYRHN	P26	28.5
918	MGSWVEFYERLNAIEYRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLREHAAIYRQWLQAYRHN	P26	28.7
919	MGSWVEFYHRLDAIFDRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRANAAGIRSWLQAYRHN	P26	20
920	MGSWSEFTDRLFAIEDRLLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRMHAASIRLWLQAYRHN	P26	25.4
921	MGSWHEFYDRLYAIWDRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEGLRNAAVIRIFLQAYRHN	P26	22.91
922	MGSWFEFSNRLYAIWHRLTALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRTQAAFIRILQAYRHN	P26	15.25
923	MGSWFEFSDRLYAIWERLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRFQAAFIYRQLQAYRHN	P26	18.99
924	MGSWFEFEDRLFIAIWRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRQSAASIRWLLQAYRHN	P26	10.89
925	MGSWHEFSERLFAIWRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRQSAAFIRVMLQAYRHN	P26	8.21

926	MGSWGFTVRLYAIIDRLDALGGSEAEALAAFEKEIAAFSESELQAYKGKGNP EVEELRRFAALIRAFLLQAYRHN	P26	8.54
927	MGSWYEFDRHLMASIFRLVALGGSEAEALAAFEKEIAAFSESELQAYKGKGNP EVETLRRRAANIRHLLQAYRHN	P26	20.1
928	MGSWISIFKYHLADIKLLEALGGSEAEALAYFEFLIADFETLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	20.21
929	MGSWHHFKYFLADIKSILEALGGSEAEALIFEVQIAYFEDLLQSYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	8
930	MGSWLYFKYNLAVIKHWLEALGGSEAEALIFEMSIADFEYELQWYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	13.3
931	MGSWFYFKYELAWIKHWLEALGGSEAEALASFETHIAFFEHQLQYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	13.7
932	MGSWADFKWTLAYIKHRLEALGGSEAEALAFFEMEIAFFEQLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	31.5
933	MGSWAYFKQLLAYIKSGLEALGGSEAEALAYFELRIAYFEHWLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	11.4
934	MGSWENFKDTLAWIKYLEALGGSEAEALAGFEHRIAFEHYQLQYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	19.2
935	MGSWVLFKDYLADIKHYLEALGGSEAEALANFEHLIANFEGDLQTYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	13.8
936	MGSWSLFKHRLANIKVYLEALGGSEAEALADFETFIAYFEKDLQYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	19.6
937	MGSEWHFKVELAGIKAYLEALGGSEAEALALFEWAIADFESILQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	18.1
938	MGSWIYFKDELAGIKYLEALGGSEAEALAMFEVAIADFEAILQKYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	15.9
939	MGSWVLFKQELAWIKWLLEALGGSEAEALAFEEQIARFEHDLQKYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	29.5
940	MGSWVLFKQELAWIKWYLEALGGSEAEALAFWEIAAFEQRLQIYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	22.5
941	MGSWVLFKSELAWIKWRLEALGGSEAEALAYFEYQIAEFEFWLQSYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	25.8
942	MGSWLFLKSELAWIKWYLEALGGSEAEALAEFEWNIAEFKLNQKYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	25.7
943	MGSWLFLKSDLAWIKWRLEALGGSEAEALAEFEESIAMFEHWLQYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	33.3
944	MGSWLYFKSDLAWIKWRLEALGGSEAEALADFEETIAEFQALQIYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	21.2
945	MGSWKLFKYELAWIKWRLEALGGSEAEALADFEASIAQFEKYLQTYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	23.4
946	MGSWYLFKNELAWIKWRLEALGGSEAEALADFEMVIAMFEDHLQYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	31.1
947	MGSWVYFKAHLAFIKWELEALGGSEAEALANFESTIAEFKYLQVYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	20.8
948	MGSWMYFKSHLAWIKWELEALGGSEAEALAFFEDNIAQFEYWLQLYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	19.8
949	MGSWTLFKWDLAFIKWQLEALGGSEAEALAWFEYEIAAFEDSLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	12.1
950	MGSWILFKEDLAFIKWQLEALGGSEAEALAWFETTIANFESDLQKYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	23.3
951	MGSWYFFKSRLAYIKVYLEALGGSEAEALAGFEWEIAHFEEWLQRYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	30.1
952	MGSWYIFKSELAWIKWYLEALGGSEAEALANFEVEIATFETWLQGYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	29.6
953	MGSWYIFKQELASIKLSLEALGGSEAEALAHFEAEIAWFEEWLQWYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	19.4

954	MGSWVRFKTELAYIKESLEALGGSEAEALAMFESEIAI FEHSLQTYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	20.5
955	MGSWYLFKTELAIAIKYRLEALGGSEAEALASFEYEIAWFEHILQFYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	20.1
956	MGSWYWFKYELAEIKWHLEALGGSEAEALAHFEHSAIVFESQLQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	21.5
957	MGSWVVFKKTLAEIKWTLALGGSEAEALAYFEAEIAFFEFILQQYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	18.6
958	MGSWVYFKDHLAEIKSQLEALGGSEAEALALFEYDIWFEFILLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	22.1
959	MGSWVYFKHRLAEIKDQLEALGGSEAEALAEFETDIWFEWMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	11.1
960	MGSWIIFKTDLARIKNYLEALGGSEAEALATFERDIWFEFMLQIYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	16.7
961	MGSWMHFKQDLAEIKGYLEALGGSEAEALAI FEMDIWFEYMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	18.9
962	MGSWQIFKQDLAAIKDYLEALGGSEAEALAI FEFDIWFEHMLQWYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	17.4
963	MGSWLAFKEDLAHIKSILEALGGSEAEALAEFEHDIWFEYMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	18.6
964	MGSWVYFKEDLAGIKFILLEALGGSEAEALAMFETDIWFEYMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	14.2
965	MGSWTHFKEDLAHIKDRLEALGGSEAEALAAFELDIWFEFMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	30.4
966	MGSWYFYKERLAAIKDRLEALGGSEAEALAI FEADIWFEFMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	31.5
967	MGSWYTFKGS LAEIKNRLEALGGSEAEALAMFESDIWFEFMLQFYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	32.3
968	MGSWFTFKDDLAQIKNRLEALGGSEAEALANFEMSIWFEFMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	30.8
969	MGSWVLFKQDLAMIKQRLEALGGSEAEALAMFEYDIWFEHMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	29.7
970	MGSWVEFKRDLANIKQRLEALGGSEAEALAQFEMQIAWFEHTLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	30.4
971	MGWSYFKEDLANIKSSLEALGGSEAEALAWFESSIAWFEHTLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	11.6
972	MGWSIFKQDLADIKDSLEALGGSEAEALAMFEMDIWFEHTLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	16.6
973	MGSWEIFKDDLASIKKVLEALGGSEAEALALFESDIWFEMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	27.9
974	MGWSIFKDDLAVIKERLEALGGSEAEALAHFEQDIWFEHLLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	25.6
975	MGWSVFKDDLAQIKDRLEALGGSEAEALAQFELDIWFEYVLQFYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	30.3
976	MGSWAVFKDSLAIKIDVLEALGGSEAEALALFEMDIWFEYVLQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	24.1
977	MGSWIAFKDHLAIKQRLEALGGSEAEALARFEFEIAWFEWMLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	29.9
978	MGSWIHFKNDLAVIKDELEALGGSEAEALARFEIMIWFEDALQWYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	17.9
979	MGSWMVFKQDLAEIKANLEALGGSEAEALADFEFAIAWFEYELQWYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	17.8
980	MGSWKNFKLELALIKSKLEALGGSEAEALAQFEADIAFFEWSLQWYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	20.6
981	MGSWHSFKQDLAYIKYLLEALGGSEAEALAQFEELIAFFEYLLQTYKGKGNP EVEALRKEAAAIRDELQAYRHN	P26	25.6

982	MGSWVVKSSLAQIKILLEALGGSEAEALAEFEVKIAHFEQELQYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	P26	8.6
983	MGSWDQFKNSLASIKRVLEALGGSEAEALAEFEVKIAHFEHFLQYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	P26	15.6
984	MGSWNNFKSSLASIKQVLEALGGSEAEALAVFELQIAHFERELQYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	P26	24.1
985	MGSWVEFGHRLWAIDQRLYALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEKLRQRAAFIRFRLQAYRHN	CD137	
986	MGSWVEFANRLWAIDQRLFALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEHLRDQAAFIIRHKLQAYRHN	CD137	
987	MGSWYEFHRHLWAIDQRLYALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEGLREAAAFIRAKLQAYRHN	CD137	
988	MGSWYEFMRHLWAIDQRLYALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRAKAAIIRWKLQAYRHN	CD137	
989	MGSWYEFHRLWAIDQRLYALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEYLRETAAHIRTRLQAYRHN	CD137	
990	MGSWYEFHYRLWAIDQRLYALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEELRIKAAFIIRDLQAYRHN	CD137	
991	MGSWAEFKQRLAAIKTRLEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALGREAAAIIRMLQAYRHN	CD137	
992	MGSWYEFDLRLHAIYDRLVALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEILRDNAAYIRQMLQAYRHN	CD47	
993	MGSWTEFTYRLSAIEWRLWALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALKHEAGAILNLMAYRHN	CD47	
994	MGSWAEFDHRLHAIRERLHALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEILRGNAAYIRALLQAYRHN	CD47	
995	MGSWTEFVGRLLAAIEFRLWALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALREEAGAIMELKAYRHN	CD47	
996	MGSWTEFYRLEAIWVRLQALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALHEEAIAIRKELAAAYRHN	CD47	
997	MGSWHEFHDLQAIHERLYALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVESLRIAAAHIRQVLQAYRHN	CTLA4	
998	MGSWNYFKDHLAWIKNSLEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
999	MGSWLYFKEHLAHIKAWLEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
1000	MGSWVYFKEHLAWIKTELEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
1001	MGSWFYFKQHLAWIKSYLEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
1002	MGSWHYFKDHLAEIKGLLEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
1003	MGSWHYFKGHLAEIKNHLEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
1004	MGSWIYFKEHLAYIKKELEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
1005	MGSWTYFKEHLAEIKYMLEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
1006	MGSWWLFKDHLAEIKTALEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRKEAAAIIRDELQAYRHN	DR5	
1007	MGSWSEFYNRDLAIESRLALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEALRGEARAIIRFALYAYRHN	KIR	
1008	MGSWYEFYNRLYAIEIRLYALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVERLRVRAAKIRVILQAYRHN	KIR	
1009	MGSWLWFKI FLAEIKYFLEALGGSEAEALAEFEKEIAAFESSELQAYKKGKGNP EVEVLREVAEIRWDLQAYRHN	KIR	

1010	MGSWTEFQSRDLAIHSRLRALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRDDAAFI RHFLQAYRHN	PDL1	
1011	MGSWQEFDDRLNAIKARLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRDDAAFI RHFLQAYRHN	PDL1	
1012	MGSWYEFQNRHLHAIHERLNALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVELLRDDAAFI RHFLQAYRHN	PDL1	
1013	MGSWFEFQDRLTAINERLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRSDAAFI RHFLQAYRHN	PDL1	
1014	MGSWYEFESRLDAIHERLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRGDAAFI RHFLQAYRHN	PDL1	
1015	MGSWYEFNHRDLAISKRNLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRGDAAFI RHFLQAYRHN	PDL1	
1016	MGSWFEFENRLHAIHVRLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRADAAFI RHFLQAYRHN	PDL1	
1017	MGSWVVFVKVDLATIKYILEALGGSEAEALAEFEKEIAGFEYSLQFYKGKGNP EVEALRKEAAAI RDELQAYRHN	TIM3	
1018	MGSWTIFKEWLAFIKTDLEALGGSEAEALAEFEKEIASFEMELQKYKGKGNP EVEALRKEAAAI RDELQAYRHN	PD1	
1019	MGSWVMFKWLLADIKSHLEALGGSEAEALAEFEKEIAAFETHLQVYKGKGNP EVEALRKEAAAI RDELQAYRHN	PD1	
1020	MGSWYAFKDYLDIKGWLEALGGSEAEALAEFEKEIFIARFELELQAYKGKGNP EVEALRKEAAAI RDELQAYRHN	PD1	
1021	MGSWAEFKQRLAAIKTRLEALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEALRKEAAAI RDELQAYRHN	None known	
1030	MGSWEEFELRLNAIEERLYALGGSEAEALAEFEKEIAAFETHLQVYKGKGNP EVEALYFEADAI FEELVAYRHN	CD19	
1031	MGSWFEFNHRLWAI FERLMALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYL RAMAAVIRYHLQAYRHN	CD19	
1032	MGSWEEFDGRLFAIEQRLQALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEVLRWFAAGIRDFLQAYRHN	CD19	
1033	MGSWAEFYHRLYAIETRLSALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYL RHWAAWIRTYLQAYRHN	CD19	
1034	MGSWVEFSDRLYAI EERLWALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEELRELAAI IRHSLQAYRHN	CD19	
1035	MGSWWEFEGRLYAI EERLTALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYLREWAAWIRQMLQAYRHN	CD19	
1036	MGSWWEFEHRLYAI EERLVALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYL RNWAAI RYRMALQAYRHN	CD19	
1037	MGSWWEFEARLYAIEFRLSALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYLRSWAAI IRTSLQAYRHN	CD19	
1038	MGSWWEFEARLWAI ESRLKALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYL RHWAAYIRVILQAYRHN	CD19	
1039	MGSWWEFEARLYAIEFRLSALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYLRSWAAI IRTSLQAYRHN	CD19	
1040	MGSWEEFYHRLDAIELRLYALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYL RWYAAEIREILQAYRHN	CD19	
1041	MGSWYEFYERLDAIDTRLWALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEFLREYAAEIRHFLQAYRHN	CD19	
1042	MGSWNEFFDRLDAI LYRLDALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEYLRFVAADIRSWLQAYRHN	CD19	
1043	MGSWIEFDDRLLAIMDRWLALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEDLRDVAADIRHYLQAYRHN	CD19	
1044	MGSWYEFWERLDAITFRLYALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEDLRTWAADIRAILQAYRHN	CD19	
1045	MGSWEEFYIRLDAIMERLWALGGSEAEALAEFEKEIAAFESSELQAYKGKGNP EVEDLRYAAADIRHFLQAYRHN	CD19	

1046	MGSWIEFEERLYAIETRLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRVVAADIREWLQAYRHN	CD19	
1047	MGSWIEFEHRLSAINDRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLREWAADIRSLQAYRHN	CD19	
1048	MGSWFEFEMRLDAIMARLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRYAAADIRDYLQAYRHN	CD19	
1049	MGSWYEFVYRLDAIYDRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRYAAADIRDFLQAYRHN	CD19	
1050	MGSWVEFEDRLDAILERLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRELAADIRDFLQAYRHN	CD19	
1051	MGSWFEFEERLIAIEERLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEYLWIAADIRDLVQAYRHN	CD19	
1052	MGSWIEFADRLDAILDRLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLREIAADIRAYLQAYRHN	CD19	
1053	MGSWLEFEYRLDAILDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLREVAADIRMLQAYRHN	CD19	
1054	MGSWYEFHDLRLDAITNRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRDWAADIRVWLQAYRHN	CD19	
1055	MGSWQEFQRLDAINWRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELREWAADIRIFLQAYRHN	CD19	
1056	MGSWYEFYSLRLDAIDSRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRDYAAEIRRYLQAYRHN	CD19	
1057	MGSWEEFHDLRLDAISDLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRDWAADIRFYLQAYRHN	CD19	
1058	MGSWWEFDERLYAIEDRLFALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRIVAADIREILQAYRHN	CD19	
1059	MGSWEEFEYRLMAIEVRLWALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLREIAADIRQILQAYRHN	CD19	
1060	MGSWVVFQRLAYIKDLLEALGGSEAEALAYFEMSIAFFEDLQVYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD22	
1061	MGSWYEFKNDLAWIKVHLEALGGSEAEALAYFEFRIAHFENALQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	CD22	
1062	MGSWVEFYNRLWAIDHRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRYHAASIRVTLQAYRHN	CD22	
1063	MGSWSEFYDRLHAIHRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRDTAAAFIRTRLQAYRHN	CD22	
1064	MGSWKEFHRLHAIHRLIALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEFLRAKAANIRTHLQAYRHN	CD22	
1065	MGSWFEFHRLHAIYGRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRAHAHIRDHLQAYRHN	CD22	
1066	MGSWYEFADRLHAIHQRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRMTAAAFIRSRLQAYRHN	CD22	
1067	MGSWNEFYNRLHAIHQRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRQTAAYIRDRLQAYRHN	CD22	
1068	MGSWNEFADRLHAIHQRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRMTAAAFIRSRLQAYRHN	CD22	
1069	MGSWTEFSYRLGAIQSRHLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEHLRYNAAKIRHFLQAYRHN	CD22	
1070	MGSWQEFTRLEAIYHRLRALGGSEAEALANFEGFIAEFEGNLQMYKGKGNP EVEALVHEAYAIMELHAYRHN	DR5	
1071	MGSWVEFFDRLKAIHDRLEALGGSEAEALAHFEKLIHFEHRLQNYKGKGNP EVEALEKEADAILYELAAYRHN	DR5	
1072	MGSWYFYKHLAWIKMELEALGGSEAEALAHFESSIASFERDLQYYKGKGNP EVEALRKEAAAIRDELQAYRHN	DR5	
1073	MGSWVEFHRLHAIQYRLYALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRHWAAFIRLQLQAYRHN	DR5	

1074	MGSWNEFHDRINAHERLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRDDAAFIIRRLQAYRHN	PDL1	
1075	MGSWYEFTRVLEAHERLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEILRDDAAFIIRRLQAYRHN	PDL1	
1076	MGSWKEFDDRLNAIKARLQALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRDDAAFIIRRLQAYRHN	PDL1	
1077	MGSWYEFDDRLNAIHDRQLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEDLRDDAAFIIRRLQAYRHN	PDL1	
1078	MGSWNEFKNRDLAIHKRLNALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVENLRDDAAFIIRHFLQAYRHN	PDL1	
1079	MGSWTEFEQRLEAIHNRQLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEELRNDAAFIIRHFLQAYRHN	PDL1	
780	MGSWVEFEARLSAIYERLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRRHAAGIRSNLQAYRHN	CS1	
781	MGSWVEFFVRDLAIWERLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRFHAAGIRQKLQAYRHN	CS1	
782	MGSWTEFNRLDAIYERLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEALRWHAAGIRQQLQAYRHN	CS1	
783	MGSWMEFYDRDLAIWVRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRFAAGIREQLQAYRHN	CS1	
784	MGSWHEFNGRLWAIYARLDALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRRHAAGIRGILQAYRHN	CS1	
785	MGSWYEFVQRLHAIINDRLSALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRRAAGIRYTLQAYRHN	CS1	
786	MGSWAEFYQRLNAIWNRLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEVLRRAAGIRGQLQAYRHN	CS1	
787	MGSWVEFNERLHAIYLRDLALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRRHAAGIRWQLQAYRHN	CS1	
788	MGSWNEFKLELAFIKDWLEALGGSEAEALANFEEAIAEFEAGLQGYKGKGNP EVEALRKEAAAIRDELQAYRHN	CS1	
789	MGSWMEFEARLEAIWDRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVESLRFHAAGIRQHLQAYRHN	CS1	
790	MGSWVEFEDRLNAIWRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEKLRRHAAGIRTQLQAYRHN	CS1	
791	MGSWHHFKMHLAGIKLQLEALGGSEAEALAEFEWIADEFEGALQDYKGKGNP EVEALRKEAAAIRDELQAYRHN	CS1	
792	MGSWAEFFARLDAIWERLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRFHAAGIRQKLQAYRHN	CS1	
793	MGSWAEFFARLDAIWDRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLRFHAAGIRQKLQAYRHN	CS1	
794	MGSWAEFFARLDAIWERLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLKFHAAGIRQKLQAYRHN	CS1	
795	MGSWAEFFARLDAIWDRLEALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVETLKFHAAGIRQKLQAYRHN	CS1	
800	MGSWHEFRWRFLAIWQRLHALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRDLAALIRVMLQAYRHN	HER2	10.02
801	MGSWAEFRWRLHAIWLKLGELGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLREDAEQIKYILQAYRHN	HER2	
802	MGSWAEFRWALHAIWLKLGELGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLREDAEQIKYILQAYRHN	HER2	
803	MGSWAEFRWRLHAIWLKLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRQDAAQIKYILQAYRHN	HER2	
804	MGSWAEFRWRLHAIWLQLGALGGSEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRQDAAQIKYILQAYRHN	HER2	
805	MGSWAEFRWRLHAIWRLGALGGTEAEALAAFEKEIAAFESSELQAYKGKGNP EVEWLRQDAAQIKYILQAYRHN	HER2	

806	MGSWAEFRWRLHAIWLRLGALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEWLRQDAAQIKYILQAYRHN	HER2	
807	MGSWAEFRWKLEAIWLRLGALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEWLRQDAAQIKYILQAYRHN	HER2	
808	MGSWAEFRWKLGAIWLRLGALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEWLRQDAAQIKYILQAYRHN	HER2	
809	MGSWYEFWRWRLHAIWLRLGALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEWLRQDAAQIRYILQAYRHN	HER2	7.18
810	MGSWHEFLRRLLAIEMLRYALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEHLRVRAASIRQMLQAYRHN	HER2	8.15
811	MGSWWGFKNVLAWIKWKLEALGGSEAEALAYFELWIANFEHSLQEYKGKGNP EVEALRKEAAAIRDELQAYRHN	HER2	8.69
812	MGSWVNFKTHLARIKVHLEALGGSEAEALALFEHDIANFEQVLQYQYKGKGNP EVEALRKEAAAIRDELQAYRHN	HER2	7.91
813	MGSWLVFKDELAKIKNYLEALGGSEAEALATFEQDIWFQWLQNYKGKGNP EVEALRKEAAAIRDELQAYRHN	HER2	3.28
814	MGSWKTFKIELAGIKLELEALGGSEAEALAGFENAIQFESSLQYQYKGKGNP EVEALRKEAAAIRDELQAYRHN	HER2	4.95
815	MGSWWEFKVRLSAIQYRLYALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEALREQAALIRTILQAYRHN	HER2	5.17
816	MGSWWEFHIRLHAINRYLAALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEALRELAAKIRGDLQAYRHN	HER2	11.90
817	MGSWWEFQVRLRAIQYRLNALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEYLRGLAAQIRFDLQAYRHN	HER2	14.39
818	MGSWWEFKIRLYAIEYRLNALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEALRAKAAQIRYNLQAYRHN	HER2	4.49
819	MGSWWFEFNIRLHAIYRLKALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEELRNYAASIRKLLQAYRHN	HER2	7.86
820	MGSWWFEFIRLRAIEYRLSALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEKLRELAAEIRYALQAYRHN	HER2	7.75
821	MGSWWFEFKIRLYAIEYRLSALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEELRNLAIEIRHSLQAYRHN	HER2	13.08
822	MGSWWFEFKVRLRAIEYRLSALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEELRVLAASIRIHLQAYRHN	HER2	10.09
823	MGSWSEFWFRLHAILYRLQALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVETLRDAAAEIRVALQAYRHN	HER2	14.79
824	MGSWIEFWVRLNAILYRLYALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEALRDSAAEIRRWLQAYRHN	HER2	3.91
825	MGSWWVEFWIRLNAIKYRLALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEKLRQDAADIRELLQAYRHN	HER2	10.62
826	MGSWTEFWWRLSAIVYRLNALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEELRDMAADIRSLQAYRHN	HER2	5.76
827	MGSWWFEFYRLRAISYRLQALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEGLRQDAAEIRKLLQAYRHN	HER2	5.10
828	MGSWWFEFVRLRAIEYRLLEALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEQLRLIAANIRHLLQAYRHN	HER2	5.48
829	MGSWWFEFVRLKAIEYRLALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEDLRYIAANIRQLLQAYRHN	HER2	4.56
830	MGSWWFEFKVRLKAIEYRLALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEDLRYIAANIRQLLQAYRHN	HER2	
831	MGSWWFEFQVRLAAIEYRLKALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVENLRQLAAHIRSVLQAYRHN	HER2	6.33
832	MGSWWFEFQVRLSAIEYRLTALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEELRQKAARIRSLQAYRHN	HER2	9.61
833	MGSWWFEFNIRLHAIDYRLKALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVELLREKAAQIRAQLQAYRHN	HER2	9.75

834	MGSWWEFVRLEAIDYRLKALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEYLRKKAATIRAILQAYRHN	HER2	6.82
835	MGSWYEFDIRLEAIKYRLSALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEYLRKKAIVIRSMQLQAYRHN	HER2	5.35
836	MGSWWEFRIIRLEAIWYRLHALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEDLRIFAANIRSKLQAYRHN	HER2	8.04
837	MGSWWEFNVRLQAIKYRLSALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEDLRKTAHIRWQLQAYRHN	HER2	5.23
838	MGSWWEFNVRLSAIRYRLALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEDLRASAAQIRAMLQAYRHN	HER2	6.73
839	MGSWWEFNMRLSAIKYRLYALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEILRRLAADIRERLQAYRHN	HER2	3.08
840	MGSWWEFHIRLRAIKYRLYALGGSEAEALAAFEKEIAAFESELQAYKGKGNP EVEDLRILAAEIRAQLQAYRHN	HER2	14.79

Table 4. Exemplary Antigenic Determinant Sequences

SEQ ID	Antigen	Sequence
2	CD19	MPPPRLLFFLLFLTPEVVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRESPLKPFLL KLSLGLPGLGIHMRPLAIWLFIFNVSQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGELFRW NVSDLGGLGCGLKNRSSEGPPSPSGKLMSPKLYVWAKDRPEIWEGEPPCLPPRDSLNQSLSQ DLTMAPGSTLWLSGCVPPDSVSRGPLSWTHVHPKGPKSLLSLELKDDRPARDMWMETGLLL PRATAQDAGKYYCHRGNLTMSEHLEITARPVLWHWLLRTGGWK
3	CD19 - Signal	PEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTWSRESPLKPFLLKLSLGLPGLGIHMRPLAIW LFIFNVSQMGGFYLCQPGPPSEKAWQPGWTVNVEGSGELFRWNVSDLGGLGCGLKNRSSEG PPSPSGKLMSPKLYVWAKDRPEIWEGEPPCLPPRDSLNQSLSQDLTMAPGSTLWLSGCVPPD SVSRGPLSWTHVHPKGPKSLLSLELKDDRPARDMWMETGLLLPRATAQDAGKYYCHRGNL TMSEHLEITARPVLWHWLLRTGGWK
4	BCMA	MLQMAGQCSQNEYFDSLHACIPQCLRCSSNTPPLTCQRYCNASVTNSVKGTNAILWTCLGL SLIISLAVFVLMFLLRKINSEPLKDEFKNTGSGLLGMANIDLEKSRGTDEIILPRGLETYVE ECTCEDCIKSKPKVDSHCFPLPAMEEGATILVTTKTNDYCKSLPAALSATEIEKSISAR
5	BCMA_ECD	MLQMAGQCSQNEYFDSLHACIPQCLRCSSNTPPLTCQRYCNASVTNSVKGTNA
6	CD20	AGIYAPI
7	CD20	FLKMESLNFIRAHTP
8	CD20	EPANPSEK
9	CD20	KISHFLKMESLNFIRAHTPYINIYNCEPANPSEKNSPSTQYCYSIQS
10	CD20	PICVTV
11	CD123 - Signal	TKEDPNPPITNLRMKAKAQQLTWDLNRNVTDIECVKDADYSMPAVNNSYCQFGAISLCEVTN YTVRVANPPFSTWILFPENSGKPWAGAENLTCWIHDVDFLSCSWAVGPGAPADVQYDLYLNV ANRRQQYECLHYKTDAGTRIGCRFDDISRLSSGSQSSHILVRGRSAAFIPCTDKFVVSQ IEILTTPNMTAKCNKTHSFMHWKMRSHFNKFRYELQIQKRMQPVITEQVRDRTSFQLLNPG TYTVQIRARERVYEFSAWSTPQRFECDEEGANTRAWR
12	CD37	DKTSFVSFVGLAFVPLQIWSK
13	CD37	RAQLERSLRDVVEKTIQKYGTNPEETAEEESWDYVQFQLRCCGWHYPQDWFQVLIILRNGSE AHRVPCSCYNLSATNDSTILDKVILPQLSRLGHLARSRHSADICAVPAESHIYREGCAQGLQ KWLHNN

14	AFP	MKWVESIFLIFLLNFTESTRTLHRNEYGIASILDSYQCTAEISLADLATIFFAQFVQEATYKE VSKMVKDALTAIEKPTGDEQSSGLENQLPAFLEELCHEKEILEKYGHSDCCSQSEEGRHNC FLAHKKPTPASIPLFQVPEPVTSCAEYEEDRETFMNKFITYEIAARRHPFLYAPTILLWAARYD KIIPSCCKAENAVECFQTKAATVTKELRESSLLNQHACAVMKNFGTRTFQAITVTKLSQKFT KVNFTETIQKLVLDVAHVHEHCCRGDVLDCIQDGEKIMSYICSQDDTLNKNITECCKLTTLER GQCIHAENDEKPEGLSPNLNREFLGDRDFNQFSSGEKNIFLASFVHEYSSRRHPQLAVSVILR VAKGYQELLEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVA YTKKAPQLTSSELMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNP VGQCCTSSYANRRPCFSSLVVDETYVPPAFSDDKFI FHKDLCQAQGVALQTMKQEFNLINLVK QKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCFAEEGQKLI SKTRALGV
15	AFP - Signal	RTLHRNEYGIASILDSYQCTAEISLADLATIFFAQFVQEATYKEVSKMVKDALTAIEKPTGD EQSSGLENQLPAFLEELCHEKEILEKYGHSDCCSQSEEGRHNCFLAHKKPTPASIPLFQVP EPVTSCAEYEEDRETFMNKFITYEIAARRHPFLYAPTILLWAARYDKIIPSCCKAENAVECFQTKAATVT KELRESSLLNQHACAVMKNFGTRTFQAITVTKLSQKFTKVNFTETIQKLVLDVAHVH EHCCRGDVLDCIQDGEKIMSYICSQDDTLNKNITECCKLTTLERGQCIHAENDEKPEGLSP NLNREFLGDRDFNQFSSGEKNIFLASFVHEYSSRRHPQLAVSVILRVAKGYQELLEKCFQTENP LECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITR KMAATAATCCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSS LVVDETYVPPAFSDDKFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFS GLLEKCCQGQEQEVCFAEEGQKLI SKTRALGV
16	P26	LEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQL TSSELMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSS YANRRPCFSSLVVDETYVPPAFSDDKFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEE QLEAVIADFSGLLEKCCQGQEQEVCFAEEGQKLI SKTRALGV
1117	P26Q217P	LEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQL TSSELMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSS YANRRPCFSSLVVDETYVPPAFSDDKFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEE QLEAVIADFSGLLEKCCQGQEQEVCFAEEGPKLI SKTRALGV
1118	P26 (Q26- V229)	QESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAFSDD KFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQEVC FAEEGQKLI SKTRALGV
1119	P26 (Q26- V229) Q217P	QESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAFSDD KFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQEVC FAEEGPKLI SKTRALGV
1120	p26 (K23- V229)	KYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQL SEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAF SDDKFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQ EVCFAEEGQKLI SKTRALGV
1121	p26 (K23- V229) Q217P	KYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQL SEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAF SDDKFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQ EVCFAEEGPKLI SKTRALGV
1122	p26 (G17- V229)	GEEELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATA ATCCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSSLVVDET YVPPAFSDDKFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGLLEK CQGQEQEVCFAEEGQKLI SKTRALGV
1123	p26 (G17- V229) Q217P	GEEELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATA ATCCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSSLVVDET YVPPAFSDDKFI FHKDLCQAQGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGLLEK CQGQEQEVCFAEEGPKLI SKTRALGV

