[0005] Six-Transmembrane Epithelial Antigen of the Prostate 1 (STEAP1) is a cell surface antigen that is highly expressed in several carcinomas (e.g., prostate, breast, and bladder cancer). Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) is a cell surface glycoprotein, and member of the carcinoembryonic (CEA) antigen family. CEACAM5 is overexpressed in numerous tumor types including gastrointestinal, breast, and lung. Since these antigens are overexpressed on a variety of tumors, STEAP1 and CEACAM5 are potential candidates for targeted cancer therapeutic development.

[0006] While immunotherapies targeting STEAP1 and CEACAM5 have been tried, there still remains a need for novel immune response enhancing compositions for the treatment of STEAP1-associated and CEACAM5-associated cancers.

SUMMARY

[0007] Provided herein are novel anti-CD28 x anti-STEAP1 and anti-CD28 x anti-CEACAM5 antibodies and methods of using such antibodies for the treatment of related cancers (e.g., STEAP1 or CEACAM5-associated cancers). Subject anti-CD28 x anti-STEAP1 antibodies are capable of agonistically binding to CD28 costimulatory molecules on T cells and STEAP1 on tumor cells. Subject anti-CD28 x anti-CEACAM5 antibodies are capable of agonistically binding to CD28 costimulatory molecules on T cells and CEACAM5 on tumor cells. Thus, such antibodies selectively enhance anti-tumor activity at tumor sites while minimizing peripheral toxicity. The subject antibodies provided herein are particularly useful in combination with other anti-cancer therapies, including, for example, bispecific antibodies for the treatment of STEAP1- and CEACAM5-associated cancers.

[0008] In a first aspect, the present disclosure provides a heterodimeric antibody comprising: a) a first monomer comprising: i) a single chain variable fragment (scFv); and ii) a first Fc domain, wherein the scFv is covalently attached to the N-terminus of the first Fc domain using a domain linker; b) a second monomer comprising, from N-terminal to C-terminal, a VH1-CH1-hinge-CH2-CH3, wherein VH1 is a first variable heavy domain and CH2-CH3 is a second Fc domain; and c) a light chain comprising, from N-terminal to C- terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain, wherein the scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2), wherein the VH1 and the VL1 together form a first antigen binding domain (ABD) and the VH2 and the VL2 together form a second ABD,

and wherein one of the first ABD and the second ABD is a CD28 binding domain and the other of the first ABD and second ABD is a Six Transmembrane Epithelial Antigen of Prostate 1 (STEAP1) binding domain, wherein VH1 and VL1 are selected from the following: a) a VH according to the amino acid sequence of SEQ ID NO:1694 and a VL according to the amino acid sequence of SEQ ID NO:1811, b) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39, or c) a VH from Figure 31 and a VL from Figure 32; and wherein VH2 and VL2 are selected from the following: a) a VH according to the amino acid sequence of SEQ ID NO:2491 and a VL according to the amino acid sequence of SEQ ID NO:110, b) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant thereof, or c) a VH from Figures 15 ,16, or 46; and (ii) a VL from Figures 15, 17, or 82.

[0008a] In a first example, provided herein is an anti-CD28 x anti-STEAP1 heterodimeric antibody that comprises a) a first monomer; b) a second monomer; and c) a light chain. The first monomer comprises: i) a single chain variable fragment (scFv); and ii) a first Fc domain, wherein the scFv is covalently attached to the N-terminus of the first Fc domain using a domain linker. The second monomer comprises, from N-terminal to C-terminal, a VH1-CH1-hinge-CH2-CH3, wherein VH1 is a first variable heavy domain and CH2-CH3 is a second Fc domain. The light chain comprises, from N-terminal to C- terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2). The VH1 and the VL1 together form a first antigen binding domain (ABD) and the VH2 and the VL2 together form a second ABD. Further, one of the first ABD and the second ABD is a CD28

binding domain and the other of the first ABD and second ABD is Six Transmembrane Epithelial Antigen of Prostate 1 (STEAP1) binding domain.

