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.

SUMMARY

[0005a] In one aspect, provided herein is the use of a therapeutically effective dose of cells expressing a chimeric antigen receptor (CAR) in the manufacture of a medicament for treating a lymphoma or myeloma, wherein the therapeutically effective dose of cells is to be administered to a subject in need thereof, and wherein the CAR comprises (i) a D domain that binds to BCMA (B cell maturation antigen) and comprises amino acid residues 21 to 93 of SEQ ID NO:1166 or a sequence having at least 90% sequence to amino acid residues 21 to 93 of SEQ ID NO:1166, and (ii) amino acid residues 94 to 327 of SEQ ID NO:1166.

[0006] In some embodiments, the disclosure provides:

[1.] A composition comprising:

[1.] A method of treating a lymphoma or leukemia comprising administering to a subject in need thereof

a. a therapeutically effective dose of cells expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a D domain that binds to AFP p26 or a variant thereof, (ii) a transmembrane domain, and (iii) an intracellular domain; and

b. one or more therapeutically effective dose of an Adapter comprising (i) AFP p26 or a variant thereof and (ii) a D domain that binds to BCMA;

[2.] the method of [1], wherein the lymphoma or leukemia comprises cells expressing BCMA;

[3.] the method of [1] or [2], wherein the lymphoma or leukemia is a B cell lymphoma or leukemia;

[4.] the method of [1] or [2], wherein the lymphoma or leukemia is multiple myeloma;

[5.] a method of delivering an immune response to a multiple myeloma cell comprising administering to a subject in need thereof

a. a therapeutically effective dose of cells expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a D domain that binds to AFP p26 or a variant thereof, (ii) a transmembrane domain, and (iii) an intracellular domain; and

b. one or more therapeutically effective dose of an Adapter comprising (i) AFP p26 or a variant thereof and (ii) a D domain that binds to BCMA;

[6.] a method a method of killing a multiple myeloma cell comprising administering to a subject in need thereof

a. a therapeutically effective dose of cells expressing a chimeric antigen receptor (CAR), wherein the CAR comprises (i) a D domain that binds to AFP p26 or a variant thereof, (ii) a transmembrane domain, and (iii) an intracellular domain; and

b. one or more therapeutically effective dose of an Adapter comprising (i) AFP p26 or a variant thereof and (ii) a D domain that binds to BCMA;

[7.] a method of depleting multiple myeloma cells comprising administering to a subject in need thereof

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/lL3Ra, 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, MARTI, 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-23Hl, 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.

[0155] 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 SLAM7, 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 (MAGSPTCLTLIYILWQLTGSAA, SEQ ID NO: 1137) and an extracellular domain comprising the 226 N-terminal residues (SEQ ID NO: 1138), has Genbank Accession No. NP_067004 (SEQ ID NO: 1139). 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.

[0156] 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-Barr syndrome, Hashimoto's disease, hemolytic anemia, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis, pemphigus vulgaris, psoriasis, rheumatic fever, rheumatoid arthritis, sarcoidosis, scleroderma, Sjogren's syndrome, spondyloarthropathies, thyroiditis, vasculitis, vitiligo, myxedema, pernicious anemia, ulcerative colitis, among others.

X_{40} 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.

[0233] 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 KLPPGWX_7KX_9WS$X_{12}X_{13}X_{14}$GRVX_{18}YX_{20}NX_{22}ITX_{25}AX_{27}QWERP (SEQ ID NO: 37), wherein X_7,X_9,X_{12}, X_{13}, X_{14}, X_{18}, X_{20}, X_{22}, X_{25}, and X_{27} represent any amino acid, and X_{14} is optionally absent.

[0234] In some embodiments, the WW domain-based AD binding scaffold comprises the sequence KLPPGWX_7KX_9WS$X_{12}X_{13}$GRVX_{17} YX_{19}NX_{21}ITX_{24}AX_{26}QWERP (SEQ ID NO: 38), wherein X_7,X_9,X_{12}, X_{13}, X_{17}, X_{19}, X_{21}, X_{24}, and X_{26} represent any amino acid, and X_{14} is optionally absent.