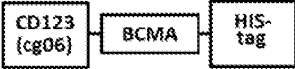
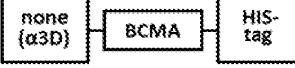
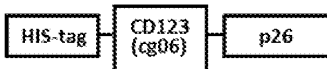
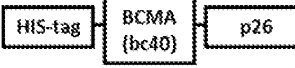
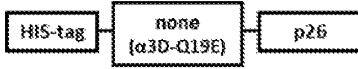
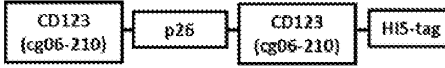
41	CD22 mature ECD	DSSKWVFEHPETLYAWEGACVWIPCTYRALDGDLESFILFHNPEYNKNTSKFDGTRLYESTKDGKVPSE QKRQVQFLGDKNKNCTLSIHPVHLNDSGQLGLRMESKTEKWMERIHLNVSERPFPPHIQLPPEIQESQEV TLTCLLNFSYCYGPIQLQWLLEGVPMRQAAVTSTSLTIKSVFTRSELKFSPOWSSHGKIVTCQLQDADG KFLSNDTVQLNVKHTPKLEIKVTPSDAIVREGDSVTMTCEVSSSNPEYTTVSWLKDGTSLKKQNTFTLN LREVTQDQSGKYCCQVSNDVGPGRSEEVFLQVQYAEPEPSTVQILHSPAVEGSQVEFLCMLANPLPTNY TWYHNGKEMQGRTEEKVHI PKILPWHAGTYSVAENILGTGQRGPGAELDVQYPPKVTTVIQNPMPIR EGDVTVTLSCNYSNPNPVS TRYEWKPHGAWEEPSLGVLKI QNVGWDNTTIIAACNSWCSWASPVALNVQ YAPRDVVRKI KPLSEIHSNVSLSQCD FSSSHPKVQFFWEKNGRLLGKESQLNFDISI SPEDAGSYSC WVNNSIGQTASKAWTLEVLYAPRRLRVSMSPGDQVMEGKSATLTCESDANPVPVSHYTFWDWNQSLPYH SQKLRLEPVKVQHSGAYWCQGTNSVGKGRSPLSTLTVYVSPETIGRR
1081	CD137 mature ECD	LQDPCSNCPAGTFCDNNRNQICSPCPNFSFSSAGGQRTCDICRQCKGVFRTRKECSSTSNACEDCTPGF HCLGAGCSMCEDQCKQGEELTKKGKDCCKCFGTNDQKRGICRPWTNCSLDGKSVLVNGTKERDVVCGFS PADLSPGASSVTPPAPAREPGHSPQ
1102	Human CD45RABC	MTMYLWLKLLAFGFAFLDTEVFTVGTQGSPTPSPTGLTTAKMPSPVLSDDLPHHTTAFSPASTFERENDF SETTTSLSPDNTSTQVSPDSLNDASAFNTTGVSSVQTPHLPHTADSQTPSAGTDTQTFSGSAANAKLNP TPGSNAISDVPGERSTASTFPTDVPVSLPTTTLSLAHHSAAALPARTSNTTITANTSDAYLNASETTTSL PSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLF TAKLNVNENVECGNNTCTNNEVHNLTEC KNASVSI SHNSCTAPDKTLILDVPPGVEKFQ LHDCTQVEKADTTICLWKNIETFTCDTQNTITYRFQCG NMI FDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKI IKTDGSGPGEQI IFCRSEAAHQGVITWNP PQRSFHNFTLCYIKETEKDCLNLDKNLIKDYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSA PPSQVWNMTVSMTSDNSMHVKCRPPDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTF KAYFHNGDYPGEPFII LHHSTSYN SKALIAFLAFLI IVTSIALLVLYKI YDLHKKRSCNLDEQQELVER DDEKQLMNVEPIHADILLETYKRKIADEGRFLAEFQSI PRVFSKFP I KEARKPFNQKNRYVDILPYD YNRVELSEINGDAGSNYINASYIDGFKPRKYIAAQGPRDETVD DFWRMIEWQKATVIMVTRCEEENR NKCAEYWP SMEEGTRAFGDVVVKINQHKRCPDYIIQKLNIVNKKKATGREVTHIQFTSWPDHGVPEDP HLLKLRRRVNAFNSNFFSGPIV VHC SAGVGRTGTIYIGIDAMLEGLEAENKVDVYGVVVKLRQRCLMVQ VEAQYIILIHQALVEYNQFGETEVLNSELHPYLHNMMKKRDPPEPSPLEAEFQRLPSYRSWRTQHIGNQE ENKSKNRNSNVI PYDYNRVPLKHELEMSKESEHDSDESSDDSDSEEPSKYINASFIMS YWKPEVMIAA QGPKLETIGDFWQMI FQRKVVI VMLTELKHGDQEI CAQYWGEGKQTYGDI EVDLKD TDKSSTYTLRVF ELRHSKRKDSRTVYQYQYTNWVSEQLPAEPKELI SMIQVVKQKLPQKNSSEGNKHHKSTPLLIHCRDGS QQTGIFC ALLN LLES AETEEVVDI FQVVKALRKARP GMVSTFEQYQFLYDVIASTYPAQNGQVKKNNHQ EDKIEFDNEVDKVKQDANCVNPLGAPEKLP EAKEQAEGSEPTSGTEGPEHSVNGPASPALNQGS
1103	Human CD45RO	MTMYLWLKLLAFGFAFLDTEVFTVGTQGSPTPSPTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDE KYANITVDYLYNKETKLF TAKLNVNENVECGNNTCTNNEVHNLTECKNASVSI SHNSCTAPDKTLILDV PPGVEKFQ LHDCTQVEKADTTICLWKNIETFTCDTQNTITYRFQCGNMI FDNKEIKLENLEPEHEYKCD SEILYNNHKFTNASKI IKTDGSGPGEQI IFCRSEAAHQGVITWNP PQRSFHNFTLCYIKETEKDCLNLD KNLIKDYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCR PPDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFII LHHSTSYN SKALIAFLAFLI IVTSIALLVLYKI YDLHKKRSCNLDEQQELVERDDEKQLMNVEPIHADILLETYKR KIADEGRFLAEFQSI PRVFSKFP I KEARKPFNQKNRYVDILPYDYNRVELSEINGDAGSNYINASYI DGFKPRKYIAAQGPRDETVD DFWRMIEWQKATVIMVTRCEEENR NKCAEYWP SMEEGTRAFGDVVVK INQHKRCPDYIIQKLNIVNKKKATGREVTHIQFTSWPDHGVPEDPHLLKLRRRVNAFNSNFFSGPIV HCSAGVGRTGTIYIGIDAMLEGLEAENKVDVYGVVVKLRQRCLMVQVEAQYIILIHQALVEYNQFGETE VLNSELHPYLHNMMKKRDPPEPSPLEAEFQRLPSYRSWRTQHIGNQEENKSKNRNSNVI PYDYNRVPLKH ELEMSKESEHDSDESSDDSDSEEPSKYINASFIMS YWKPEVMIAA QGPKLETIGDFWQMI FQRKVVI VMLTELKHGDQEI CAQYWGEGKQTYGDI EVDLKD TDKSSTYTLRVFELRHSKRKDSRTVYQYQYTNWV SEQLPAEPKELI SMIQVVKQKLPQKNSSEGNKHHKSTPLLIHCRDGSQQTGIFC ALLN LLES AETEEVVD IFQVVKALRKARP GMVSTFEQYQFLYDVIASTYPAQNGQVKKNNHQEDKIEFDNEVDKVKQDANCVNPL GAPEKLP EAKEQAEGSEPTSGTEGPEHSVNGPASPALNQGS
1104	Rhesus CD45RABC	MTMCLWLKLLAFVFAFLDTEVFTVGTQGSTLSPTGRRTTKMPSPVLSDDLPHHTTAFSPASISERENDF SETTTPSLSDNTSTHVS PDSLNDASAFNTTGVSSALT PHLPHTHADSQTPSTGTDQTFSGSAANTTSLP TPRSNDISDVPGERSTASTFPTDPI SPLATTLI PARNSSAALPARTSNTTITANTS VSYLNASETTTPS PSGSTVISTPTIATTTSKPTCAEKYATIPVDYLYNNKTKLF TAKLNVNENVECTNNHNTNCTNNEVL NLPECKEMNVFVSHNSCTDRHKELKLDVPEVEKFQ LDDCTPDVEANTTICLWKNIETFACDKSKITY RFQCGNKTYNKEGIYLENLEPEHEYKCDSEILYNNHKYINITKLIKTDFFIGPQGVNVCRHEDAHQGV ITWNP PQRSFHNFTLCYVSKTAKKCLSLDKHLTTHYHLQNLKPYTNYSLSLHAYIIAKVQRNGTAATCNF TTESAPPSQVQNMIVSTSDNSMRVKCEGPRDVNGPTGLYHLEVEAGNTLVRNLSQSKCDFSVNNLQYST YYNLKAYYHNGKYSGEPIV LRESTSYNSKALIAFLAFLI IVTSIALLVLYKI YDLHKKRSCNLDEQQE LVERDDEKQLMNVEPIHADILLETYKRKIADEGRFLAEFQSI PRVFSKFP I KEARKPFNQKNRYVDI LPYDYNRVELSEINGDAGSNYINASYIDGFKPRKYIAAQGPRDETVD DFWRMIEWQKATVIMVTRCE EGNRNKCAEYWP SMEEGTRAFGDVVVKINQHKRCPDYIIQKLNIVNKKKATGREVTHIQFTSWPDHGV PEDPHLLKLRRRVNAFNSNFFSGPIV VHC SAGVGRTGTIYIGIDAMLEGLEAENKVDVYGVVVKLRQRCLMVQ

		LMVQVEAQYILIHQALVEYNQFGETEVNLSLHPYLNHMKKRDPPSEFSPLEAEFQRLPSYRSWRTQHI GNQEENKNKNRNSNVI PYDYNRVPLKHELEMSKESDHDSDESSDDSDSEEPSKYINASFIMSYWKPEV MIAAQGPLKETIGDFWQMI FQRKVKVI VMLTELKHGDQEICAQYWGEGKQTYGDI EVDMDKNTKSSSTYT LRVFELRHSSKRKDSRTVYQYQYTNWSVEQLPAEPKELVSLIQVLKEKLPQKNSSEGNKHHKSTPLLIHC RDGSQQGTGIFCALLNLLESAAETEEVVDIFQVVKALRKARPGMVSTFEQYQFLYDI IASTYPAQNGQVKK NNHQEDKIEFDNEVDKVKQDANCVNPLGATEKLEPAKEQATGSEPTSGTEGEPHSVNGPASPALNQGS
1105	cynomolg us CD45RABC	MTMCLWLKLLAFVFAFLDTEVFVTGQGSTLSPTGRRTTKMPSVPLSSDPLPHTHTTAFSPASISERENDF SETTPSLSSDNTSTQVSPDSDLNASAFNTTGVSSALTPHLPHTHADSQTPSTGTDQTPSPGSAKNAATTLSP TPRSNDISDVPPERSTASTFPTDFI SPLATTLI PARNSSAALPARTSNTTITANTSVSYLNASETTTPS PSGSTVISTPTIATTTSKPTCAEKYATIPVDYLYNNKTKLFTAKLVNENVECTNNHTNICTNNEVL NLPECKEMNVFVSHNSCTDRHKELKLDVPPVEVEKFQDDCTPDVEANTTICLKWKI IETFACDKSKITY RFQCGNKTYNKEGIYLENLEPEYKCDSEI LYNNHKYINITKLIKTDGFI PGQPQNVVCRHEDAHQGV ITWNPPQRSFHNFTLCYVKNPAKKCLILDKHLTTYHLQNLKPYTNYSLSLHAYIIAKVQRNGTAATCNF TTESAPPSQVQNMIVSTSDNSMHVKCEVPRDVGPTGLYHLEVEAGNTLVRNLSQSKCDFSVNNLQYST YYNLKAYYHNGKYSGEPIVIRESTSYNSKALIAFLAFLI IVTSIALLVVLYKIYDLHKKRSNCLDEQQE LVERDDEKQLMNVPIHADILLETYKRKIADEGRFLAEFQSI PRVFSKFP I KEARKFPNQKNAATTLSP LPYDYNRVSELSEINGDAGSNYINASYIDGFKEPKRYIAAQGPRDETVDDFWRMIWEQKATVIMVTRCE EGNRNKCAEYWPMSMEEGTRAFGDIVVKINQHKRCPDYIIQKLNIVNKEKATGREVTHIQFTSWPDHGV PEDPHLLKLRRRVNAFNSFFSGPIVHCASAGVGRGTGYIGIDAMLEGLEAENKVDVGYVVKLRQRRC LMVQVEAQYILIHQALVEYNQFGETEVNLSLHPYLNHMKKRDPPSEFSPLEAEFQRLPSYRSWRTQHI GNQEENKNKNRNSNVI PYDYNRVPLKHELEMSKESDHDSDESSDDSDSEEPSKYINASFIMSYWKPEV MIAAQGPLKETIGDFWQMI FQRKVKVI VMLTELKHGDQEICAQYWGEGKQTYGDI EVDMDKNTKSSSTYT LRVFELRHSSKRKDSRTVYQYQYTNWSVEQLPAEPKELVSLIQVLKEKLPQKNSSEGNKHHKSTPLLIHC RDGSQQGTGIFCALLNLLESAAETEEVVDIFQVVKALRKARPGMVSTFEQYQFLYDI IASTYPAQNGQVKK NNHQEDKIEFDNEVDKVKQDANCVNPLGATEKLEPAKEQATGSEPTSGTEGEPHSVNGPASPALNQGS
1106	Human CD45RABC ECD	QSPTPSPTGLTTAKMPSVPLSSDPLPHTHTTAFSPASTFERENDFSETTSLSPDNTSTQVSPDSDLNAS AFNTTGVSSVQTPHLPHTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAI SDVPPERSTASTFPTDFV SPLTTTSLAHSSAALPARTSNTTITANTS DAYLNASETTTLSPSGSAVI STTTIATTPSKPTCDEKY ANITVDYLYNKETKLFTAKLVNENVECGNNTCTNNEVHNLTECKNASVSI SHNSCTAPDKTLILDVPP GVEKFQLDHCTQVEKADTTICLKWKNIETFTCDTQNTITYRFQCGNMI FDNKEIKLENLEPEHEYKCDSE I LYNNHKFTNASKIIKTDFGSPGEPQII FCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYII NLIKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTTSAPPQVWNMTVSMSTSDNSMHVKCRPP RDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSSTSYNSK
1107	Human CD45RO ECD	QSPTPSPTDAYLNASETTTLSPSGSAVI STTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLVN ENVECGNNTCTNNEVHNLTECKNASVSI SHNSCTAPDKTLILDVPPGVEKFQLDHCTQVEKADTTICLK WKNIETFTCDTQNTITYRFQCGNMI FDNKEIKLENLEPEHEYKCDSEI LYNNHKFTNASKIIKTDFGSPG EPQII FCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYII IAKVQRNGSAAMCHFTTTSAPPQVWNMTVSMSTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRN ESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSSTSYNSK
1108	Human CD45RA ECD	QSPTPSPTGLTTAKMPSVPLSSDPLPHTHTTAFSPASTFERENDFSETTSLSPDNTSTQVSPDSDLNAS AFNTTDAYLNASETTTLSPSGSAVI STTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLVNENVE CGNNTCTNNEVHNLTECKNASVSI SHNSCTAPDKTLILDVPPGVEKFQLDHCTQVEKADTTICLKWKNI IETFTCDTQNTITYRFQCGNMI FDNKEIKLENLEPEHEYKCDSEI LYNNHKFTNASKIIKTDFGSPGEPQ II FCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYIIA KVQRNGSAAMCHFTTTSAPPQVWNMTVSMSTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESH KNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSSTSYNSK
1109	Human CD45RB	QSPTPSPTGVSSVQTPHLPHTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAI SDAYLNASETTTLSP SGSAVI STTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLVNENVECGNNTCTNNEVHNLTECK NASVSI SHNSCTAPDKTLILDVPPGVEKFQLDHCTQVEKADTTICLKWKNIETFTCDTQNTITYRFQCG MIFDNKEIKLENLEPEHEYKCDSEI LYNNHKFTNASKIIKTDFGSPGEPQII FCRSEAAHQGVITWNPP QRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYIIIAKVQRNGSAAMCHFTTTSAP PSQVWNMTVSMSTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFK AYFHNGDYPGEPFILHHSSTSYNSK
2010	Human CD45RAB ECD	QSPTPSPTGLTTAKMPSVPLSSDPLPHTHTTAFSPASTFERENDFSETTSLSPDNTSTQVSPDSDLNAS AFNTTGVSSVQTPHLPHTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAI SDAYLNASETTTLSPSGS AVI STTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLVNENVECGNNTCTNNEVHNLTECKNAS VSI SHNSCTAPDKTLILDVPPGVEKFQLDHCTQVEKADTTICLKWKNIETFTCDTQNTITYRFQCGNMIF

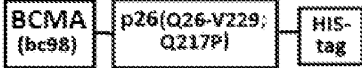
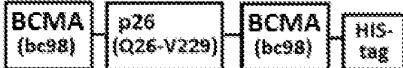
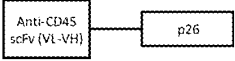
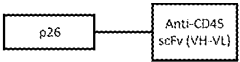
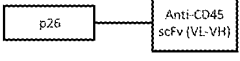
		DNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPQRS FHNFTLCYIKETEKDCLNLDKNLIKDYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQ VWNMTVSMTSDNSMHVKCRPPDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYF HNGDYPGEPFILHSTSYNSK
2011	Human CD45RAC ECD	QSPTPSPTGLTTAKMPSVPLSSDPLPHTHTAFSPASTFERENDFSETTSLSPDNTSTQVSPDSLDNAS AFNTTDPGERSTASTFPTDPVSPLTTTSLAHSSAALPARTSNTTITANTSDAYLNASETTTLSPSG SAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFATAKLVNENVECGNNTCTNNEVHNLTECKNA SVSISHNSCTAPDKTLILDVPPGVEKFLHDCTQVEKADTTICLKWKNIETFTCDTQNTITYRFQCGNMI FDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPQRS SFHNFTLCYIKETEKDCLNLDKNLIKDYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPS QVWNMTVSMTSDNSMHVKCRPPDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYF HNGDYPGEPFILHSTSYNSK
2012	Human CD45RBC ECD	QSPTPSPTGVSVQTPHLPHTHADSQTSPAGTDQTQFSGSAANAKLNPTPGSNAISDVPERSTASTFPT DPVSPLTTTSLAHSSAALPARTSNTTITANTSDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCD EKYANITVDYLYNKETKLFATAKLVNENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILD VPPGVEKFLHDCTQVEKADTTICLKWKNIETFTCDTQNTITYRFQCGNMIFDNKEIKLENLEPEHEYKCD DSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPQRSFHNFTLCYIKETEKDCLN LDKNLIKDYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVK RPPDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHSTSY NSK
2013	Human CD26	MKTPWKVLLGLLGAALVTIITVPVLLNKGTDADATADSRKTYTLTDYLNKTYRLKLYSLRWISDHEYL YQENNILVFNAEYGNSSVFLNSTFDEFHGSINDYSISPDGQFILLEYNVYKQWRHSYTASYDIYDLN KRQLITEERIPNNTQWVTWSPVGHKLAYVWVNDIYVKIEPNLPSYRITWTGKEDIYNGITDWVYEEV FSAYSALWVSPNGTFLAYAQFNDTEVPLIEYSFYSDESLLQYPKTVRVPYKAGAVNPTVKFFVNTDSL SSVTNATSIQITAPASMLIGDHYLCDVTWATERISLQWLRRIQNYSVMDICDYDESSGRWNCVLVARQH IEMSTTGWVGRFRPSEPHFTLDGNSFYKISNEEGYRHCYFQIDKKDCTFITKGTWEVIGIEALTSY LYYISNEYKGMPPGRNLYKIQLSDYTKVTCLSCELNPERCQYYSVSFSKEAKYQRLCSGPGPLPLYTLH SSVNDKGLRVLEDNSALDKMLQNVQMPKSKLDFIILNETKFWYQMIPLPHFDKSKKYPPLLDVYAGPCS QKADTVFRLNWATYLASTENIIVASFDGRSGYGQDKIMHAINRRLGTFEVEDQIEAARQFSKMGFVDN KRIAIWGSYGGYVTSMLVLSGSGVFCGIAVAPVSRWEYDVSVYTERYMGPLTPEDNLDHYNSTVMS RAENFKQVEYLLIHGTADDNVHFQQAQISKALVDVGVDFAAMWYTDHGHASSTAHQHIYTHMSHFI KQCFSLP
2014	Human CD30	MRVLLAALGLLFLGALRAFPQDRPFEDTCHGNP SHYYDKAVRRCCYRCPMGLFPTQCCPQRPTDCRQC EPDYLLDEADRCTACVTCSDRLDVEKTPCAWNSSRVCECRPGMFCSTSAVNSCARCFHVSVCAGMIVK FPGTAQKNTVCEPASPGVSPACASPENCKEPPSSGTPQAKPTVPSPATSSASTMPVRGGTRLAQEAASK LTRAPDS PSSVGRPSSDPGLSPQPCPEGSGDCRQCEPDYLLDEAGRCTACVSCSRDDLVEKTPCAWV SSRTCECRPGMICATSATNSCARCVPYPICAAETVTKPDMAEKDITFEAPPLGTQPD CNPTPENGEAP ASTSPTQSLLVDSQASKTLPIPTSAFVALSSGKPVLDAGPVLFWVLVLVSVVGSFAFLCHRRACRK RIRQKLHLCPVQTSQPKLELVDSRPRRSSTQLRSGASVTEPVAEERGLMSQPLMETCHSVGAAYLES LPLQDAS PAGGPSSPRDLPEPRVSTEHNTNKEIKIYIMKADTVIVGTVAELPEGRGLAGPAEPELEEL EADHTPHYPEQETEPPLGSCSDVMSLVEEKGEDPLPTAASGK
2015	Human CD33	MPLLLLLPLWAGALAMPNFWLQVQESVTVQEGLCVLVPCTFFHPIPYDKNSPVHGYWFREGAII SR DSPVATNKLQEVQEETQGRFRLLDGDSRNCSLSIVDARRRDNGSYFFRMERGSTKYSYKSPQLSVHV TDLTHRPKILIPGTLEPGHSKNLTCSVSWACEQGTPIFSWLSAAPTSLGPRTHSSVLIITPRPQDHG TNLTQVKFAGAGVTERTIQLNVTYVPQNPTTGIFFPGDGSQKQETRAGVVGAIAGGAGVTALLALCLC LIFFIKTHRRKAARTAVGRNDTHPTTGSASPKHQKSKLHGPTTETSSCSGAAPTVMDEELHYASLNF HGMNPSKDTSTEYSEVRTQ
2016	Human CD38	MANCEFSVPVSGDKPCCRLSRAQLCLGVSIILVILVVLAVVPRWRQOWSGPGTTKRFPETVLARCVK YTEIHPEMRHVDCQSVWDAFKGAFISKHPCNITEEDYQPLMKLGTQTVPCNKILLWSRIKDLAQHTQV QRDMFTLEDTLGLYLAADDLTWCGEFNTSKINYQSCPDWRKDCSNNPVSVFWKTVSRFAEACDVVHVM LNGSRSKI FDKNSTFGSVEVHNLQPEKVQTLAEAWIHGGREDSRDLCDQDPTIKELESII SKRNIQFSCK NIYRPDKFLQCCKNPEDSSCTSEI
1138	CS1 mature ECD	SGPVKELVGSVGGAVTFPLKSKVKQVDSI VWTFTNTPLVTIQPEGGTII VQTQNRNRERVD FPDGGYSLK LSKLKKNDSGIYVGIYSSSLQQPSTQEVVLHVYEHLSKPKVTMGLQSNKNGTCVTNLTCCMEHGEEDV IYTWKALQGAANESHNGSILPISWRWGESDMTFICVARNPVS RNFSSPILARKLCEGAADDPDSSM
1139	CS1	MAGSPTCLTLIYILWQLTGSAAAGPVKELVGSVGGAVTFPLKSKVKQVDSI VWTFTNTPLVTIQPEGGT IIVTQNRNRERVD FPDGGYSLKLSKLKKNDSGIYVGIYSSSLQQPSTQEVVLHVYEHLSKPKVTMGLQ SNKNGTCVTNLTCCMEHGEEDVIYTWKALQGAANESHNGSILPISWRWGESDMTFICVARNPVS RNFSS PILARKLCEGAADDPDSSMVLCLLLVPLLLSLFVLGLFLWFLKRERQEEYIEKKRVDICRETPNICP HSGENTYDITI PHTNRTILKEDPANTVYSTVEIPKKMENPHSLTMDPTPRLFAYENVI