[0009] In some examples, the scFv comprises, from N-terminal to C-terminal, VH2-scFv linker-VL2. In some examples, the scFv comprises, from N-terminal to C-terminal, VL2-scFv linker-VH2.

[0010] In exemplary examples, the first ABD is the STEAP1 binding domain and the second ABD is the CD28 binding domain. In some examples, VH1 and VL1 are selected from one of the following: a) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39 or a variant thereof; or b) a VH from Figure 31 and a VL from Figure 32 or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0011] In some examples, the first Fc domain and second Fc domain are each variant Fc domains.

[0012] In some examples, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering.

[0013] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0014] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0015] In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises amino acid variants

E233P/L234V/L235A/G236del/S267K/L368D/K370S/N208D/Q295E/N384D/Q418E/N421D and the first Fc domain comprises amino acid variants E233P/L234V/L235A/G236del/S267K/S364K/E357Q, wherein numbering is according to EU numbering. In exemplary examples, the first and second variant Fc domains each further comprise amino acid variants 428L/434S.

[0016] In some examples, the scFv linker is GKPGSGKPGSGKPGSGKPGS.

[0017] In another example, provided herein is an anti-CD28 x anti-STEAP1 heterodimeric antibody that comprises a) a first monomer; b) a second monomer; c) a first light chain; and d) a second light chain. The first monomer comprises, from N-terminal to C-terminal, VH1-CH1-first domain linker-scFv-second domain linker-CH2-CH3, wherein VH1 is a first variable heavy domain, and CH2-CH3 is a first Fc domain. The second monomer comprises, from N-terminal to C-terminal, a VH1-CH1-hinge-CH2-CH3, wherein CH2-CH3 is a second Fc domain. The first light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The second light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2). The VH1 of the first monomer and the VL1 of the first light chain and the VH1 of the second monomer and the VL1 of the second light chain each form a first antigen binding domain (ABD), and the VH2 and the VL2 form a second ABD. Further, the first ABDs are STEAP1 binding domains and the second ABD is a CD28 binding domain, or the first ABDs are CD28 binding domains and the second ABD is a STEAP1 binding domain.

[0018] In some examples, the scFv comprises, from N-terminal to C-terminal, VH2-scFv linker-VL2. In some examples, the scFv comprises, from N-terminal to C-terminal, VL2-scFv linker-VH2.

[0019] In exemplary examples, the first ABDs are the STEAP1 binding domains and the second ABD is the CD28 binding domain. In some examples, VH1 and VL1 are selected from one of the following: a) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39 or a variant thereof; or b) a VH from Figure 31 and a VL from Figure 32, or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant

thereof; or 2) (i) a VH from Figures 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0020] In some examples, the first Fc domain and second Fc domain are each variant Fc domains.

[0021] In some examples, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering

[0022] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0023] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0024] In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises amino acid variants E233P/L234V/L235A/G236del/S267K/L368D/K370S/N208D/Q295E/N384D/Q418E/N421D and the first Fc domain comprises amino acid variants E233P/L234V/L235A/G236del/S267K/S364K/E357Q, wherein numbering is according to EU numbering. In exemplary examples, the first and second variant Fc domains each further comprise amino acid variants 428L/434S.

[0025] In some examples, the scFv linker is GKPGSGKPGSGKPGSGKPGS.

[0026] In another example, provided herein is an anti-CD28 x anti-STEAP1 heterodimeric antibody that comprises a) a first monomer; b) a second monomer c) a first light chain; and d) a second light chain. The first monomer comprises, from N-terminal to C-terminal, VH1-CH1-hinge-CH2-CH3-domain linker-scFv, wherein VH1 is a first variable heavy domain, and CH2-CH3 is a first Fc domain. The second monomer comprises, from N-terminal to C-

terminal, a VH1-CH1-hinge-CH2-CH3, wherein VH1 is a first variable heavy domain and CH2-CH3 is a second Fc domain. The first light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The second light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2). The VH1 of the first monomer and the VL1 of the first light chain and the VH1 of the second monomer and the VL1 of the second light chain each form a first antigen binding domain (ABD), and the VH2 and the VL2 form a second ABD. Further, the first ABDs are STEAP1 binding domains and the second ABD is a CD28 binding domain, or the first ABDs are CD28 binding domains and the second ABD is a STEAP1 binding domain.

