[0006] In one aspect, provided herein are proteins comprising a D Domain (DD) target binding domain (DDpp) wherein the DD specifically binds CS1. In some embodiments, CS1 is human CS1, or a fragment thereof (e.g., SEQ ID NO: 1). In some embodiments, the DDpp are monovalent or multivalent. In some embodiments, the DDpp are monospecific or multispecific. In further embodiments, the DDpp are monospecific and multivalent. In other embodiments, the DDpp are multispecific and multivalent. Fusion proteins comprising one or more DD are also provided, as are methods of making and using the fusion proteins. Nucleic acids encoding the DDpps and vectors and host cells containing the nucleic acids are also provided. Non-limiting examples of such uses include, but are not limited to target analysis, and diagnostic and therapeutic applications. In some embodiments, the DDpp comprises a CS1-binding DD comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 41-106. In some embodiments, the DDpp comprises a DD comprising the amino acid sequence of SEQ ID NO: 46. In some embodiments, the DDpp comprises a DD comprising the amino acid sequence of SEQ ID NO: 60.

[0006a] In one aspect, provided herein is a protein comprising a D Domain target binding domain that specifically binds CS1 and comprises the amino acid sequence of any one of SEQ ID NOs: 41-106.

[0007] In one aspect, the disclosure provides a chimeric antigen receptor (CAR) which comprises a target binding domain comprising a DD that binds CS1 and comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 41-105 and 106. In some embodiments, the CS1-specific DD comprises the amino acid sequence of SEQ ID NO: 46. In some embodiments, the CS1-specific DD comprises the amino acid sequence of SEQ ID NO: 60. In some embodiments, the CAR comprises, a target binding domain, a transmembrane domain, and an intracellular signaling domain. In some embodiments the CAR further comprises a second target binding domain having the same or a different target than the DD target binding domain. In some embodiments, the CAR is expressed in an immune cell. In some embodiments, the immune cell is an autologous cell. In some embodiments, the immune cell is an allogenic cell. In some embodiments, the immune cell is an immune effector cell. In some embodiments, the immune cell is a T cell (CAR-T cell) or a natural killer (NK) cell (CAR-NK cell). In some embodiments, the cell is an autologous immune cell. In some embodiments the cell is an autologous T cell (CAR-T cell) or an autologous natural killer (NK) cell. In some embodiments, the cell is an allogenic immune cell. In some embodiments the cell is an allogenic T cell (CAR-T cell) or an allogenic natural killer (NK) cell. In some embodiments, the CAR is expressed in an immune cell derived from human embryonic stem cells (CAR-hESCs) or induced pluripotent stem cells (CAR-iPSC cell).

[0008] Nucleic acids encoding the disclosed DDpp (*e.g.*, DDpp fusion protein, CAR, or Adapter) are also provided. Additionally provided are vectors (*e.g.*, plasmids, viral vectors, and non-viral vectors) containing nucleic acids encoding the DDpp (*e.g.*, DDpp fusion protein, CAR, or Adapter) and host cells containing the nucleic acids and vectors. In some embodiments, the vector comprises a nucleotide sequence which regulates the expression of the polypeptide encoded by the nucleic acid molecule. In further embodiments, the vector comprises an inducible promoter sequence. In additional embodiments, the vector includes one or more additional standard components for expression of a protein encoded a

nucleic acid (*e.g.*, promoters, packaging components, *etc.*). In some embodiments, the vector is a lentiviral vector.

[0008a] In one aspect, provided herein is an isolated polynucleotide encoding the protein as described herein.

[0008b] In one aspect, provided herein is a vector comprising the polynucleotide as described herein.

[0009] In one aspect, the disclosure also provides host cells that comprise the nucleic acid molecules encoding a target-binding DDpp disclosed herein. In some embodiments, the host cells (*e.g.*, cells of a cell line) are engineered to express a protein containing a DD disclosed herein (*e.g.*, a DD having the amino acid sequence of SEQ ID NO: 41-106). In some embodiments, the expression of the DDpp (*e.g.*, DDpp fusion protein, or Adapter) by the host cells allows production and isolation of the DDpp. In some embodiments, the expression results in the DDpp (e.g., CAR) being expressed on the surface and/or integral to the membrane of the host cells. In some embodiments, the host cell is a bacterial, yeast, fungal, or plant cell. In other embodiments, the host cell is a mammalian cell. In a further embodiment, the mammalian cell is an immune cell. In one embodiment, the host cell is a human immune cell. In some embodiments, the human immune cell is a T cell. In other embodiments, the human immune cell is a natural killer (NK) cell. In some embodiments, the immune cell is an autologous cell. In some embodiments, the immune cell is an allogenic cell. In some embodiments, the human immune cell displays the DDpp (e.g., CAR) on its cell surface.

[0009a] In one aspect, provided herein is a host cell comprising the polynucleotide as described herein or the vector as described herein.