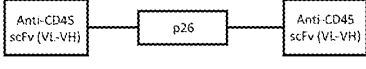
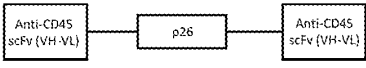
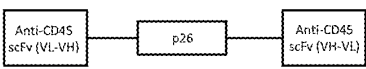
42	HER2 mature ECD	TQVCTGTDMKRLPASPETHLDMRLRHLVYQGCQVVGQGNLELTYLPTNASLSFLQDIQEVQGYVLIHNVQ RQVPLQRLRIVRGTOLEFEDNYALAVLDNGDPLNNTTPVTGASPGGLRELQRLSLTEILKGGVLIQRNPQ LCYQDITILWKDIFHKNNQLALTLIDTNRSRACHPCSPMKGSRGWGESSEDCQSLRTVCAGGCARCKG PLPTDCCHEQCAAGCTGPKHSDCLACLFHNSGICELHCPALVTYNTDTFESMPNPEGRYTFGASCVTA CPYNYLSTDVGSCTLVCPHNVQEVTAEDGTQRCEKCSKPCARVCYGLGMEHLREVRVAVTSANIQEFAGC KKIFGSLAFLPESFDGDPASNTAPLQPEQLQVFETLEEITGYLYISAWPDSLPDLSVFQNLQVIRGRIL HNGAYSLTLQGLGISWGLRLSRLRELGSGLALIHNNHLCFVHTVPWDQLFRNPHQALLHTANRPEDCV GEGLACHQLCARGHCWGPPTQCVNCSQFLRGQECVEECRVLQGLPREYVNAHCLPCHPECPQNGSV TCFGPEADQCVACAHYKDPFPCVARCPSGVKPDLSPYMPIWKFPDEEGACQPCFINCTHSCVDLDDKGCP AEQRASPLT
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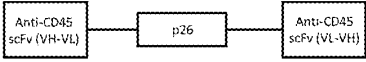
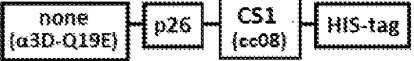
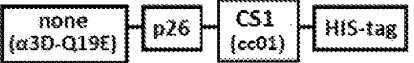
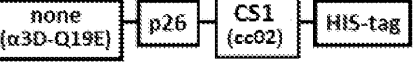
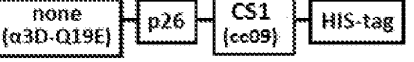
TABLE: 5 Exemplary Adapters

SEQ ID NO:	Adapter Design	Adapter Sequence
1082		DEMGSWDEFGRRLYAI EWRLYALGGSEAEAAFEKEIAAFESEL QAYKGKGNPEVEKLR EIAAVIRSNLQAYRHNGGGSGGGSGGG GSGMLQ MAGQCSQNEYFDSLHACIPCQLRCSSNTPLTCQRYC NASVTNSVKGTNAGGGSGGGSGGGSGGGSHHHHHHHHHH
1083		DEGGGSMGSWAEFKQRLAAIKTRLQALGGSEAEAAFEKEIAA FESELQAYKGKGNPEVEALRKEAAAI RDELQAYRHNGGGSGGG GSGGGSGMLQ MAGQCSQNEYFDSLHACIPCQLRCSSNTPLT CQRYCNASVTNSVKGTNAGGGSGGGSGGGSGGGSHHHHHHHHHH
1084		DEHHHHHHHHHKL ENLYFQGGGGSGMSWDEFGRRLYAI EWRL YALGGSEAEAAFEKEIAAFESELQAYKGKGNPEVEKLR EIAAV IRSNLQAYRHNGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGG EELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQL TSSELMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCI RHEMTFVNPVGVCCTSSYANRRPCFSSLVDETYVPPAFSDDK FI FHKDL CQAQGVALQTMKQEF LINLVKQKPQITEEQLEAVIAD FSGLLEKCCQGGQEQEVCF AEEGQKLI SKTR AALGV
1085		DEHHHHHHHHHKL ENLYFQGGGGSGMSWSEFWRLGAI RERL DALGGSEAEAAFEKEIAAFESELQAYKGKGNPEVEKLR EIAAV IRFLQAYRHNGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGG EELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQL TSSELMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCI RHEMTFVNPVGVCCTSSYANRRPCFSSLVDETYVPPAFSDDK FI FHKDL CQAQGVALQTMKQEF LINLVKQKPQITEEQLEAVIAD FSGLLEKCCQGGQEQEVCF AEEGQKLI SKTR AALGV
1086		DEHHHHHHHHHKL ENLYFQGGGGSGMSWAEFKQRLAAIKTRL EALGGSEAEAAFEKEIAAFESELQAYKGKGNPEVEALRKEAAA IRDELQAYRHNGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGG EELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQL TSSELMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCI RHEMTFVNPVGVCCTSSYANRRPCFSSLVDETYVPPAFSDDK FI FHKDL CQAQGVALQTMKQEF LINLVKQKPQITEEQLEAVIAD FSGLLEKCCQGGQEQEVCF AEEGQKLI SKTR AALGV
1087		DEGGGSMGSWDEFGRRLYAI EWRLYALGGTEAEAAFEKEIAA FESELQAYKGKGNPEVEKLR EIAAVIRSNLQAYRHNGGGSGGG GSGGGSGGLEKCFQ TENPLECQDKGEEELQKYIQESQALAKRSC GLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAAT CCQLSEDKLLACGEGAADIIIGHLCI RHEMTFVNPVGVCCTSS YANRRPCFSSLVDETYVPPAFSDDKFI FHKDL CQAQGVALQTM KQEF LINLVKQKPQITEEQLEAVIADFSGLLEKCCQGGQEQEVCF AEEGQKLI SKTR AALGVGGGGSGGGSGGGSGGGSGMSWDEFGRRLY AIEWRLYALGGTEAEAAFEKEIAAFESELQAYKGKGNPEVEKL REIAAVIRSNLQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH
1088		DEGGGSMGSWSEFWRLGAI RERLDALGGSEAEAAFEKEIAA FESELQAYKGKGNPEVEKLR EIAAVIRFLQAYRHNGGGSGGG GSGGGSGGLEKCFQ TENPLECQDKGEEELQKYIQESQALAKRSC GLFQKLGEYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAAT

		CCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSS YANRRPCFSSLVVDETYVPPAFSDDKFI FHKDLCAQAGVALQTM KQEFNLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCF AEEGQKLI SKTRALGVGGGSGGGSGGGSGGGSGGGSGGGSGGG AIRERLDALGGSEAEAAFEKEIAAFESSELQAYKKGKNPEVEKL RYTATIRRLQAYRHNNGGGSGGGSGGGSGGGSGGGSGGGSGGG
1124		DEGGGSGMGSWSEFWARLGAI RERLDALGGSEAEAAFEKEIAA FESELQAYKKGKNPEVEKLRYTAGTI KRFLQAYRHNNGGGDGGG SGGGSGGLEKCFQ TENPLECQDKGEEELQKYIQESQALAKRSC GLFQKLGEYYLQNAFLVAYTKKAPQLTSSSELMAITRKMAATAAT CCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSS YANRRPCFSSLVVDETYVPPAFSDDKFI FHKDLCAQAGVALQTM KQEFNLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCF AEEGQKLI SKTRALGVGGGSGGGSGGGSGGGSGGGSGGGSGGG
1125		DEMGSWSEFWARLGAI RERLDALGGSEAEAAFEKEIAAFESSEL QAYKKGKNPEVEKLRYTAGTI KRFLQAYRHNNGGGDGGGSGGG SGGLEKCFQ TENPLECQDKGEEELQKYIQESQALAKRSCGLFQK LGEYYLQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLS EDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRR PCFSSLVVDETYVPPAFSDDKFI FHKDLCAQAGVALQTMKQEF NLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCF AEEGQKLI SKTRALGVGGGSGGGSGGGSGGGSGGGSGGGSGGG
1126		DEMGSWSEFWARLGAI RERLDALGGSEAEAAFEKEIAAFESSEL QAYKKGKNPEVEKLRYTAGTI KRFLQAYRHNNGGGDGGGSGGG SGGQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSS LMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCIRHEM TPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAFSDDKFI FHK DLCAQAGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGL LEKCCQGQEQEVCFAEEGQKLI SKTRALGVGGGSGGGSGGGSGGG SGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGG
1127		DEMGSWSEFWARLGAI RERLDALGGSEAEAAFEKEIAAFESSEL QAYKKGKNPEVEKLRYTAGTI KRFLQAYRHNNGGGDGGGSGGG SGGKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLT SSELMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCIR HEMTPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAFSDDKFI FHKDLCAQAGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFS GLLEKCCQGQEQEVCFAEEGQKLI SKTRALGVGGGSGGGSGGGSGGG SGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGG
1128		DEMGSWSEFWARLGAI RERLDALGGSEAEAAFEKEIAAFESSEL QAYKKGKNPEVEKLRYTAGTI KRFLQAYRHNNGGGDGGGSGGG SGGEEELQKYIQESQALAKRSCGLFQKLGEYYLQNAFLVAYTK KAPQLTSSSELMAITRKMAATAATCCQLSEDKLLACGEGAADII IGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPA FSDDKFI FHKDLCAQAGVALQTMKQEFNLINLVKQKPQITEEQLE AVIADFSGLLEKCCQGQEQEVCFAEEGQKLI SKTRALGVGGGSGGG SGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGGSGGG
1129		DEGGGSGMGSWSEFWARLGAI RERLDALGGSEAEAAFEKEIAA FESELQAYKKGKNPEVEKLRYTAGTI KRFLQAYRHNNGGGDGGG SGGGSGGLEKCFQ TENPLECQDKGEEELQKYIQESQALAKRSC GLFQKLGEYYLQNAFLVAYTKKAPQLTSSSELMAITRKMAATAAT CCQLSEDKLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSS YANRRPCFSSLVVDETYVPPAFSDDKFI FHKDLCAQAGVALQTM KQEFNLINLVKQKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCF AEEGQKLI SKTRALGVGGGSGGGSGGGSGGGSGMGSWSEFWARLG AIRERLDALGGSEAEAAFEKEIAAFESSELQAYKKGKNPEVEKL RYTAGTI KRFLQAYRHNNGGGDGGGSGGGSGGGSGGGSGGGSGGG
1130		DEMGSWSEFWARLGAI RERLDALGGSEAEAAFEKEIAAFESSEL QAYKKGKNPEVEKLRYTAGTI KRFLQAYRHNNGGGDGGGSGGG SGGQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSS LMAITRKMAATAATCCQLSEDKLLACGEGAADIIIGHLCIRHEM TPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAFSDDKFI FHK DLCAQAGVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGL LEKCCQGQEQEVCFAEEGPKLI SKTRALGVGGGSGGGSGGGSGGG

		GSMGSWSEFWARLGAI RERLDALGGSEAE LA AFEKEIA AFESEL QAYKGKGNPEVEKLRYTAGTIKRFLQAYRHNGGGSGGGSGGG GSHHHHHHHHHH
1131		DEMGSWSEFWARLGAI RERLDALGGSEAE LA AFEKEIA AFESEL QAYKGKGNPEVEKLRYTAGTIKRFLQAYRHNGGGSGGGSGGG GSGQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSE LMAITRKMAATAATCCQLSEDKLLACGEGAADII IGHLCIRHEM TPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAFSDDKFI FH KDLCAQGVVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGL LEKCCQGGQEQEVCFAEEGPKLI SKTRALGVGGGSGGGSGGG GSHHHHHHHHHH
1132		DEMGSWSEFWARLGAI RERLDALGGSEAE LA AFEKEIA AFESEL QAYKGKGNPEVEKLRYTAGTIKRFLQAYRHNGGGSGGGSGGG GSGQESQALAKRSCGLFQKLGEYYLQNAFLVAYTKKAPQLTSSE LMAITRKMAATAATCCQLSEDKLLACGEGAADII IGHLCIRHEM TPVNPVGVCCTSSYANRRPCFSSLVVDETYVPPAFSDDKFI FH KDLCAQGVVALQTMKQEFNLINLVKQKPQITEEQLEAVIADFSGL LEKCCQGGQEQEVCFAEEGPKLI SKTRALGVGGGSGGGSGGG GSMGSWSEFWARLGAI RERLDALGGSEAE LA AFEKEIA AFESEL QAYKGKGNPEVEKLRYTAGTIKRFLQAYRHNGGGSGGGSGGG GSHHHHHHHHHH
1401		QVQLVESGGGLVQPGGSLKLSCAASGFD FSR YWMSWVRQAPGKG LEWIG EINTSSTINFTPSLKD KVFISRDNAKNTLYLQMSKVR S EDTALYYCARGNYYRYGDAMDYWGQGT SVTVSGGGSGGGSGG GSDIVLTQSPASLAVSLGQRATISCRASKSVSTSGSYLHWYQ QKPGQPPKLLIY LASNLESGV PARFSGSGSGTDFTLNIHPVEE DAATYYCQHSREL PFTFGSGTKLEIKGGGSGGGSGGGSGGLE KCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYY LQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSEDKLL ACGEGAADII IGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSS LVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFNLINLVK QKPQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKLISK TRALGV
1402		DIVLTQSPASLAVSLGQRATISCRASKSVSTSGSYLHWYQKQK GQPKLLIY LASNLESGV PARFSGSGSGTDFTLNIHPVEEEDAA TYCQHSREL PFTFGSGTKLEIKGGGSGGGSGGGSGGQVQLVE SGGGLVQPGGSLKLSCAASGFD FSR YWMSWVRQAPGKLEWIG EINTSSTINFTPSLKD KVFISRDNAKNTLYLQMSKVRSEDTALY YCARGNYYRYGDAMDYWGQGT SVTVSGGGSGGGSGGGSGGLE KCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYY LQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSEDKLL ACGEGAADII IGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSS LVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFNLINLVK QKPQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKLISK TRALGV
1403		LEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGE YYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSEDK LLACGEGAADII IGHLCIRHEMTPVNPVGVCCTSSYANRRPCF SSLVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFNLIN VKQKPQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKLISK TRALGVGGGSGGGSGGGSGGQVQLVESGGGLVQPGGSLK LSCAASGFD FSR YWMSWVRQAPGKLEWIG EINTSSTINFTPS LKD KVFISRDNAKNTLYLQMSKVRSEDTALYYCARGNYYRYGDA MDYWGQGT SVTVSGGGSGGGSGGGSDIVLTQSPASLAVSLG QRATISCRASKSVSTSGSYLHWYQKPGQPPKLLIY LASNLESG V PARFSGSGSGTDFTLNIHPVEEEDAAATYYCQHSREL PFTFGS GTKLEIK
1404		LEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGE YYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSEDK LLACGEGAADII IGHLCIRHEMTPVNPVGVCCTSSYANRRPCF SSLVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFNLIN

		VKQKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCFAEEGQKLI SKTRAAALGVGGGSGGGGSGGGSGDIVLTQSPASLAVSLGQRA TISCRASKSVSTSGYSYLHWYQQKPGQPPKLLIYLASNLESGVP ARFSGSGSGTDFTLNHPVEEEDAATYYCQHSRELPTFTGSGTK LEIKGGGSGGGGSGAGGGSQVQLVESGGGLVQPGGSLKLSCAAS GFDFSRYSWMSWVRQAPGKGLEWIGEINPTSSSTINFTPSLKDQVF ISRDNANTLYLQMSKVRSEDTALYYCARGNYRYGDAMDYWGQ GTSVTVS
1405		DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYLHWYQQK GQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNHPVEEEDA TYYCQHSRELPTFTGSGTKLEIKGGGSGGGGSGAGGGSQVQLVE SGGGLVQPGGSLKLSCAASGFDFSRYSWMSWVRQAPGKLEWIGE INPTSSSTINFTPSLKDQVFISRDNANTLYLQMSKVRSEDTALY YCARGNYRYGDAMDYWGQGTSTVTVSGGGSGGGGSGGGSGLE KCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYY LQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSEDKLL ACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSS LVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFLLNLVK QKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCFAEEGQKLI SKTRAAALGVGGGSGGGGSGGGSGDIVLTQSPASLAVSLGQRAT ISCRASKSVSTSGYSYLHWYQQKPGQPPKLLIYLASNLESGVPAR FSGSGSGTDFTLNHPVEEEDAATYYCQHSRELPTFTGSGTKLE IKGGGSGGGGSGAGGGSQVQLVESGGGLVQPGGSLKLSCAASGF DFSRYSWMSWVRQAPGKLEWIGEINPTSSSTINFTPSLKDQVFIS RDNANTLYLQMSKVRSEDTALYYCARGNYRYGDAMDYWGQGT STVTVS
1406		QVQLVESGGGLVQPGGSLKLSCAASGFDFSRYSWMSWVRQAPGK LEWIGEINPTSSSTINFTPSLKDQVFISRDNANTLYLQMSKVR SEDTALYYCARGNYRYGDAMDYWGQGTSTVTVSGGGSGGGGSGAG GGSDIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYLHWYQ QKPGQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNHPVEE DAATYYCQHSRELPTFTGSGTKLEIKGGGSGGGGSGGGSGLE KCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYY LQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSEDKLL ACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSS LVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFLLNLVK QKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCFAEEGQKLI SKTRAAALGVGGGSGGGGSGGGSGGVQLVESGGGLVQPGGSLKLS CAASGFDFSRYSWMSWVRQAPGKLEWIGEINPTSSSTINFTPSL KDQVFISRDNANTLYLQMSKVRSEDTALYYCARGNYRYGDAMD YWGQGTSTVTVSGGGSGGGGSGAGGSDIVLTQSPASLAVSLGQR ATISCRASKSVSTSGYSYLHWYQQKPGQPPKLLIYLASNLESGV PARFSGSGSGTDFTLNHPVEEEDAATYYCQHSRELPTFTGSGT KLEIK
1407		DIVLTQSPASLAVSLGQRATISCRASKSVSTSGYSYLHWYQQK GQPPKLLIYLASNLESGVPARFSGSGSGTDFTLNHPVEEEDA TYYCQHSRELPTFTGSGTKLEIKGGGSGGGGSGAGGGSQVQLVE SGGGLVQPGGSLKLSCAASGFDFSRYSWMSWVRQAPGKLEWIGE INPTSSSTINFTPSLKDQVFISRDNANTLYLQMSKVRSEDTALY YCARGNYRYGDAMDYWGQGTSTVTVSGGGSGGGGSGGGSGLE KCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYY LQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSEDKLL ACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSS LVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFLLNLVK QKPQITEEQLEAVIADFSGLLEKCCQGQEQEVCFAEEGQKLI SKTRAAALGVGGGSGGGGSGGGSGGVQLVESGGGLVQPGGSLKLS CAASGFDFSRYSWMSWVRQAPGKLEWIGEINPTSSSTINFTPSL KDQVFISRDNANTLYLQMSKVRSEDTALYYCARGNYRYGDAMD YWGQGTSTVTVSGGGSGGGGSGAGGSDIVLTQSPASLAVSLGQR ATISCRASKSVSTSGYSYLHWYQQKPGQPPKLLIYLASNLESGV PARFSGSGSGTDFTLNHPVEEEDAATYYCQHSRELPTFTGSGT KLEIK

1408		<p>QVQLVESGGGLVQPGGSLKLSCAASGFDPSRYWMSWVRQAPGKG LEWIGEINPTSSSTINFTPSLKDQVFI SRDNAKNTLYLQMSKVR EDTALYYCARGNYRYGDAMDYWGQGTSTVTVSGGGSGGGSGG GGSDIVLTQSPASLAVSLGQRATISCRASKSVSTSGSYLHWYQ QKPGQFPKLLIYLASNLESGVPARFSGSGGTDFTLNIHPVEEE DAATYYCQHSRELPTFTFGSGTKLEIKGGGSGGGSGGGSGGLE KCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLGEYY LQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSEDKLL ACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPCFSS LVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFLLNLVK QKPQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKLISK TRAALGVGGGSGGGSGGGSGGGSDIVLTQSPASLAVSLGQRATI SCRASKSVSTSGSYLHWYQKPGQFPKLLIYLASNLESGVPAR FSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPTFTFGSGTKLE IKGGGSGGGSGAGGSQVQLVESGGGLVQPGGSLKLSCAASGFD PSRYWMSWVRQAPGKLEWIGEINPTSSSTINFTPSLKDQVFI S RNAKNTLYLQMSKVRSEDTALYYCARGNYRYGDAMDYWGQGT SVTVS</p>
1500	<p>α3D Q19E-p26-cc08.HIS</p> 	<p>MGSWAEFKQRLAAIKTRLEALGGSEAEELAAFEKEIAAFESSELQA YKKGKNPEVEALRKEAAAI RDELQAYRHNGGGSGGGSGGGSGG GLEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKL EYYLQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFLLN LVKQKQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKL ISKTRAALGVGGGSGGGSGGGSGGGSGMGSWVEFNERLHAIYLR DALGSEAEELAAFEKEIAAFESSELQAYKKGKNPEVETLRRHAAG IRWQLQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1501	<p>α3D Q19E-p26-cc01.HIS</p> 	<p>MGSWAEFKQRLAAIKTRLEALGGSEAEELAAFEKEIAAFESSELQA YKKGKNPEVEALRKEAAAI RDELQAYRHNGGGSGGGSGGGSGG GLEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKL EYYLQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFLLN LVKQKQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKL ISKTRAALGVGGGSGGGSGGGSGGGSGMGSWVEFEARLSAIYERL EALGSEAEELAAFEKEIAAFESSELQAYKKGKNPEVEKLRRHAAG IRSNLQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1502	<p>α3D Q19E-p26-cc02.HIS</p> 	<p>MGSWAEFKQRLAAIKTRLEALGGSEAEELAAFEKEIAAFESSELQA YKKGKNPEVEALRKEAAAI RDELQAYRHNGGGSGGGSGGGSGG GLEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKL EYYLQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFLLN LVKQKQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKL ISKTRAALGVGGGSGGGSGGGSGGGSGMGSWVEFFVRLDAIWERL EALGSEAEELAAFEKEIAAFESSELQAYKKGKNPEVETLRFHAAG IRQKLQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1503	<p>α3D Q19E-p26-cc09.HIS</p> 	<p>MGSWAEFKQRLAAIKTRLEALGGSEAEELAAFEKEIAAFESSELQA YKKGKNPEVEALRKEAAAI RDELQAYRHNGGGSGGGSGGGSGG GLEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKL EYYLQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDLCAQGVVALQTMKQEFLLN LVKQKQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKL ISKTRAALGVGGGSGGGSGGGSGGGSGMGSWNEFKLELAFIKDWL EALGSEAEELANFEAAIAEFAGLQGYKKGKNPEVEALRKEAAA IRDELQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1504	<p>α3D Q19E-p26-cc10.HIS</p>	<p>MGSWAEFKQRLAAIKTRLEALGGSEAEELAAFEKEIAAFESSELQA YKKGKNPEVEALRKEAAAI RDELQAYRHNGGGSGGGSGGGSGG GLEKCFQTENPLECQDKGEEELQKYIQESQALAKRSCGLFQKL EYYLQNAFLVAYTKKAPQLTSSSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC</p>

		<p>FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGV ALQTMKQEF LIN LVKQKFPQIT EEQLEAVIADFSGLLEKCCQGEQEVCF AE EGGQKL ISKTR AALGVGGGSGGGSGGGSGMGSWMEFEARLEAIWDR L EALGGSEAE LA AFEKEIAAFES ELQAYKKGKNPEVESLR FHAAG IRQHLQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1505	<p>α3D Q19E-p26-cc12.HIS</p>	<p>MGSWAEFKQRLAAIKTRLEALGGSEAE LA AFEKEIAAFES ELQA YKKGKNPEVEALRKEAAAIRDELQAYRHNGGGSGGGSGGGSG GLEKCFQ TENPLECQDKGEEELQKYI QESQALAKRS CGLFQKLG EYYLQNAFLVAYTKKAPQLT SSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGV ALQTMKQEF LIN LVKQKFPQIT EEQLEAVIADFSGLLEKCCQGEQEVCF AE EGGQKL ISKTR AALGVGGGSGGGSGGGSGMGSWHFKMHLAGIKLQL EALGGSEAE LA AFEFEWIADFE GALQDYKKGKNPEVEALRKEAAA IRDELQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1506	<p>α3D(Q19E).3xGS.p26.3xGS.α3D(Q19E).HIS</p>	<p>MGSWAEFKQRLAAIKTRLEALGGSEAE LA AFEKEIAAFES ELQA YKKGKNPEVEALRKEAAAIRDELQAYRHNGGGSGGGSGGGSG GLEKCFQ TENPLECQDKGEEELQKYI QESQALAKRS CGLFQKLG EYYLQNAFLVAYTKKAPQLT SSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGV ALQTMKQEF LIN LVKQKFPQIT EEQLEAVIADFSGLLEKCCQGEQEVCF AE EGGQKL ISKTR AALGVGGGSGGGSGGGSGMGSWAEFKQRLAAIKTR L EALGGSEAE LA AFEKEIAAFES ELQAYKKGKNPEVEALRKEAAA IRDELQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1507	<p>α3D(Q19E).3xGS.p26.3xGS.eb03.HIS</p>	<p>MGSWAEFKQRLAAIKTRLEALGGSEAE LA AFEKEIAAFES ELQA YKKGKNPEVEALRKEAAAIRDELQAYRHNGGGSGGGSGGGSG GLEKCFQ TENPLECQDKGEEELQKYI QESQALAKRS CGLFQKLG EYYLQNAFLVAYTKKAPQLT SSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGV ALQTMKQEF LIN LVKQKFPQIT EEQLEAVIADFSGLLEKCCQGEQEVCF AE EGGQKL ISKTR AALGVGGGSGGGSGGGSGMGSWAEFRWRLHAIWLQL GALGGSEAE LA AFEKEIAAFES ELQAYKKGKNPEVEWLRQDAAQ IKYILQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1508	<p>α3D(Q19E).3xGS.p26.3xGS.eb04.HIS</p>	<p>MGSWAEFKQRLAAIKTRLEALGGSEAE LA AFEKEIAAFES ELQA YKKGKNPEVEALRKEAAAIRDELQAYRHNGGGSGGGSGGGSG GLEKCFQ TENPLECQDKGEEELQKYI QESQALAKRS CGLFQKLG EYYLQNAFLVAYTKKAPQLT SSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGV ALQTMKQEF LIN LVKQKFPQIT EEQLEAVIADFSGLLEKCCQGEQEVCF AE EGGQKL ISKTR AALGVGGGSGGGSGGGSGMGSWKTFKIELAGIKLEL EALGGSEAE LAGFENAI AQFES SLQYYKKGKNPEVEALRKEAAA IRDELQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1509	<p>α3D(Q19E).3xGS.p26.3xGS.eb05.HIS</p>	<p>MGSWAEFKQRLAAIKTRLEALGGSEAE LA AFEKEIAAFES ELQA YKKGKNPEVEALRKEAAAIRDELQAYRHNGGGSGGGSGGGSG GLEKCFQ TENPLECQDKGEEELQKYI QESQALAKRS CGLFQKLG EYYLQNAFLVAYTKKAPQLT SSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGV ALQTMKQEF LIN LVKQKFPQIT EEQLEAVIADFSGLLEKCCQGEQEVCF AE EGGQKL ISKTR AALGVGGGSGGGSGGGSGMGSWHEFLRLLAIEMRL YALGGSEAE LA AFEKEIAAFES ELQAYKKGKNPEVEHLRVRAAS IRQMLQAYRHNGGGSGGGSGGGSGGGSHHHHHHHHHH</p>
1510	<p>α3D(Q19E).3xGS.p26.3xGS.eb06.HIS</p>	<p>MGSWAEFKQRLAAIKTRLEALGGSEAE LA AFEKEIAAFES ELQA YKKGKNPEVEALRKEAAAIRDELQAYRHNGGGSGGGSGGGSG GLEKCFQ TENPLECQDKGEEELQKYI QESQALAKRS CGLFQKLG EYYLQNAFLVAYTKKAPQLT SSELMAITRKMAATAATCCQLSED KLLACGEGAADIIIGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGV ALQTMKQEF LIN LVKQKFPQIT EEQLEAVIADFSGLLEKCCQGEQEVCF AE EGGQKL ISKTR AALGVGGGSGGGSGGGSGMGSWWEFRVRLEAIDYRL</p>

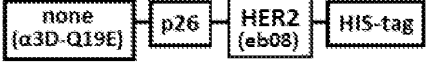
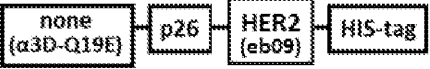
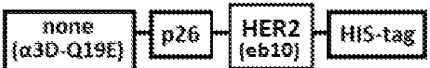
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1511	$\alpha 3D(Q19E).3xGS.p26.3xGS.eb08.HIS$ 	MGSWAEFKQRLAAIKTRLEALGGSEAEIAAFEKEIAAFESELQA YKKGKNPEVEALRKEAAAI RDELQAYRHNGGGGSGGGGSGGGG GLEKCFQ TENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLG EYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSED KLLACGEGAADI I IGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGVALQTMKQEF LIN LVKQKQPQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKL ISKTRAAALGVGGGSGGGGSGGGGSGMGSWYEFWRRLHAIWLRL KALGGSEAEIAAFEKEIAAFESELQAYKKGKNPEVEWLRQDAAQ IRYILQAYRHNGGGGSGGGGSGGGGSHHHHHHHHHH
1512	$\alpha 3D(Q19E).3xGS.p26.3xGS.eb09.HIS$ 	MGSWAEFKQRLAAIKTRLEALGGSEAEIAAFEKEIAAFESELQA YKKGKNPEVEALRKEAAAI RDELQAYRHNGGGGSGGGGSGGGG GLEKCFQ TENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLG EYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSED KLLACGEGAADI I IGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGVALQTMKQEF LIN LVKQKQPQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKL ISKTRAAALGVGGGSGGGGSGGGGSGMGSWWFEFNRHLHAIWRL KALGGSEAEIAAFEKEIAAFESELQAYKKGKNPEVELLREKAAQ IRAQLQAYRHNGGGGSGGGGSGGGGSHHHHHHHHHH
1513	$\alpha 3D(Q19E).3xGS.p26.3xGS.eb10.HIS$ 	MGSWAEFKQRLAAIKTRLEALGGSEAEIAAFEKEIAAFESELQA YKKGKNPEVEALRKEAAAI RDELQAYRHNGGGGSGGGGSGGGG GLEKCFQ TENPLECQDKGEEELQKYIQESQALAKRSCGLFQKLG EYYLQNAFLVAYTKKAPQLTSSELMAITRKMAATAATCCQLSED KLLACGEGAADI I IGHLCIRHEMTPVNPVGVCCTSSYANRRPC FSSLVVDETYVPPAFSDDKFI FHKDL CQAQGVALQTMKQEF LIN LVKQKQPQITEEQLEAVIADFSGLLEKCCQGGQEQEVCFAEEGQKL ISKTRAAALGVGGGSGGGGSGGGGSGMGSWWFEFNMRLSAIKYRL YALGGSEAEIAAFEKEIAAFESELQAYKKGKNPEVEILRRLAAD IRERLQAYRHNGGGGSGGGGSGGGGSHHHHHHHHHH

TABLE: 6 Exemplary ADBD CAR Sequences

SEQ ID NO:	CAR Design	CAR Sequence
1089	CTsp-Flag-GSlinker- $\alpha 3D(Q19E)$ -GSlinker-CD8H-TM-41BB-CD3 ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGSWAEFKQRLAAIKTRLEALGGSE AELAAFEKEIAAFESELQAYKKGKNPEVEALRKEAAAI RDELQAYRHNGGAGSGTTTPAPR PPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLY CKRGRKKLLYIFKQPFMRPVQTTQEEDGCSRFPEEEEGGCEL RVKFSRSADAPAYKQGQ QLYNELNLGRREYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEI GMKGE RRRGKHDGLYQGLSTATKDTYDALHMQALPPR
1090	CTsp-Flag-GSlinker-cg06-GSlinker-CD8H-TM-41BB-CD3 ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGSWDEFGRRLYAI EWRLYALGGSE AELAAFEKEIAAFESELQAYKKGKNPEVEKLREIAAVIRSNLQAYRHNGGGGSGGGSGTT TPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSL VITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSRFPEEEEGGCEL RVKFSRSADAPAY KQGQQLYNELNLGRREYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKHDGLYQGLSTATKDTYDALHMQALPPR
1091	CTsp-Flag-GSlinker-bc40-GSlinker-CD8H-TM-41BB-CD3 ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGSWSEFWRLGAIRERLDALGGSE AELAAFEKEIAAFESELQAYKKGKNPEVEKLRYTAATIRRFQAYRHNGGGGSGGGSGSTT TPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSL VITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSRFPEEEEGGCEL RVKFSRSADAPAY KQGQQLYNELNLGRREYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKHDGLYQGLSTATKDTYDALHMQALPPR
1092	CTsp-Flag-GSlinker-af03-GSlinker-CD8H-TM-41BB-CD3 ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGSWFEFYDRLNAIDARLWALGGSE AELAAFEKEIAAFESELQAYKKGKNPEVENLRVHAAAI REWLQAYRHNGGGGSGGGSGSTT TPAPRPPTPAPTIA SQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAP LAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSRFPEEEEGGCEL RVKFSRSADAPAY KQGQQLYNELNLGRREYDVLDKRRGRDP EMGGKPRRKNPQEGLYNELQKDKMAEAYSEI GMKGERRRGKHDGLYQGLSTATKDTYDALHMQALPPR

		VKFSRSADAPAYKQGQNLQYLNELNLGRREYDVLDKRRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKHDGLYQGLSTATKDTYDALHMQALPFR
1093	CTsp-Flag-GSlinker-af05-GSlinker-CD8H-TM-41BB-CD3ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGWSWLEFYHRLNAIDSRWLALGGSEAEAAFEKEIAAFESSELQAYKGKGNPEVESLRDHAAHIREWLQAYRHNGGGSGGGSGGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNLQYLNELNLGRREYDVLDKRRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKHDGLYQGLSTATKDTYDALHMQALPFR
1133	CTsp-Flag-GSlinker-af59-GSlinker-CD8H-TM-41BB-CD3ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGWSWFEFYDRLNAIDARLWALGGSEAEAAFEKEIAAFESSELQAYKGKGNPEVESLRVHAAAIREWLOAYRHNGGGSGGGSGGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNLQYLNELNLGRREYDVLDKRRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKHDGLYQGLSTATKDTYDALHMQALPFR
1134	CTsp-Flag-GSlinker-af83-GSlinker-CD8H-TM-41BB-CD3ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGWSWSEFYDRLNAIDARLWALGGSEAEAAFEKEIAAFESSELQAYKGKGNPEVESLRVHAAAIREWLOAYRHNGGGSGGGSGGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNLQYLNELNLGRREYDVLDKRRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKHDGLYQGLSTATKDTYDALHMQALPFR
1135	CTsp-Flag-GSlinker-af99-GSlinker-CD8H-TM-41BB-CD3ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGWSWFEFYDRLNAIDARLWALGGSEAEAAFEKEIAAFESSELQAYKGKGNPEVESLRHAAAIREWLOAYRHNGGGSGGGSGGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNLQYLNELNLGRREYDVLDKRRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKHDGLYQGLSTATKDTYDALHMQALPFR
1136	CTsp-Flag-GSlinker-af101-GSlinker-CD8H-TM-41BB-CD3ζ	MAFLWLLSCWALLGTTFGDYKDDDDKGGGSGGGGSMGWSWSEFYDRLNAIDARLWALGGSEAEAAFEKEIAAFESSELQAYKGKGNPEVESLRHAAAIREWLOAYRHNGGGSGGGSGGTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNLQYLNELNLGRREYDVLDKRRGRDPPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRRGKHDGLYQGLSTATKDTYDALHMQALPFR

Example 2. D-domain CAR T cells kill tumor cells expressing the D domain target

[0697] The cytolytic activity of ADBD CAR expressing T cells was assessed on a panel of tumors using effector cell to target cell ratios ranging from 1: 4 to 1: 64. The cytolytic activity of a CD123-binding CAR (cg06, SEQ ID NO: 1090); a BCMA binding CAR (bc40, SEQ ID NO: 1091) were compared to a CAR with no known target-specificity (α3D-Q19E, SEQ ID NO: 1089).