[0027] In some examples, the scFv comprises, from N-terminal to C-terminal, VH2-scFv linker-VL2. In some examples, the scFv comprises, from N-terminal to C-terminal, VL2-scFv linker-VH2.

[0028] In exemplary examples, the first ABDs are the STEAP1 binding domains and the second ABD is the CD28 binding domain. In some examples, VH1 and VL1 are selected from one of the following: a) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39 or a variant thereof; or b) a VH from Figure 31 and a VL from Figure 32, or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0029] In some examples, the first Fc domain and second Fc domain are each variant Fc domains.

[0030] In some examples, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering.

[0031] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0032] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0033] In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises amino acid variants E233P/L234V/L235A/G236del/S267K/L368D/K370S/N208D/Q295E/N384D/Q418E/N421D and the first Fc domain comprises amino acid variants E233P/L234V/L235A/G236del/S267K/S364K/E357Q, wherein numbering is according to EU numbering. In exemplary examples, the first and second variant Fc domains each further comprise amino acid variants 428L/434S.

[0034] In some examples, the scFv linker is GKPGSGKPGSGKPGSGKPGS.

[0035] In another example, provided herein is an anti-CD28 x anti-STEAP1 heterodimeric antibody that comprises a) a first monomer; b) a second monomer; c) a first light chain; and d) a second light chain. The first monomer comprises, from N-terminal to C-terminal, a VH1-CH1-domain linker-VH1-CH1-hinge-CH2-CH3, wherein each of the VH1s is a first variable heavy domain, and CH2-CH3 is a first Fc domain. The second monomer comprises, from N-terminal to C-terminal, an scFv-domain linker-CH2-CH3, wherein VH1 is a first variable heavy domain and CH2-CH3 is a second Fc domain. The first light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The second light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2). The VH1 of the first monomer and the VL1 of the first light chain and the VH1 of the second monomer and the VL1 of the second light chain each form a first antigen binding domain (ABD), and the VH2 and the VL2 form a second ABD. Further, the first ABDs are STEAP1 binding domains and the second ABD is a CD28 binding domain, or the first ABDs are CD28 binding domains and the second ABD is a STEAP1 binding domain. In some examples, the scFv comprises, from N-terminal to C-terminal, VH2-scFv linker-

VL2. In some examples, the scFv comprises, from N-terminal to C-terminal, VL2-scFv linker-VH2.

[0036] In exemplary examples, the first ABDs are the STEAP1 binding domains and the second ABD is the CD28 binding domain. In some examples, VH1 and VL1 are selected from one of the following: a) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39 or a variant thereof; or b) a VH from Figure 31 and a VL from Figure 32, or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0037] In some examples, the first Fc domain and second Fc domain are each variant Fc domains.

[0038] In some examples, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering.

[0039] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0040] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0041] In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises amino acid variants E233P/L234V/L235A/G236del/S267K/L368D/K370S/N208D/Q295E/N384D/Q418E/N421D, the first Fc domain comprises amino acid variants E233P/L234V/L235A/G236del/S267K/S364K/E357Q, wherein numbering is according to

EU numbering. In exemplary examples, the first and second variant Fc domains each further comprise amino acid variants 428L/434S.

[0042] In some examples, the scFv linker is GKPGSGKPGSGKPGSGKPGS.