Table 2. Exemplary loop-based ASBDs

ASBD	Sequence
Avimer1	EFX_3CX_5NGX_8CIP$X_{12}X_{13}$WX_{15}C DGX_{19}DDCGDX_{25}SDE (SEQ ID NO: 33)
Fynomer1	GVTLFVALYDY$X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}X_{22}$LSFHKGEK FQILSTHEYE$X_{41}X_{42}$ $X_{43}X_{44}X_{45}X_{46}X_{47}$ 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	GVTLFVALYDY$X_{12}X_{13}X_{14}X_{15}X_{16}X_{17}X_{18}X_{19}X_{20}X_{21}X_{22}$LSFHKGEKFQILSTHEYEDWWE ARSLTTGETGYIPSNYVAPVDSIQ, wherein X_{16}-X_{21} are optionally absent (SEQ ID NO: 35)
Kunitz1	MHSFCAFKADX_{11}GX_{13}CX_{15} $X_{16}X_{17}X_{18}X_{19}$RFFFNIFTRQCEEFX_{34} YGGC$X_{39}X_{40}$NQNR FES LEECKK MCTRDGA (SEQ ID NO: 36)
WW1	KLPPGWX_7KX_9WS$X_{12}X_{13}X_{14}$GRVX_{18} YX_{20}NX_{22}ITX_{25}AX_{27}QWERP (SEQ ID NO: 37)
WW2	KLPPGWX_7KX_9WS$X_{12}X_{13}$GRVX_{17} YX_{19}NX_{21}ITX_{24}AX_{26}QWERP (SEQ ID NO: 38)
X = all amino acid residues	

IV.Linkers

[0235] Linkers are peptide or other chemical linkages located between two or more otherwise independent functional domains of the Adapter or CAR.

[0236] 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.

[0237] 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

[0623] 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: 1122) 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) (SEQ ID NO: 1118) 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.

[0624] 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.

[0625] 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

[0626] 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

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

[0629] 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

[0630] 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 α3DQ19E (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**
α3D Q19E-p26-cc08.HIS	1150	787	cc08
α 3D Q19E-p26-cc01.HIS	1151	780	cc01
α 3D Q19E-p26-cc02.HIS	1152	781	cc02
α 3D Q19E-p26-cc09.HIS	1153	788	cc09
α 3D Q19E-p26-cc10.HIS	1154	789	cc10
α 3D Q19E-p26-cc12.HIS	1155	791	cc12

[0631] 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).

[0632] The cc02 CS1 ADBD (SEQ ID NO: 781) was fused to p26 and either the non-binding α3DQ19E 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-α3DQ19E adapter and the monospecific CS1-binding α3DQ19E-p26-cc02 adapter.

[0633] 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 α3D(Q19E)-p26-Eb(08), or Affibody/Darpin-Based adaptors

[0634] 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 α3DQ19E (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**
α3D(Q19E).3xGS.p26.3xGS. α3D(Q19E).HIS	**1156**	N/A	N/A
α3D(Q19E).3xGS.p26.3xGS.eb03.HIS	**1157**	804	eb03
α3D(Q19E).3xGS.p26.3xGS.eb04.HIS	**1158**	814	eb04
α3D(Q19E).3xGS.p26.3xGS.eb05.HIS	**1159**	810	eb05
α3D(Q19E).3xGS.p26.3xGS.eb06.HIS	**1160**	834	eb06
α3D(Q19E).3xGS.p26.3xGS.eb08.HIS	**1161**	809	eb08
α3D(Q19E).3xGS.p26.3xGS.eb09.HIS	**1162**	833	eb09
α3D(Q19E).3xGS.p26.3xGS.eb10.HIS	**1163**	839	eb10

[0635] 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.

[0636] 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.