[0698] 10,000 T cells expressing the indicated CARs were incubated with increasing numbers of a CD123⁺/BCMA⁻ tumor target (MOLM13)(FIG. 1A); a CD123⁺/BCMA⁺ tumor target (H929)(FIG. 1B); a CD123⁻ tumor target (RAJI)(FIG. 1C); or a CD123⁺/BCMA⁻ tumor target (MOLM13)(FIG. 1D). After 16 hours, cells were washed and luciferase activity was assessed.

Example 3. Adapter binding associates with Adapter and CAR binding specificity

[0699] Jurkat NFAT-Luciferase reporter cells were transduced with a negative control CAR (α3D-Q19E, SEQ ID NO: 1089), an p26-binding CAR (af03, SEQ ID NO: 1092), or a BCMA-binding CAR (bc40, SEQ ID NO: 1091). In FIG. 2A, CAR transduced Jurkat cells were incubated with 0.5μg of Adapter protein (SEQ ID NO: 1082-1085) at 4°C for 20 minutes, washed, and then stained with anti-HIS PE (clone J095G46, 4°C for 20 minutes). CAR expression based on FLAG staining (clone L5) versus mock transduced Jurkat cells was also evaluated (FIG. 2B).

Example 4. Adapter binding of matching CAR: Adapter and Target: Adapter specificity drives lysis of target cells

[0700] 40,000 CD123⁺BCMA⁻ MOLM13-GFP/Luciferase cells were incubated with various Adapters (SEQ ID NO: 1082-1084) in the presence or absence of 20,000 T cells (E: T ratio of 1: 2, donor D14-053017, Day 7) transduced with BCMA-binding CAR (bc40, SEQ ID NO: 1091) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of MOLM13-GFP/Luciferase cultured in the absence of T cells or Adapter protein (*see*, FIG. 3A). A control of CD123-specific CAR T cells (cg06, SEQ ID NO: 1090) cultured at the same ratio was used as a positive control for lysis.

[0701] In FIG. 3B, 40,000 CD123⁺BCMA⁻ MOLM13-GFP/Luciferase cells were incubated with Adapter (cg06-p26, SEQ ID NO: 1084) in the presence or absence of 20,000 T cells (E: T ratio of 1: 2, donor D16-061317, Day 7) transduced with p26-binding CARs (Af03, SEQ ID NO: 1092) or Af05, SEQ ID NO: 1093) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of MOLM13-GFP/Luciferase cultured in the absence of T cells or Adapter protein. A control of CD123-binding CAR T cells (cg06, SEQ ID NO: 1090) cultured at the same ratio was used as a positive control for lysis.

[0702] In FIG. 3C, 40,000 BCMA⁺ NCI H929-GFP/Luciferase cells were incubated with Adapter (bc40-p26, SEQ ID NO: 1085) in the presence or absence of 10,000 T cells (E: T ratio of 1: 4, donor D15-062017, Day 8) mock transduced, or transduced with p26-binding CARs (Af03, SEQ ID NO: 1092 or Af05, SEQ ID NO: 1093) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of NCI-H929-GFP/Luciferase cultured in the absence of T cells or Adapter protein.

Example 5. Adapter binding of matching CAR: Adapter and Target: Adapter specificity drives cytokine production by CAR T-cells

[0703] Donor D14-053017 T cells transduced with BCMA-binding CAR (bc40, SEQ ID NO: 1091) were cultured overnight with various Adapters (cg06-BCMA, SEQ ID NO: 1082; α3D-BCMA, SEQ ID NO: 1083; or cg06-p26, SEQ ID NO: 1084) in the presence or absence of CD123⁺BCMA⁻ MOLM13 cells (25,000 T cells and target cells). Cultured supernatants were collected and assessed for the production of IL-2 (FIG. 4A) and IFN-γ (FIG. 4B). In FIGS. 4C and 4D, donor D15-062017 T cells transduced with p26-binding CARs (Af03, SEQ ID NO: 1092 or Af05, SEQ ID NO: 1093) were cultured overnight with CD123 binding Adapter (cg06p26, SEQ ID NO: 1084) Adapter in the presence or absence of CD123⁺BCMA⁻ MOLM13 cells (25,000

T cells and target cells). Cultured supernatants were collected and assessed for the production of IL-2 (**FIG. 4C**) and IFN- γ (**FIG. 4D**).

Example 6. CAR T cells proliferate following exposure to an Adapter that is bound by the CAR and bound to a tumor expressing the AD recognized by the Adapter

[0704] In **FIG. 5**, Donor D16-062717 cells transduced with AFP-binding CAR (Af03, SEQ ID NO: 1092) were CFSE labeled (10 minutes at 0.5 μ M), then cultured (25,000) in the presence of CD123-binding Adapter (cg06-p26, SEQ ID NO: 1084) or BCMA-binding Adapter (bc40-p26, SEQ ID NO: 1085) in the presence or absence of mitomycin-C treated CD123⁻BCMA⁺ NCI-H929 cells (25,000) for 72 hours. At 72 hours, cells were stained for CD3, then analyzed for absolute numbers of CD3⁺ cells via flow cytometry.

Example 7. Adapter binding of matching CAR: Adapter and Target: Adapter specificity signaling by CAR T cells

[0705] 50,000 reporter cells previously transduced with a BCMA-binding CAR (bc40, SEQ ID NO: 1091) were cultured for 5 hours in the presence of various Adapters (cg06-BCMA, SEQ ID NO: 1082; α 3D-BCMA, SEQ ID NO: 1083; or cg06-p26, SEQ ID NO: 1084) in the presence or absence of 50,000 CD123⁺BCMA⁻ MOLM14 cells, then assessed for luciferase activity (**FIG. 6A**).

[0706] 50,000 reporter cells previously transduced with an p26-binding CAR (af03, SEQ ID NO: 1092) were cultured for 5 hours in the presence of Adapters (α 3DQ19E-BCMA, SEQ ID: 1086; bc40-p26, SEQ ID NO: 1085) in the presence or absence of 50,000 BCMA⁺ NCI-H929 cells, then assessed for luciferase activity (**FIG. 6B**).

[0707] **FIGS. 6A and 6B** show that Adapter binding of matching CAR: Adapter and Target: Adapter drives signaling by CAR-expressing Jurkat NFAT-Luciferase reporter cells.

Example 8. Adapters containing D domains or ScFvs drive CAR cell: Adapter mediated lysis of target cells

[0708] A CD123-binding Adapter with a BCMA AD (SEQ ID NO: 1082) was evaluated for its ability to function with a control CAR (α 3DQ19E, SEQ ID NO: 1089), a BCMA-binding CAR (bc40, SEQ ID NO: 1091) or a BCMA-specific scFv CAR (c11D5-3) obtained from WO 2010/104949 A2.

[0709] 40,000 CD123⁺BCMA⁻ MOLM13-GFP/Luciferase cells were incubated with the Cg06-BCMA Adapter (SEQ ID NO: 1082) in the presence or absence of 20,000 T cells (E: T ratio of 1: 2, donor D14-062717, Day 9) transduced with a control CAR (SEQ ID NO: 1089), the BCMA-binding CAR (SEQ ID NO: 1091), or the BCMA-binding scFv CAR (c11D5-3) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of MOLM13-GFP/Luciferase cultured in the absence of T cells or Adapter protein. Solid lines indicate calculated 3-parameter non-linear

curves, while the dashed line for c11D5-3 is present for illustrative purposes only (**FIG. 7A**).

CD123⁺BCMA⁻ MOLM13-GFP/Luciferase cells were cultured in the same experiment as in **FIG. 7A** with transduced T cells in the absence of Adapter protein (**FIG. 7B**).

[0710] **FIGS. 7A and 7B** show that the CD123-specific Adapter with a BCMA antigenic determinant can function with either a BCMA-specific D domain CAR (bc40) or a BCMA-specific scFv CAR (c11D5-3).

Example 9. Use of multiple Adapters target a CAR cell to multiple antigen targets

[0711] 10⁵ Jurkat NFAT-Luciferase transduced with a p26-binding CAR (af03, SEQ ID NO: 1092) were incubated with a total of 0.5µg of Adapters (SEQ ID NO: 1084, SEQ ID NO: 1085) at the indicated ratios at 4°C for 20 minutes, washed, and then incubated with CD123-Fc and biotinylated BCMA (0.5µg of each) (4°C for 20 minutes), washed, then binding detected with Anti-Fc A488 and Streptavidin-PE. **FIG. 8A** presents a flow cytometric analysis of CD123-binding and BCMA-binding to their respective target proteins, **FIG. 8B** provides a comparison of mean fluorescence intensity (MFI) of A488 MFI (CD123-binding, left axis) and PE MFI (BCMA-binding, right axis) flow cytometric data presented in **FIG. 8A**.

[0712] **FIGS. 8A and 8B** show that AFP-specific CARs can simultaneously have CD123 and BCMA-binding capacity via incubation with multiple Adapter proteins.

Example 10. Use of dual binding domain Adapters to enhance CAR signaling

[0713] 50,000 reporter cells previously transduced with an p26-binding CAR (af03, SEQ ID NO: 1092) were cultured for 5 hours in the presence of the CD123-binding Adaptor (cg06-p26, SEQ ID NO: 1084) or the bivalent Adaptor (cg06-p26-cg06, SEQ ID NO: 1087) in the presence of 50,000 CD123⁺ MOLM13 or CD123-deficient MOLM13 cells, then assessed for luciferase activity. CD123 deficient cells were generated using CRISPR/Cas9 genetic engineering technology (**FIG. 9A**). 50,000 reporter cells previously transduced with an p26-binding CAR (af03, SEQ ID NO: 1092) were cultured for 5 hours in the presence of the BCMA-binding Adaptor (bc40-p26, SEQ ID NO: 1085) or the bivalent Adapter ((bc40-p26-bc40, SEQ ID NO: 1088) in the presence or absence of 50,000 BCMA⁺ U266 cells, then assessed for luciferase activity (**FIG. 9B**).

[0714] **FIGS. 9A and 9B** show that dual-binding domain adaptor proteins drive enhanced signaling by CAR-expressing Jurkat cells over single-binding domain adaptor proteins.

Example 11. CD45 specific D-domain CAR T cells kill CD45 expressing target cells

[0715] T-cells will be transduced with a CAR comprising a CD45 specific D domain. CD45- CAR T-cells expressing a CAR comprising a human CD45 specific D domain will be generated using CRISPR/Cas9 genetic engineering technology. CD45 specific gRNA and crRNA and Cas9 will be obtained from commercial sources. The self-lysing activity of the CD45- CAR T cells will be assessed using assays for cell proliferation, viability and/or cytotoxicity, for example 7-AAD staining and chromium release assay. Self-lysing of CD45- CAR T-cells will be compared to CD45⁺ control CAR T-cells expressing the same CAR comprising the CD45 specific D domain.

[0716] The cytolytic activity of CD45- T cells expressing a CAR comprising a human CD45 specific D domain will be assessed on a panel of CD45+ target cells using effector cell to target cell ratios ranging from 1: 4 to 1: 64. The cytolytic activity of the CD45- CAR T cells will be compared to a CAR with no known target-specificity.

Example 12. CD45 specific Adapter directed lysis of target cells

[0717] CD45- CAR T-cells will be generated using CRISPR/Cas9 genetic engineering technology. CD45 specific gRNA and crRNA and Cas9 will be obtained from commercial sources. The self-lysing activity of the CD45- CAR T cells will be assessed using assays for cell proliferation, viability and/or cytotoxicity, for example 7-AAD staining and chromium release assay. Self-lysing of CD45- CAR T-cells will be compared to CD45+ control CAR T-cells.

[0718] The cytolytic activity of CD45- T cells expressing a CAR comprising a human CD45 specific D domain will be assessed on a panel of CD45+ target cells using effector cell to target cell ratios ranging from 1: 4 to 1: 64. The cytolytic activity of the CD45- CAR T cells will be compared to a CAR with no known target-specificity.

[0719] CD45+ target cells will be incubated with various Adapters comprising a CD45 specific D domain and p26 in the presence or absence of CD45- T cells transduced with a p26-binding CAR for 16 hours. After 16 hours, cells will be washed and luciferase activity will be assessed. Percent lysis will be assessed based on wells of target cells cultured in the absence of T cells or Adapter protein. A control of CD45-specific CAR T cells cultured at the same ratio will be used as a positive control for lysis.

Example 13. Adapter comprising truncated p26 have improved bioactivity in cytotoxicity assay

[0720] Analysis of p26 structure revealed an N-terminal stretch of residues that were predicted to increase the potential for aggregation and/or proteolysis. This N-terminal sequence also contains a predicted disulfide bond pair, which could potentially destabilize the protein if the cysteines are un-paired, or reinforce a suboptimal protein conformation if the disulfide bond is formed. To eliminate these potential developmental liabilities, N-terminal truncated variants of p26 were prepared. In p26(G17-V229) (SEQ ID NO: 1118) the first 16 residues of p26 were removed to eliminate the disulfide pair of cysteines (C4 - C13). In p26(K23-V229) (SEQ ID NO: 1120) the first 22 residues of p26 were removed to additionally eliminate the beginning of a predicted albumin 3 domain. In p26(Q26-V229) the first 25 residues were removed to eliminate two hydrophobic residues (YI) beyond the K23 truncation and thus make the N-terminus flush with the predicted globular region of p26. The binding of full length and truncated p26 to FcRn was assessed using ELISA. Adapters comprising full-length p26 or the truncated p26(Q26-V229) variant bind to FcRn in a pH dependent manner, with higher binding affinity observed at pH 6.0 than at pH 7.4.

[0721] The bioactivity of Adapters comprising full length p26 or the truncated p26(G17-V229), p26(K23-V229) or p26(Q26-V229) variants were tested in various Luciferase-based Cytotoxicity Assays. Surprisingly, Adapters comprising truncated p26 had higher bioactivity than Adapters comprising full-length p26.