[0043] In another aspect, the present disclosure provides a bispecific antibody comprising: a) a Six Transmembrane Epithelial Antigen of Prostate 1 (STEAP1) binding domain comprising i) a first variable heavy domain (VH1), and ii) a first variable light domain (VL1); and b) an anti-CD28 binding domain comprising i) a second variable heavy domain (VH2), and ii) a second variable light domain (VL2), wherein VH1 and VL1 are selected from the following: a) a VH according to the amino acid sequence of SEQ ID NO:1694 and a VL according to the amino acid sequence of SEQ ID NO:1811, b) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39, or c) a VH from Figure 31 and a VL from Figure 32; and wherein VH2 and VL2 are selected from the following: a) a VH according to the amino acid sequence of SEQ ID NO:2491 and a VL according to the amino acid sequence of SEQ ID NO:110, b) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant thereof, or c) a VH from Figures 15 ,16, or 46; and (ii) a VL from Figures 15, 17, or 82.

[0043a] In another example, provided herein is a bispecific antibody that comprises: a) a STEAP1 binding domain comprising i) a first variable heavy domain (VH1), and ii) a first variable light domain (VL1); and b) an anti-CD28 binding domain comprising i) a second variable heavy domain (VH2), and ii) a second variable light domain (VL2). In some examples, VH1 and VL1 are selected from one of the following: a) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39 or a variant thereof; or b) a VH from Figure 31 and a VL from Figure 32, or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0044] In some examples of the bispecific antibodies, the first Fc domain and second Fc domain are each variant Fc domains.

[0045] In some examples of the bispecific antibodies, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering.

[0046] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0047] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0048] Also provided herein are nucleic acid compositions comprising nucleic acids encoding the antibodies described herein, expression vector compositions that include such

nucleic acids, host cells for making the antibodies that comprise the expression vector compositions, and methods of making the antibodies.

[0048a] In another aspect, the present disclosure provides a nucleic acid composition comprising: a) a first nucleic acid encoding the first monomer as disclosed herein; b) a second nucleic acid encoding the second monomer as disclosed herein; and c) a third nucleic acid encoding the light chain as disclosed herein. In a further aspect, the present disclosure provides an expression vector composition comprising: a) a first expression vector comprising the first nucleic acid as disclosed herein; b) a second expression vector comprising the second nucleic acid as disclosed herein; and c) a third expression vector comprising the third nucleic acid as disclosed herein; respectively. In a further aspect the present disclosure provides a host cell comprising the nucleic acid composition as disclosed herein.

[0048b] In another aspect, the present disclosure provides a method of making a heterodimeric antibody as disclosed herein comprising culturing the host cell as disclosed herein under conditions wherein the heterodimeric antibody is expressed and recovering the heterodimeric antibody.

[0049] In another aspect, the present disclosure provides a use of a heterodimeric antibody as disclosed herein or the bispecific antibody as disclosed herein in the manufacture of a medicament for treating a STEAP-associated cancer in a patient in need thereof

[0049a]In another example, provided herein is a method of treating a STEAP1-associated cancer in a patient in need thereof, comprising administering to the patient an anti-CD28 x anti-STEAP1 bispecific antibody as described herein.

[0050] In another aspect, the present disclosure provides a use of a heterodimeric antibody as disclosed herein or the bispecific antibody as disclosed herein and an anti-CD3 x anti-STEAP1 bispecific antibody in the manufacture of a medicament for treating a STEAP-associated cancer in a patient in need thereof.

[0050a] In another aspect, the present disclosure provides a use of a heterodimeric antibody as disclosed herein or the bispecific antibody as disclosed herein in the manufacture of a first medicament and use of an anti-CD3 x anti-STEAP1 bispecific antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating a STEAP-associated cancer in a patient in need thereof.

[0050b] In another aspect, the present disclosure provides a use of a heterodimeric antibody as disclosed herein or the bispecific antibody as disclosed herein in the manufacture of a medicament for use in combination therapy for treating a STEAP-associated cancer in a patient in need thereof, wherein the medicament is to be administered in combination with an anti-CD3 x anti-STEAP1 bispecific antibody.

[0050c] In another example, provided herein is a method of treating a STEAP1-associated cancer in a patient in need thereof, comprising administering to the patient an anti-CD28 x anti-STEAP1 bispecific antibody as described herein; and an anti-CD3 x anti-STEAP1 bispecific antibody.