[0010] In one aspect, the disclosure further provides a host cell expressing a protein comprising a DD disclosed herein. In some embodiments, the host cell expresses a chimeric antigen receptor (CAR) comprising a DD disclosed herein. In some embodiments, the CAR comprises a target binding domain that comprises a DD comprising an amino acid sequence selected from SEQ ID NO: 41-106 and a transmembrane domain. In some embodiments, the CS1-specific DD comprises the amino acid sequence of SEQ ID NO: 46. In some embodiments, the CS1-specific DD comprises the amino acid sequence of SEQ ID NO: 60. In some embodiments, the CAR further comprise an intracellular domain (comprising a signaling domain). In some embodiments, the CAR immune cell is a T cell. In some embodiments, the CAR immune cell is a NK cell. In some embodiments, the CAR immune cell is not a T cell or an NK cell. In some embodiments, the CAR immune cell is an autologous immune cell. In some embodiments, the CAR immune cell is an allogenic immune cell. In some embodiments, the host cell is an immune effector cell that further comprises a second CAR polypeptide having a DD or other binding domain (*e.g.*, scFv) that specifically binds the same or a different target (*e.g.*, a different epitope of the same target, or a second target of interest) expressed by the cancer cell) as the first CAR expressed by the host immune cell.

[0011] Pharmaceutical compositions containing a protein comprising a DD disclosed herein, nucleic acids disclosed herein encoding the proteins, vectors disclosed herein containing the nucleic acids, viruses encoding the proteins, and host cells disclosed herein containing the nucleic acids and or vectors are also provided. As are kits containing one or more of the disclosed target-binding DDpps (*e.g.*, DDpp fusion proteins such as DD-Fc and DD-CAR, or Adapter), nucleic acid molecules, vectors, and host cells (*e.g.*, a therapeutic kit, a diagnostic kit, a kit for research use, *etc.*).

[0012] DDpp provided herein possess activities that include but are not limited to the ability to specifically bind CS1 *in vitro* or *in vivo* and the ability to serve as a reactive site for linking or associating a protein such as a DDpp fusion protein with one or more additional moieties (*e.g.*, a solid support), and/or other modifications. The DDpp provided herein can also possess additional desirable properties and/or functionalities useful in manufacturing, formulation and biological, diagnostic, and therapeutic applications.

[0013] Methods of using DDpp in diagnostic and therapeutic applications are also provided. In one embodiment, the disclosure provides a method of treating a disease or disorder comprising administering a therapeutically effective amount of a DDpp (*e.g.*, a DDpp fusion protein, CAR and/or Adapter) that specifically binds CS1 to a subject in need thereof. In some embodiments, the disease or disorder is cancer, a B cell malignancy (e.g., multiple myeloma), a disease or disorder of the immune system, or an infection. Methods of treating a disease or disorder that comprises co-administering an additional therapeutic agent along with a disclosed DDpp are also provided. In some embodiments, the disease or disorder is myeloma. In some embodiments, the disease or disorder is multiple myeloma.

[0013a] In one aspect, provided herein is a method of delivering an immune response to or killing one or more target cells comprising contacting a composition comprising the target cell with a cell expressing the CAR as described herein.

[0013b] In one aspect, provided herein is a method of delivering an immune response to or killing one or more target cells comprising contacting a composition comprising the target cell with the protein of as described herein, 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 an antigenic determinant (AD) other than CS1, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the protein as described herein comprises (i) a D domain that binds to CS1 and (ii) the AD bound by the CAR.

[0013c] In one aspect, provided herein is a use of a composition comprising a cell expressing the CAR as described herein in the manufacture of a medicament for treating cancer.

[0013d] In one aspect, provided herein is a use of a composition comprising the protein as described herein in the manufacture of a medicament for treating cancer, wherein (a) the composition further comprises a cell expressing a CAR, wherein the CAR comprises (i) an antigenic determinant binding domain (ADBD) that binds to an antigenic determinant (AD) other than CS1, (ii) a transmembrane domain, and (iii) an intracellular domain; and (b) the protein as described herein comprises (i) a D domain that binds to CS1 and (ii) the AD bound by the CAR.

[0013e] In one aspect, provided herein is a composition comprising a cell expressing the CAR as described herein or a composition comprising the protein as described herein for use in therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1. Luciferase based cytotoxicity assay on MM1S-GFP-luc cells using AFPDD101-CAR cells and CS1-targeting adaptor proteins comprising the CS1DD006 or CS1DD020 CS1-specific D domains. % lysis of MM1S-GFP-luc cells is shown.

[0015] Figure 2. CS1 expression by multiple myeloma cell lines.

[0016] Figure 3. CS1DD006 and CS1DD020 comprising Adaptors induce cytokine release by AFPDD101-CAR cells in the presence of CS1 expressing target cells. IFN gamma release in the presence of L363, MM1S, U266, OPM2 and H929 multiple myeloma cells is shown.

[0017] Figure 4. CS1 and BCMA expression by MM1S and H929 multiple myeloma cell lines.

[0018] Figure 5. Bispecific targeting response varies with antigen densities. % cell lysis of MM1S-GFP-luc and H929-GFP-luc cells is shown. % cell lysis by AFPDD101-CAR cells in the presence of CS1, BCMA or CS1xBCMA specific Adapters and CS1 expressing MM1S (panel A) and H929 (panel B) target cells.

[0019] Figure 6. Bispecific targeting response varies with antigen densities. IFN gamma and IL-2 release by AFPDD101-CAR cells in the presence of CS1DD020 or BCMADDXX comprising mono or bivalent Adaptors and CS1 expressing MM1S and H929 target cells is shown.

[0020] Figure 7. In vivo characterization of CS1-targeting bivalent Adapters. Proliferation of MM1S-GFP-luc cells in mice following various treatments is shown.

[0021] Figure 8. Degranulation assay using AFPDD101-CAR T cells and CS1-targeting adaptor proteins with or without MM1S target cells. %CD107a+ cells among CD3+FLAG+CD4+ cells is shown.