[0722] 40,000 BCMA⁺ NALM6/Luciferase cells were incubated with Adapters BCMA(bc98)-p26 JPE (SEQ ID NO: 1124), BCMA(bc98)-p26 (SEQ ID NO: 1125), BCMA(bc98)-p26(Q26-V229) (SEQ ID NO: 1126), BCMA(bc98)-p26(K23-V229) (SEQ ID NO: 1127), or BCMA(bc98)-p26(G17-V229) (SEQ ID NO: 1128), in the presence of 10,000 T cells (E: T ratio of 1: 4) transduced with a p26-binding CAR (Af59, SEQ ID NO: 1133) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of NALM6/Luciferase cultured in the absence of T cells or Adapter protein. Adapters comprising the truncated p26 variants had higher bioactivity than the Adapters comprising the full-length p26. The EC50 values measured for the Adaptors were as follows:

Adapter	EC50
BCMA(bc98)-p26 JPE	1.135
BCMA(bc98)-p26	1.962
BCMA(bc98)-p26(Q26-V229)	0.1294
BCMA(bc98)-p26(K23-V229)	0.2232
BCMA(bc98)-p26(G17-V229)	0.367

[0723] 40,000 BCMA⁺ NCI H929/Luciferase cells were incubated with Adapters BCMA(bc98)-p26 JPE (SEQ ID NO: 1124), BCMA(bc98)-p26 (SEQ ID NO: 1125), BCMA(bc98)-p26(Q26-V229) (SEQ ID NO: 1126), BCMA(bc98)-p26(K23-V229) (SEQ ID NO: 1127), or BCMA(bc98)-p26(G17-V229) (SEQ ID NO: 1128), in the presence of 10,000 T cells (E: T ratio of 1: 4) transduced with a p26-binding CAR (Af59, SEQ ID NO: 1133) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of NCI-H929/Luciferase cultured in the absence of T cells or Adapter protein. Adapters comprising the truncated p26 variants had higher bioactivity than the Adapters comprising the full-length p26. The EC50 values measured for the Adaptors were as follows:

Adapter	EC50
BCMA(bc98)-p26 JPE	0.367
BCMA(bc98)-p26	0.3869
BCMA(bc98)-p26(Q26-V229)	0.04357
BCMA(bc98)-p26(K23-V229)	0.06069
BCMA(bc98)-p26(G17-V229)	0.1318

[0724] The presence of the Q127P substitution in the truncated p26 did not alter the Adapter's bioactivity. 40,000 BCMA⁺ NCI H929/Luciferase cells were incubated with Adapters BCMA(bc98)-p26 (SEQ ID NO: 1124), BCMA(bc98)-p26(Q26-V229) (SEQ ID NO: 1126), or BCMA(bc98)-p26(Q26-V229)Q217P (SEQ ID

NO: 1131), in the presence of 10,000 T cells (E: T ratio of 1: 4) transduced with a p26-binding CAR (Af59, SEQ ID NO: 1133) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of NCI-H929/Luciferase cultured in the absence of T cells or Adapter protein. Adapters comprising the truncated p26 variants had higher bioactivity than the Adapters comprising the full-length p26. Adapters comprising the truncated p26 variants with or without the Q217P substitution had substantially the same bioactivity. The EC50 values measured were as follows:

Adapter	EC50
BCMA(bc98)-p26	0.5243
BCMA(bc98)-p26(Q26-V229)	0.1142
BCMA(bc98)-p26(Q26-V229)Q217P	0.143

[0725] Bivalent Adapters comprising a truncated p26 variant also performed better than a corresponding Adapter comprising full-length p26. 40,000 BCMA⁺ NCI H929 /Luciferase cells were incubated with Adapters BCMA(bc98)-p26-BCMA(bc98) (SEQ ID NO: 1129), BCMA(bc98)-p26(Q26-V229)-BCMA(bc98) (SEQ ID NO: 1132), or BCMA(bc98)-p26(Q26-V229)Q217P-BCMA(bc98) (SEQ ID NO: 1130), in the presence of 10,000 T cells (E: T ratio of 1: 4) transduced with a p26-binding CAR (Af59, SEQ ID NO: 1133) for 16 hours. After 16 hours, cells were washed and luciferase activity was assessed. Percent lysis was assessed based on wells of NCI-H929/Luciferase cultured in the absence of T cells or Adapter protein. Adapters comprising the truncated p26 variants had higher bioactivity than the Adapters comprising the full-length p26. Adapters comprising the truncated p26 variants with or without the Q217P substitution had substantially the same bioactivity. The EC50 values measured for the Adaptors were as follows:

Adapter	EC50
BCMA(bc98)-p26-BCMA(bc98)	0.008227
BCMA(bc98)-p26(Q26-V229)-BCMA(bc98)	0.00256
BCMA(bc98)-p26(Q26-V229)Q217P-BCMA(bc98)	0.001812

Example 14. Binding of truncated and full length p26 to human FcRn is pH dependent

[0726] The binding of full length and truncated p26 to FcRn was assessed using an ELISA format in which wells of 96-well plate were coated with adapter (bc40-p26 (SEQ ID NO:1085), bc98-p26(Q26-V229)-bc98 (SEQ ID NO:1132), HSA, bc40 (SEQ ID NO:197 with HIS-tag) or uncoated) overnight at 4°C. Wells were then blocked with PBS + 1% fish gelatin for 1 hour at 22°C. Parallel wells were then washed with PBS + 0.1% Tween at pH 6.0 or 7.4. Biotinylated human FcRn in PBS + 1% fish gelatin (either pH 6.0 or 7.4) was serially diluted and added to wells and incubated for 1 hour at 22°C. After washing with PBS + 0.1% Tween at pH 6.0 or 7.4, streptavidin-HRP (in PBS + 1% fish gelatin at pH 6.0 or 7.4) was added. After a final wash, signal was developed using TMB reagent and quantified by reading absorbance at A450. As shown in Figure

10, adapters comprising full-length p26 or the truncated p26(Q26-V229) variant bind to FcRn in a pH dependent manner, with higher binding affinity observed at pH 6.0 than at pH 7.4.

Example 15. Adapters comprising CS1 (SLAMF7, CRACC, CD319) specific ADBD modulate intracellular signaling and killing of CS1 positive tumors

[0727] CS1 binding domains (ADBD) were isolated by panning ADBD phage libraries on the extracellular domain of human CS1 protein. Representative CS1 binding ADBD were fused to p26 in a bispecific format with non-binding α 3DQ19E (SEQ ID NO: 1021) to generate adapter proteins for functional testing in combination with af59-CAR (SEQ ID NO: 1133) expressing JNL10 cells or human T cells expressing af59-CAR.

CS1 (SLAMF7, CRACC, CD319) Adapter Constructs	Adapter SEQ ID NO:	CS1 ADBD SEQ ID NO:	CS1 ADBD clone ID
□3D Q19E-p26-cc08.HIS	1500	787	cc08
□3D Q19E-p26-cc01.HIS	1501	780	cc01
□3D Q19E-p26-cc02.HIS	1502	781	cc02
□3D Q19E-p26-cc09.HIS	1503	788	cc09
□3D Q19E-p26-cc10.HIS	1504	789	cc10
□3D Q19E-p26-cc12.HIS	1505	791	cc12

[0728] Among the adapters tested in, the cc02 and cc08 ADBD displayed the most potent NFAT signaling when cultured in the presence of af59-CAR expressing JNL10 cells and the CS1 positive tumor cell line, MM.1S (Figure 11A).

[0729] The cc02 CS1 ADBD (SEQ ID NO: 781) was fused to p26 and either the non-binding α 3DQ19E DD (SEQ ID NO: 1021) or the BCMA-binding bc98 DD (SEQ ID NO: 201). The ability of the resulting adapters to induce signaling in af59-CAR expressing JNL10 cells in the presence of the BCMA positive and CS1 positive cell line, MM.1S was assessed. As shown in Figure 11B, the bispecific bc98-p26-cc02 adapter capable of binding both CS1 and BCMA was more potent in its ability to signal than were the monospecific BCMA-binding bc98-p26- α 3DQ19E adapter and the monospecific CS1-binding α 3DQ19E-p26-cc02 adapter.

[0730] The af59-CAR (SEQ ID NO: 1133) was transduced into normal human T cells and the ability of those cells to kill H929 (BCMA++, CS1+) and MM.1S (BCMA++, CS1++) tumors using the indicated adapters was assessed. The data shown in Figures 11C and D indicate the bispecific bc98-p26-cc02 is an effective adapter in killing HT929 (high expression of both BCMA and CS1) and MM.1S (high BCMA, low CS1).

Example 16. Adapters comprising HER2 binding ADBD induce signaling in Af59-CAR expressing JNL10-cells cultured with HER2-positive SKBR3 tumor cells α 3D(Q19E)-p26-Eb(08), or Affibody/Darpin-Based adapters

[0731] HER2 (ERBB2, CD340) binding domains (ADBD) were isolated by panning ADBD phage libraries on the extracellular domain of human HER2 protein. Representative HER2 binding ADBD were fused to p26 in a bispecific format with non-binding α 3DQ19E (SEQ ID NO: 1021) to generate adapter proteins for functional testing in combination with af59-CAR (SEQ ID NO:1133) expressing JNL10 cells or human T cells expressing af59-CAR.

HER2 (erbB2) Adapter Constructs	Adapter Construct SEQ ID NO:	HER2 ADBD SEQ ID NO:	ADBD clone ID
α 3D(Q19E).3xGS.p26.3xGS. α 3D(Q19E).HIS	1506	N/A	N/A
α 3D(Q19E).3xGS.p26.3xGS.eb03.HIS	1507	804	eb03
α 3D(Q19E).3xGS.p26.3xGS.eb04.HIS	1508	814	eb04
α 3D(Q19E).3xGS.p26.3xGS.eb05.HIS	1509	810	eb05
α 3D(Q19E).3xGS.p26.3xGS.eb06.HIS	1510	834	eb06
α 3D(Q19E).3xGS.p26.3xGS.eb08.HIS	1511	809	eb08
α 3D(Q19E).3xGS.p26.3xGS.eb09.HIS	1512	833	eb09
α 3D(Q19E).3xGS.p26.3xGS.eb10.HIS	1513	839	eb10

[0732] The adapters demonstrated a range of activities in their ability to induce JNL10 NFAT signaling when cultured in the presence of af59-CAR expressing JNL10 cells and HER2 positive SKBR3 tumor cells. As shown in Figure 12A, the adapter comprising eb08 was the most potent stimulator in this assay.

[0733] The adapter comprising eb08 was then compared to other adapters containing a HER2 binding domains derived from affibodies (zHER2(4) and zHER2(342)) or DARPins (9.29 and G3). As shown in Figure 12B, the NFAT signaling in JNL10 cells mediated by the adapter comprising eb08 is greater than that of mediated by the adapter comprising zHERs:4, comparable to that of mediated by the adapter comprising 9.29, and less than that of G3 and zHER2:342.

[0734] The ability of adapters comprising the HER2-binding eb08 and eb04 domain to induce tumor (SKBR3) kill was compared with adapters containing other HER2 binding domains derived from affibodies (zHER2(4) and zHER2(342)) or DARPins (9.29 and G3). Each adapter was incubated with normal human T cells transduced with af59-CAR that binds p26 found in each adapter. SKBR3 lysis was quantitated in a 16-hour luciferase-based assay at an effector to target ratio of 1:5. The results of the assay shown in Figure 12C demonstrate that adapters comprising eb08 or eb04 modulate tumor lysis in a dose-dependent manner.

[0735] Throughout this application, various publications are referenced by author name and date, or by Patent No. or Patent Publication No. The disclosure of these publications are hereby incorporated in their entireties by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein. However, the citation of a reference herein should not be construed as an acknowledgement that such reference is prior art to the present invention.

WHAT IS CLAIMED IS:

- I. A composition suitable for use in therapy comprising a cell expressing a chimeric antigen receptor (CAR) and an Adapter, wherein
 - (a) the CAR comprises (i) a D domain that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell, wherein the first AD is AFP p26, AFP, CD123, BCMA, or CS1, and wherein the second AD is CS1, BCMA, CD19, CD22, CD45, CD123, HER2, TACI, BAFFR, or PDL1;
 - (b) the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
 - (c) the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
 - (d) the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an alternative scaffold binding domain (ASBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell;
 - (e) the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD comprising an ASBD that binds to a second AD on a target cell;
 - (f) the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain;; and the Adapter comprises (i) said first AD and (ii) a D domain that binds to a second AD on a target cell;
 - (g) the CAR comprises (i) a D domain that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a target cell; or
 - (h) the CAR comprises (i) a first D domain that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and the Adapter comprises (i) said first AD and (ii) a second D domain that binds to a second AD on a target cell.

2. The composition of claim 1, wherein the CAR is characterized by one or more of,
- (a) the CAR comprises a single-chain variable fragment (scFv) ADBD;
 - (b) the CAR comprises an alternative scaffold binding domain (ASBD) ADBD;
 - (c) the CAR comprises a D domain, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 17-26, and 27 or SEQ ID NO: 44-1078, and 1079;
 - (d) the CAR comprises 2 ADBDs;
 - (e) the CAR comprises an ASBD and a scFv;
 - (f) the CAR comprises a D domain and a scFv;
 - (g) the CAR comprises 2 ASBDs;
 - (h) the CAR comprises 2 D domains;
 - (i) the CAR intracellular domain is a signaling domain;
 - (j) the CAR intracellular domain comprises a primary signaling domain;
 - (k) the CAR intracellular domain comprises a CD3 ζ primary signaling domain;
 - (l) the CAR intracellular domain further comprises a costimulatory signaling domain;
 - (m) the CAR intracellular domain comprises a costimulatory signaling domain selected from: CD28, 41BB, CD27, and CD134;
 - (n) the CAR intracellular domain comprises a 41BB costimulatory signaling domain;
 - (o) the CAR binds to an antigen selected from: CD19, CD22, CD123, BCMA, CS1, HER2, TACI, BAFFR, and PDL1;
 - (p) the CAR binds to BCMA, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 44-338, and 339;
 - (q) the CAR binds to CD123, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 340-77 and 773;
 - (r) the CAR binds to CD19, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1030-1058, and 1059;
 - (s) the CAR binds to CD22, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1060-1068, and 1069;
 - (t) the CAR binds to CS1, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 780-794, and 795;
 - (u) the CAR binds to HER2, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 800-839, and 840;
 - (v) the CAR binds to TACI or BAFFR;
 - (w) the CAR binds to PDL1, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079;

- (x) the CAR binds to AFP p26, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 841-983, and 984;
 - (y) the CAR comprises 2 ADBDs that bind to separate targets;
 - (z) the CAR binds to CD19 and CD123;
 - (aa) the CAR binds to BCMA and CS1;
 - (bb) the CAR binds to CD22 and CD123;
 - (cc) the CAR binds to PDL1 and CD123;
 - (dd) the CAR comprises a first ASBD that binds to CD19 and a second ASBD that binds to CD123;
 - (ee) the CAR comprises a first D domain that binds to CD19 and a second D domain that binds to CD123;
 - (ff) the CAR comprises a D domain that binds to CD19 and a scFv that binds to CD123;
 - (gg) the CAR comprises a first ASBD that binds to BCMA and a second ASBD that binds to CS1;
 - (hh) the CAR comprises a first D domain that binds to BCMA and a second D domain that binds to CS1;
 - (ii) the CAR comprises a D domain that binds to CS1 and a scFv that binds to BCMA;
 - (jj) the CAR comprises a D domain that binds to BCMA and a scFv that binds to CS1;
 - (kk) the CAR comprises a first ASBD that binds to CD22 and a second ASBD that binds to CD123;
 - (ll) the CAR comprises a first D domain that binds to CD22 and a second D domain that binds to CD123;
 - (mm) the CAR comprises a D domain that binds to CD22 and a scFv that binds to CD123;
 - (nn) the CAR comprises a first ASBD that binds to PDL1 and a second ASBD that binds to CD123;
 - (oo) the CAR comprises a first D domain that binds to PDL1 and a second D domain that binds to CD123;
 - (pp) the CAR comprises a D domain that binds to PDL1 and a scFv that binds to CD123; and
 - (qq) the CAR comprises an ASBD that binds to CD19 and a scFv that binds to CD123.
3. The composition of claim 1 or claim 2, wherein the Adapter is characterized by one or more of
- (a) the Adapter comprises an AD that is an epitope of AFP p26 or AFP, and optionally comprises the amino acid residues of SEQ ID NO: 16 or 1117-1123;
 - (b) the Adapter comprises an AD of a tumor antigen wherein optionally the tumor antigen is selected from the group: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1;
 - (c) the Adapter comprises an ADBD that is a scFv;
 - (d) the Adapter comprises an ADBD that is an ASBD;

- (e) the Adapter comprises a D domain, and optionally wherein the Adapter comprises a sequence selected from the group: SEQ ID NO: 17-26, and 27, or SEQ ID NO: 44-1078, and 1079;
 - (f) the Adapter comprises two ADBDs; wherein optionally the two ADBDs (i) are the same, (ii) bind to the same antigenic determinant, (iii) bind to different ADs of the same antigen, or (iv) bind to different antigens on the same cell, or (v) bind to different antigens on different cells;
 - (g) the Adapter comprises two ASBDs;
 - (h) the Adapter comprises two D domains, and optionally wherein the Adapter comprises an amino acid sequence selected from the group: SEQ ID NO: 44-1079;
 - (i) the Adapter comprises an ADBD that is a scFv and an ADBD that is an ASBD;
 - (j) the Adapter comprises an ADBD that is a scFv and an ADBD that is a D domain;
 - (k) the Adapter comprises an ADBD that binds to a member selected from: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1;
 - (l) the Adapter comprises an ADBD that binds to BCMA, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 44-338, and 339;
 - (m) the Adapter comprises an ADBD that binds to CS1, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 780-794, and 795;
 - (n) the Adapter comprises an ADBD that binds to HER2, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 800-839, and 840;
 - (o) the Adapter comprises an ADBD that binds to CD123, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 340-772 and 773;
 - (p) the Adapter comprises an ADBD that binds to CD19, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1030-1058, and 1059;
 - (q) the Adapter comprises an ADBD that binds to binds to CD22, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1060-1068, and 1069;
 - (r) the Adapter comprises an ADBD that binds to binds to TACI;
 - (s) the Adapter comprises an ADBD that binds to BAFFR;
 - (t) the Adapter comprises an ADBD that binds to PDL1, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079;
 - (u) the Adapter is bispecific;
 - (v) the Adapter comprises an ADBD that binds to CD19 and an ADBD that binds to CD123;
 - (w) the Adapter comprises an ADBD that binds to BCMA and an ADBD that binds to CS1;
 - (x) the Adapter comprises an ADBD that binds to CD22 and an ADBD that binds to CD123; and
 - (y) the Adapter comprises an ADBD that binds to PDL1 and an ADBD that binds to CD123.
4. The composition of any of claims 1-3, wherein

- (a) the target cell is a tumor cell;
 - (b) the target cell is a tumor cell selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (c) the target cell is multiple myeloma;
 - (d) at least one target cell is a tumor cell, optionally wherein the tumor cell is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (e) the first and second target cells are tumor cells, optionally wherein the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (f) the first and second target cells are tumor cells of the same type, , optionally wherein the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (g) the first and second target cells are tumor cells tumor cells of a different type, , optionally wherein the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (h) the target cell is a cancer cell selected from: breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, colon cancer, and lung cancer; and/or
 - (i) the target cell is breast cancer or ovarian cancer.
5. The composition of any of claims 1-4,
- (a) wherein the cell expressing the CAR is an immune effector cell;
 - (b) wherein the cell expressing the CAR is a T cell; or
 - (c) wherein the cell expressing the CAR is an NK cell.
6. A method of killing a target cell comprising contacting the target cell with the composition of any one of claims 1-5.