[0051] In another example, provided herein are compositions comprising a STEAP1 antigen binding domain (ABD). In some examples, the STEAP1 includes a) a variable heavy domain having the vhCDR1-3 of any of the STEAP1 binding domain variable heavy domains in Figure 22 or Figure 31; and b) a variable light domain having the vlCDR1-3 of any of the STEAP1 binding domain variable light domains in Figure 22 or Figure 32.

[0052] In some examples, the STEAP1 ABD includes a) a variable heavy domain having at least 85% sequence identity to a STEAP1 binding domain variable heavy domain in Figure 22 or Figure 31; and b) a variable light domain having at least 85% sequence identity to a STEAP1 binding domain variable light domain in Figure 22 or Figure 32. In some examples, the variable heavy domain has at least 90% sequence identity to a STEAP1 binding domain variable heavy domain in Figure 22 or Figure 31; and the variable light domain has at least 90% sequence identity to a STEAP1 binding domain variable light domain in Figure 22 or Figure 32. In some examples, the variable heavy domain has at least 95% sequence identity to a STEAP1 binding domain variable heavy domain in Figure 22 or Figure 31; and the variable light domain has at least 95% sequence identity to a STEAP1 binding domain variable light domain in Figure 22 or Figure 32. In some examples, the variable heavy domain has at least 99% sequence identity to a STEAP1 binding domain variable heavy domain in Figure 22 or Figure 31; and the variable light domain has at least 99% sequence identity to a STEAP1 binding domain variable light domain in Figure 22 or Figure 32. In some examples, the variable heavy domain has an amino acid sequence of a STEAP1 binding domain variable heavy domain in Figure 22 or Figure 31; and the variable light domain has an amino acid sequence of a STEAP1 binding domain variable light domain in Figure 22 or Figure 32.

[0053] In some examples, the STEAP1 ABD comprises a STEAP1 binding domain variable heavy domain and a STEAP1 binding domain variable light domain selected from the following: H1 and L1, H1.1 and L1, H1.2 and L1, H1.3 and L1, H1.4 and L1, H1.5 and L1, H1.6 and L1, H1.7 and L1, H1.8 and L1, H1.9 and L1, H1.10 and L1, H1.11 and L1, H1.12 and L1, H1.13 and L1, H1.14 and L1, H1.15 and L1, H1.16 and L1, H1.17 and L1, H1.18 and L1, H1.19 and L1, H1.20 and L1, H1.21 and L1, H1.22 and L1, H1.23 and L1, H1.24 and L1, H1.25 and L1, H1.26 and L1, H1.27 and L1, H1.28 and L1, H1.29 and L1, H1.30 and L1, H1.31 and L1, H1.32 and L1, H1.33 and L1, H1.34 and L1, H1.35 and L1, H1.36 and L1, H1.37 and L1, H1.38 and L1, H1 and L1.1, H1 and L1.2, H1 and L1.3, H0 and L0, H1.21 and L1.3, H1.34 and L1.3, H1.39 and L1, H1.40 and L1, H1.41 and L1, H1.42 and L1, H1.43 and L1, H1.44 and L1, H1.45 and L1, H1.46 and L1, H1.47 and L1, H1.48 and L1, H1.49 and L1, H1.50 and L1, H1.51 and L1, H1.52 and L1, H1.53 and L1, H1.54 and L1, H1.55 and L1, H1.56 and L1, H1.57 and L1, H1.58 and L1, H1.59 and L1, H1.60 and L1, H1.61 and L1, H1.62 and L1, H1.63 and L1, H1.64 and L1, H1.65 and L1, H1.66 and L1, H1.67 and L1, H1.68 and L1, H1.69 and L1, H1.70 and L1, H1.71 and L1, H1.72 and L1, H1.73 and L1, H1.74 and L1, H1.75 and L1, H1.76 and L1, H1.77 and L1, H1.78 and L1, H1.79 and L1, H1.80 and L1, H1.81 and L1, H1.82 and L1, H1.83 and L1, H1.84 and L1, H1.85 and L1, H1.86 and L1, H1.87 and L1, H1.88, and L1, H1.89 and L1, H1.90 and L1, H1.91 and L1, H1.92 and L1, H1.93 and L1, H1.94 and L1, H1.95 and L1, H1.96 and L1, H1.97 and L1, H1.98 and L1, H1.99 and L1, H1.100 and L1, H1.101 and L1, H1.102 and L1, H1.103 and L1, H1.104 and L1, H1.105 and L1, H1.106 and L1, H1.107 and L1, H1.108 and L1, H1.109 and L1, H1.110 and L1, H1.111 and L1, H1.112 and L1, H1.113 and L1, H1.114 and L1, H1.115 and L1, H1.116 and L1, H1.117 and L1, H1.118 and L1, H1.119 and L1, H1.120 and L1, H1.121 and L1, H1.122 and L1, H1.123 and L1, H1.124 and L1, H1.125 and L1, H1.126 and L1, H1.127 and L1, H1.128 and L1, H1.129 and L1, H1.130 and L1, H1.131 and L1, H1.132 and L1, H1.133 and L1, H1.134 and L1, H1.135 and L1, H1.136 and L1, H1.137 and L1, H1.138 and L1, H1.139 and L1, H1.140 and L1, H1.141 and L1, H1.142 and L1, H1.143 and L1, H1.144 and L1, H1.145 and L1, H1.146 and L1, H1.147 and L1, H1.148 and L1, H1.149 and L1, H1.150 and L1, H1.151 and L1, H1.152 and L1, H1.153 and L1, H1.154 and L1, H1.155 and L1, H1.156 and L1, H1.157 and L1, H1.158 and L1, H1.159 and L1, H1.160 and L1, H1.161 and L1, H1.162 and L1, H1.163 and L1, H1.164 and L1, H1.165 and L1, H1.166 and L1, H1.167 and L1, H1.168 and L1, H1.169 and L1, H1.170 and L1, H1.171 and L1, H1.172 and L1, H1.173 and L1, H1.174 and L1, H1.175 and L1, H1.176 and