7. A method of killing a target cell, delivering an immune response to a target cell, treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection, or treating hematological cancer, comprising
- (a) contacting a composition comprising a target cell with an Adapter, wherein
 - (1) the composition comprising the target cell further comprises a cell expressing a CAR, wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
 - (b) contacting a composition comprising a first target cell with an Adapter, wherein
 - (1) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD on said first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
 - (c) contacting a composition comprising a target cell with an Adapter, wherein
 - (1) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
 - (d) contacting a composition comprising a target cell with an Adapter, wherein
 - (1) the composition comprising the target cell further comprises a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first AD, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;
 - (e) contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
 - (1) a first antigenic determinant (AD) is present on the target cell;

- (2) the composition comprising the first target cell further comprises an Adapter comprising
 - (i) said first AD and (ii) an antigenic determinant binding domain (ADBBD) that binds to a second AD on the target cell; and
 - (3) the CAR comprises (i) an ADBBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
 - (f) contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
 - (1) a first AD is present on a first target cell;
 - (2) the composition comprising the first target cell further comprises a second target cell and an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBBD) that binds to a second AD on a second target cell; and
 - (3) the CAR comprises (i) an ADBBD that binds to said first AD on the first target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
 - (g) contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
 - (1) a first antigenic determinant (AD) is present on the target cell;
 - (2) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBBD) that binds to said first AD on said target cell and (ii) a second AD; and
 - (3) the CAR comprises (i) an ADBBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain; or
 - (h) contacting a composition comprising a target cell with a cell expressing a chimeric antigen receptor (CAR), wherein
 - (1) a first antigenic determinant (AD) is present on the target cell;
 - (2) the composition comprising the target cell further comprises an Adapter comprising (i) an antigenic determinant binding domain (ADBBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
 - (3) the CAR comprises (i) an ADBBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.
8. A method of killing a target cell, redirecting target cell killing, delivering an immune response to a target cell, directing an immune response to a target cell, treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection, redirecting treatment of a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection, directing treatment of a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection, treating hematological cancer,

redirecting treatment of a hematological cancer, or directing treatment of a hematological cancer in a patient, comprising

- (a) administering an Adapter to the patient, wherein
 - (1) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- (b) administering an Adapter to the patient, wherein
 - (1) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a first target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
- (c) administering an Adapter to the patient, wherein
 - (1) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- (d) administering an Adapter to the patient, wherein
 - (1) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;
- (e) administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
 - (1) a first antigenic determinant (AD) and a second AD is present on the target cell;
 - (2) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to said second AD on said target

- cell; and
- (3) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- (f) administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (1) the patient has been treated with an Adapter comprising (i) a first antigenic determinant (AD) and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on the target cell; and
- (2) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- (g) administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (1) a first antigenic determinant (AD) is present on the target cell;
- (2) the patient has been treated with an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that binds to said first AD on said target cell and (ii) a second AD; and
- (3) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- (h) administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (1) a first antigenic determinant (AD) is present on the target cell;
- (2) the patient has been treated with a an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
- (3) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain;
- (i) administering an Adapter to the patient, wherein
- (1) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on said target cell, (ii) a transmembrane domain, and (iii) an intracellular domain; and
- (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- (j) administering an Adapter to the patient, wherein
- (1) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD) on a first target cell, (ii) a transmembrane

- domain, and (iii) an intracellular domain; and
- (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on a second target cell;
- (k) administering an Adapter to the patient, wherein
 - (1) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that binds to a second AD on said target cell;
- (l) administering an Adapter to the patient, wherein
 - (1) the patient has been treated with a cell expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - (2) the Adapter comprises (i) said first AD and (ii) an ADBD that is an ASBD that binds to a second AD on said target cell;
- (m) administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
 - (1) a first antigenic determinant (AD) and a second AD is present on the target cell;
 - (2) the patient has been treated with an Adapter comprising (i) said first AD and (ii) an antigenic determinant binding domain (ADBD) that binds to said second AD on said target cell; and
 - (3) the CAR comprises (i) an ADBD that binds to said first AD on the target cell or the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- (n) administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
 - (1) the patient has been treated with an Adapter comprising (i) a first antigenic determinant (AD) and (ii) an antigenic determinant binding domain (ADBD) that binds to a second AD on the target cell; and
 - (2) the CAR comprises (i) an ADBD that binds to said first AD on the Adapter, (ii) a transmembrane domain, and (iii) an intracellular domain;
- (o) comprising administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
 - (1) a first antigenic determinant (AD) is present on the target cell;
 - (2) the patient has been treated with an Adapter comprising (i) an antigenic determinant

- binding domain (ADBD) that binds to said first AD on said target cell and (ii) a second AD; and
- (3) the CAR comprises (i) an ADBD that is an ASBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain; or
- (p) administering a cell expressing a chimeric antigen receptor (CAR) to the patient, wherein
- (1) a first antigenic determinant (AD) is present on the target cell;
- (2) the patient has been treated with a an Adapter comprising (i) an antigenic determinant binding domain (ADBD) that is an ASBD that binds to said first AD on said target cell and (ii) a second AD; and
- (3) the CAR comprises (i) an ADBD that binds to said second AD, (ii) a transmembrane domain, and (iii) an intracellular domain.
9. The method of claim 7 or claim 8, wherein the proliferative disorder, cancer, or hematological cancer is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, myelodysplasia, breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, colon cancer, and lung cancer.
10. The method of any one of claims 7-9, wherein the CAR is characterized by one or more of,
- (a) the CAR comprises a single-chain variable fragment (scFv) ADBD;
 - (b) the CAR comprises an alternative scaffold binding domain (ASBD) ADBD;
 - (c) the CAR comprises a D domain, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 17-26, and 27 or SEQ ID NO: 44-1078, and 1079;
 - (d) the CAR comprises 2 ADBDs;
 - (e) the CAR comprises an ASBD and a scFv;
 - (f) the CAR comprises a D domain and a scFv;
 - (g) the CAR comprises 2 ASBDs;
 - (h) the CAR comprises 2 D domains;
 - (i) the CAR intracellular domain is a signaling domain;
 - (j) the CAR intracellular domain comprises a primary signaling domain;
 - (k) the CAR intracellular domain comprises a CD3 ζ primary signaling domain;
 - (l) the CAR intracellular domain further comprises a costimulatory signaling domain;
 - (m) the CAR intracellular domain comprises a costimulatory signaling domain selected from: CD28, 41BB, CD27, and CD134;
 - (n) the CAR intracellular domain comprises a 41BB costimulatory signaling domain;

- (o) the CAR binds to an antigen selected from: CD19, CD22, CD123, BCMA, CS1, HER2, TACI, BAFFR, and PDL1;
- (p) the CAR binds to BCMA, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 44-338, and 339;
- (q) the CAR binds to CD123, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 340-77 and 773;
- (r) the CAR binds to CD19, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1030-1058, and 1059;
- (s) the CAR binds to CD22, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1060-1068, and 1069;
- (t) the CAR binds to CS1, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 780-794, and 795;
- (u) the CAR binds to HER2, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 800-839, and 840;
- (v) the CAR binds to TACI or BAFFR;
- (w) the CAR binds to PDL1, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079;
- (x) the CAR binds to AFP p26, and optionally wherein the CAR comprises a sequence selected from the group: SEQ ID NO: 841-983, and 984;
- (y) the CAR comprises 2 ADBDs that bind to separate targets;
- (z) the CAR binds to CD19 and CD123;
- (aa) the CAR binds to BCMA and CS1;
- (bb) the CAR binds to CD22 and CD123;
- (cc) the CAR binds to PDL1 and CD123;
- (dd) the CAR comprises a first ASBD that binds to CD19 and a second ASBD that binds to CD123;
- (ee) the CAR comprises a first D domain that binds to CD19 and a second D domain that binds to CD123;
- (ff) the CAR comprises a D domain that binds to CD19 and a scFv that binds to CD123;
- (gg) the CAR comprises a first ASBD that binds to BCMA and a second ASBD that binds to CS1;
- (hh) the CAR comprises a first D domain that binds to BCMA and a second D domain that binds to CS1;
- (ii) the CAR comprises a D domain that binds to CS1 and a scFv that binds to BCMA;
- (jj) the CAR comprises a D domain that binds to BCMA and a scFv that binds to CS1;
- (kk) the CAR comprises a first ASBD that binds to CD22 and a second ASBD that binds to CD123;

- (ll) the CAR comprises a first D domain that binds to CD22 and a second D domain that binds to CD123;
 - (mm) the CAR comprises a D domain that binds to CD22 and a scFv that binds to CD123;
 - (nn) the CAR comprises a first ASBD that binds to PDL1 and a second ASBD that binds to CD123;
 - (oo) the CAR comprises a first D domain that binds to PDL1 and a second D domain that binds to CD123;
 - (pp) the CAR comprises a D domain that binds to PDL1 and a scFv that binds to CD123; and
 - (qq) the CAR comprises an ASBD that binds to CD19 and a scFv that binds to CD123.
11. The method of any one of claims 7-10, wherein the Adapter is characterized by one or more of
- (a) the Adapter comprises an AD that is an epitope of AFP p26 or AFP, and optionally comprises the amino acid residues of SEQ ID NO: 16 or 1117-1123;
 - (b) the Adapter comprises an AD of a tumor antigen wherein optionally the tumor antigen is selected from the group: BCMA, CD123, CD19, CD22, CS1, HER2, TACI, BAFFR, and PDL1;
 - (c) the Adapter comprises an ADBD that is a scFv;
 - (d) the Adapter comprises an ADBD that is an ASBD;
 - (e) the Adapter comprises a D domain, and optionally wherein the Adapter comprises a sequence selected from the group: SEQ ID NO: 17-26, and 27, or SEQ ID NO: 44-1078, and 1079;
 - (f) the Adapter comprises two ADBDs; wherein optionally the two ADBDs (i) are the same, (ii) bind to the same antigenic determinant, (iii) bind to different ADs of the same antigen, or (iv) bind to different antigens on the same cell, or (v) bind to different antigens on different cells;
 - (g) the Adapter comprises two ASBDs;
 - (h) the Adapter comprises two D domains, and optionally wherein the Adapter comprises an amino acid sequence selected from the group: SEQ ID NO: 44-1079;
 - (i) the Adapter comprises an ADBD that is a scFv and an ADBD that is an ASBD;
 - (j) the Adapter comprises an ADBD that is a scFv and an ADBD that is a D domain;
 - (k) the Adapter comprises an ADBD that binds to a member selected from: BCMA, CD123, CD19, CD22, CS1, TACI, BAFFR, and PDL1;
 - (l) the Adapter comprises an ADBD that binds to BCMA, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 44-338, and 339;
 - (m) the Adapter comprises an ADBD that binds to CS1, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 780-794, and 795;
 - (n) the Adapter comprises an ADBD that binds to HER2, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 800-839, and 840;

- (o) the Adapter comprises an ADBD that binds to CD123, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 340-772 and 773;
 - (p) the Adapter comprises an ADBD that binds to CD19, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1030-1058, and 1059;
 - (q) the Adapter comprises an ADBD that binds to binds to CD22, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1060-1068, and 1069;
 - (r) the Adapter comprises an ADBD that binds to binds to TACI;
 - (s) the Adapter comprises an ADBD that binds to BAFFR;
 - (t) the Adapter comprises an ADBD that binds to PDL1, and optionally wherein the ADBD comprises a sequence selected from the group: SEQ ID NO: 1010-1016, 1074-1078, and 1079;
 - (u) the Adapter is bispecific;
 - (v) the Adapter comprises an ADBD that binds to CD19 and an ADBD that binds to CD123;
 - (w) the Adapter comprises an ADBD that binds to BCMA and an ADBD that binds to CS1;
 - (x) the Adapter comprises an ADBD that binds to CD22 and an ADBD that binds to CD123; and
 - (y) the Adapter comprises an ADBD that binds to PDL1 and an ADBD that binds to CD123.
12. The method of any one of claims 7-11, wherein
- (a) the target cell is a tumor cell;
 - (b) the target cell is a tumor cell selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (c) the target cell is multiple myeloma;
 - (d) at least one target cell is a tumor cell, optionally wherein the tumor cell is selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (e) the first and second target cells are tumor cells, optionally wherein the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (f) the first and second target cells are tumor cells of the same type, , optionally wherein the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's

- macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
- (g) the first and second target cells are tumor cells of a different type, , optionally wherein the tumor cells are selected from: acute leukemia, chronic leukemia, polycythemia vera, lymphoma, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, myelodysplastic syndrome, hairy cell leukemia, and myelodysplasia;
 - (j) the target cell is a cancer cell selected from: breast cancer, prostate cancer, ovarian cancer, pancreatic cancer, colon cancer, and lung cancer; and/or
 - (h) the target cell is breast cancer or ovarian cancer.
13. The method of any one of claims 7-12,
- (a) wherein the cell expressing the CAR is an immune effector cell;
 - (b) wherein the cell expressing the CAR is a T cell; or
 - (c) wherein the cell expressing the CAR is an NK cell.
14. An engineered human immune effector cell comprising
- a. a chimeric antigen receptor (CAR) comprising (1) an antigenic determinant binding domain (ADBBD) that specifically binds to a human CD45 antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and
 - b. a genetic modification that eliminates the expression of the human CD45 AD on the engineered cell,
- wherein the engineered cell is capable of directing an immune response to a CD45 AD expressing cell in an in vitro assay, and wherein the engineered cell does not express the CD45 AD.
15. A method of killing a target cell or delivering an immune response to a target cell comprising contacting the engineered cell according to claim 14 with the target cell, wherein the target cell expresses human CD45.
16. A method of directing an immune response to a target cell, treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection, depleting lymphocytes, depleting memory T cell, treating an autoimmune disease or disorder, or treating a hematological cancer in a subject, or conditioning a subject for transplantation, comprising administering to the subject in need thereof an effective amount of the engineered cell according to claim 14.
17. An engineered human immune effector cell comprising
- a. a chimeric antigen receptor (CAR) comprising (1) a first antigenic determinant binding domain

- (ADBD) that specifically binds to a first antigenic determinant (AD), (2) a transmembrane domain, and (3) an intracellular domain; and
- b. a genetic modification that eliminates the expression of at least one human CD45 AD on the engineered cell,
- wherein the first AD is not the at least one human CD45 AD, wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a CD45 AD expressing cell in an in vitro assay, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the at least one human CD45 AD, and wherein the engineered cell does not express the at least one human CD45 AD.
18. A method of killing a target cell or delivering an immune response to a target cell comprising contacting the engineered cell according to claim 17 with an Adapter and the target cell, wherein the target cell expresses CD45, and wherein the Adapter comprises the first AD and a second ADBD that specifically binds to a human CD45 AD, optionally wherein the target cell is a hematological cancer cell.
19. A method of directing an immune response to a target cell, treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection, depleting lymphocytes, depleting memory T cell, treating an autoimmune disease or disorder, or treating a hematological cancer in a subject, or conditioning a subject for transplantation comprising
- a. administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to claim 17 and a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD;
- b. administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to claim 234, wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD; or
- c. administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to a human CD45 AD, wherein the subject has been administered the engineered cell according to claim 17.
20. An engineered human immune effector cell comprising:
- a. a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that bind to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
- b. a genetic modification that eliminates the expression of the first AD on the engineered cell, wherein the engineered cell does not express the first AD.
21. A method of killing a target cell or delivering an immune response to a target comprising

- a. contacting the engineered cell according to claim 20 with the target cell;
 - b. contacting the engineered cell according to claim 20 with an Adapter and the target cell, wherein the Adapter comprises an AD recognized by the CAR and a second ADBD;
 - c. contacting the engineered cell according to claim 20 with an Adapter and the target cell, and wherein the Adapter comprises an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell; or
 - d. contacting the engineered cell according to claim 20 with an Adapter and a cancer cell, wherein the Adapter comprises an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the cancer cell.
22. A method of directing an immune response to a target cell, treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection, depleting lymphocytes, depleting memory T cell, treating an autoimmune disease or disorder, or treating a hematological cancer in a subject, or conditioning a subject for transplantation comprising
- a. administering to the subject in need thereof an effective amount of the engineered cell according to claim 20;
 - b. administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to claim 20 and a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell;
 - c. administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to claim 20, wherein the subject has been administered an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell; or
 - d. administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising an AD recognized by the CAR and a second ADBD that is capable of binding a second AD on the target cell, wherein the subject has been administered the engineered cell according to claim 20.
23. An engineered human immune effector cell comprising:
- a. a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a first antigenic determinant binding domain (ADBD) that specifically binds to a first antigenic determinant (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - b. a genetic modification that eliminates the expression of a second AD on the engineered cell, wherein the engineered cell used in combination with an Adapter is capable of directing an immune

response to a cell expressing the second AD in an in vitro assay, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the engineered cell does not express the second AD.

24. An engineered human immune effector cell comprising:
 - a. a chimeric antigen receptor (CAR), wherein the CAR comprises (i) two or more antigenic determinant binding domains (ADBD) comprising a first ADBD that specifically binds to a first antigenic determinants (AD), (ii) a transmembrane domain, and (iii) an intracellular domain; and
 - b. a genetic modification that eliminates the expression of a second AD on the engineered cell,wherein the engineered cell used in combination with an Adapter is capable of directing an immune response to a cell expressing the second AD in an in vitro assay, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the engineered cell does not express the second AD.
25. A method of killing a target cell or delivering an immune response to a target cell comprising contacting the engineered cell according to claim 23 or claim 24 with an Adapter and the target cell, wherein the Adapter comprises the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the target cell, optionally wherein the target cell is a hematological cancer cell.
26. A method of directing an immune response to a target cell, treating a proliferative disorder, cancer, autoimmune disease, infection, or allograft rejection, depleting lymphocytes, depleting memory T cell, treating an autoimmune disease or disorder, or treating a hematological cancer in a subject, or conditioning a subject for transplantation comprising
 - a. administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to claim 23 or claim 24;
 - b. administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to claim 23 or claim 24 and a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein the second AD is expressed on the target cell;
 - c. administering to the subject in need thereof a therapeutically effective amount of the engineered cell according to claim 23 or claim 24, wherein the subject has been administered an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, and wherein the second AD is expressed on the target cell; or
 - d. administering to a subject in need thereof a therapeutically effective amount of an Adapter comprising the first AD and a second ADBD that specifically binds to the second AD, wherein

the subject has been administered the engineered cell according to claim 23 or claim 24, and wherein the second AD is expressed on the target cell.

27. An isolated Adapter polypeptide comprising (1) an antigenic determinant (AD) and (b) one or more antigenic determinant binding domain (ADBD), wherein at least one ADBD specifically binds to a human CD45 AD, and wherein contacting the Adaptor with a CD45 AD expressing target cell in the presence of an engineered cell according to claim 17 is capable of directing an immune response by the engineered cell to the target cell in an in vitro assay.