L1, H1.177 and L1, H1.178 and L1, H1.179 and L1, H1.180 and L1, H1.181 and L1, H1.182 and L1, H1.183 and L1, H1.184 and L1, H1.185 and L1, H1.186 and L1, H1.187 and L1, H1.188 and L1, H1.189 and L1, H1 and L1.4, H1 and L1.5, H1 and L1.6, H1 and L1.7, H1 and L1.8, H1 and L1.9, H1 and L1.10, H1 and L1.11, H1 and L1.12, H1 and L1.13, H1 and L1.14, H1 and L1.15, H1 and L1.16, H1 and L1.17, H1 and L1.18, H1 and L1.19, H1 and L1.20, H1 and L1.21, H1 and L1.22, H1 and L1.23, H1 and L1.24, H1 and L1.25, H1 and L1.26, H1 and L1.27, H1 and L1.28, H1 and L1.29, H1 and L1.30, H1 and L1.31, H1 and L1.32, H1 and L1.33, H1 and L1.34, H1 and L1.35, H1 and L1.36, H1 and L1.37, H1 and L1.38, H1 and L1.39, H1 and L1.40, H1 and L1.41, H1 and L1.42, H1 and L1.43, H1 and L1.44, H1 and L1.45, H1 and L1.46, H1 and L1.47, H1 and L1.48, H1 and L1.49, H1 and L1.50, H1 and L1.51, H1 and L1.52, H1 and L1.53, H1 and L1.54, H1 and L1.55, H1 and L1.56, H1 and L1.57, H1 and L1.58, H1 and L1.59, H1 and L1.60, H1 and L1.61, H1 and L1.62, H1 and L1.63, H1 and L1.64, H1 and L1.65, H1 and L1.66, H1 and L1.67, H1 and L1.68, H1 and L1.69, H1 and L1.70, H1 and L1.71, H1 and L1.72, H1 and L1.73, H1 and L1.74, H1 and L1.75, H1 and L1.76, H1 and L1.77, H1 and L1.78, H1 and L1.79, H1 and L1.80, H1 and L1.81, H1 and L1.82, H1 and L1.83, H1 and L1.84, H1 and L1.85, H1.42 and L1.47, H1.42 and L1.56, H1.190 and L1.3, H1.191 and L1.3, H1.192 and L1.3, H1.195 and L1.3, H1.196 and L1.3, H1.197 and L1.3, H1.198 and L1.3, H1.199 and L1.3, H1.200 and L1.3, H1.201 and L1.3, H1.202 and L1.3, H1.203 and L1.3, H1.204 and L1.3, H1.205 and L1.3, H1.206 and L1.3, H1.207 and L1.3, H1.208 and L1.3, H1.209 and L1.3, H1.210 and L1.3, H1.211 and L1.3, H1.212 and L1.3, H1.213 and L1.3, H1.214 and L1.3, H1.215 and L1.3, H1.216 and L1.3, H1.217 and L1.3, H1.218 and L1.3, H1.219 and L1.3, H1.220 and L1.3, H1.221 and L1.3, H1.222 and L1.3, H1.223 and L1.3, H1.224 and L1.3, H1.225 and L1.3, H1.226 and L1.3, H1.227 and L1.3, H1.228 and L1.3, H1.21 and L1.92, H1.21 and L1.93, H1.21 and L1.94, H1.21 and L1.95, H1.21 and L1.96, H1.21 and L1.97, H1.21 and L1.98, H1.21 and L1.99, H1.21 and L1.100, H1.21 and L1.101, H1.21 and L1.102, H1.21 and L1.103, H1.21 and L1.104, H1.21 and L1.105, H1.21 and L1.106, H1.21 and L1.107, H1.21 and L1.108, H1.21 and L1.109, H1.21 and L1.110, H1.21 and L1.111, H1.21 and L1.112, H1.21 and L1.113, H1.21 and L1.114, H1.21 and L1.115, H1.21 and L1.116, H1.21 and L1.117, H1.21 and L1.118, H1.21 and L1.119, H1.195 and L1.92, H1.195 and L1.94, H1.195 and L1.95, H1.195 and L1.104, H1.195 and L1.105, H1.195 and L1.109, H1.196 and L1.92, H1.196 and L1.94, H1.196 and L1.95, H1.196 and L1.104, H1.196 and L1.105, H1.196 and L1.109, H1.205 and L1.92, H1.205 and L1.94, H1.205 and L1.95, H1.205 and

L1.104, H1.205 and L1.105, H1.205 and L1.109, H1.193 and L1.91, H1.194 and L1.86, H1.194 and L1.87, H1.194 and L1.88, H1.194 and L1.89, or H1.194 and L1.90, or H1.2320 and L1.100, or H1.230 and L1.115 (Figures 22, 31, 32 and 39).

[0054] In one example, provided herein is an anti-CD28 x anti-CEACAM5 heterodimeric antibody that comprises a) a first monomer; b) a second monomer; and c) a light chain. The first monomer comprises: i) a single chain variable fragment (scFv); and ii) a first Fc domain, wherein the scFv is covalently attached to the N-terminus of the first Fc domain using a domain linker. The second monomer comprises, from N-terminal to C-terminal, a VH1-CH1-hinge-CH2-CH3, wherein VH1 is a first variable heavy domain and CH2-CH3 is a second Fc domain. The light chain comprises, from N-terminal to C- terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2). The VH1 and the VL1 together form a first antigen binding domain (ABD) and the VH2 and the VL2 together form a second ABD. Further, one of the first ABD and second ABD is a CD28 binding domain and the other of the first ABD and second ABD is a carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) binding domain.

[0055] In some examples, the scFv comprises, from N-terminal to C-terminal, VH2-scFv linker-VL2. In some examples, the scFv comprises, from N-terminal to C-terminal, VL2-scFv linker-VH2.

[0056] In exemplary examples, the first ABDs is the CEACAM5 binding domain and the second ABD is the CD28 binding domain. In some examples, VH1 and VL1 are a selected from the following VH and VL of any of the CEACAM5 binding domains from Figure 41 and Figure 45 or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, 21 and 65 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0057] In some examples, the first Fc domain and second Fc domain are each variant Fc domains.

[0058] In some examples, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according

to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering

[0059] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0060] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0061] In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises amino acid variants E233P/L234V/L235A/G236del/S267K/L368D/K370S/N208D/Q295E/N384D/Q418E/N421D, the first Fc domain comprises amino acid variants E233P/L234V/L235A/G236del/S267K/S364K/E357Q, wherein numbering is according to EU numbering. In exemplary examples, the first and second variant Fc domains each further comprise amino acid variants 428L/434S.

[0062] In some examples, the scFv linker is GKPGSGKPGSGKPGSGKPGS.

[0063] In another example, provided herein is an anti-CD28 x anti-CEACAM5 heterodimeric antibody that comprises a) a first monomer; b) a second monomer; c) a first light chain; and d) a second light chain. The first monomer comprises, from N-terminal to C-terminal, VH1-CH1-first domain linker-scFv-second domain linker-CH2-CH3, wherein VH1 is a first variable heavy domain, and CH2-CH3 is a first Fc domain. The second monomer comprises, from N-terminal to C-terminal, a VH1-CH1-hinge-CH2-CH3, wherein CH2-CH3 is a second Fc domain. The first light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The second light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2), wherein, the VH1 of the first monomer and the VL1 of the first light chain and the VH1 of the second monomer and the VL1 of the second light chain each form a first antigen binding domain (ABD), and the VH2

and the VL2 form a second ABD. . Further, the first ABDs are carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) binding domains and the second ABD is a CD28 binding domain, or the first ABDs are CD28 binding domains and the second ABD is an CEACAM5 binding domain .

[0064] In some examples, the scFv comprises, from N-terminal to C-terminal, VH2-scFv linker-VL2. In some examples, the scFv comprises, from N-terminal to C-terminal, VL2-scFv linker-VH2.

[0065] In exemplary examples, the first ABDs are the CEACAM5 binding domains and the second ABD is the CD28 binding domain. In some examples, VH1 and VL1 are selected from the following: 1) a VH and VL of any of the CEACAM5 binding domains from Figure 41 and Figure 45 or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, 21 and 65 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0066] In some examples, the first Fc domain and second Fc domain are each variant Fc domains.

[0067] In some examples, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering

[0068] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0069] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0070] In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises amino acid variants E233P/L234V/L235A/G236del/S267K/L368D/K370S/N208D/Q295E/N384D/Q418E/N421D, the first Fc domain comprises amino acid variants E233P/L234V/L235A/G236del/S267K/S364K/E357Q, wherein numbering is according to EU numbering. In exemplary examples, the first and second variant Fc domains each further comprise amino acid variants 428L/434S.

[0071] In some examples, the scFv linker is GKPGSGKPGSGKPGSGKPGS.

[0072] In another example, provided herein is an anti-CD28 x anti-CEACAM5 heterodimeric antibody that comprises a) a first monomer; b) a second monomer; and c) a first light chain; and d) a second light chain. The first monomer comprises, from N-terminal to C-terminal, VH1-CH1-hinge-CH2-CH3-domain linker-scFv, wherein VH1 is a first variable heavy domain, and CH2-CH3 is a first Fc domain. The second monomer comprises, from N-terminal to C-terminal, a VH1-CH1-hinge-CH2-CH3, wherein VH1 is a first variable heavy domain and CH2-CH3 is a second Fc domain. The first light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The second light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2), wherein the VH1 of the first monomer and the VL1 of the first light chain and the VH1 of the second monomer and the VL1 of the second light chain each form a first antigen binding domain (ABD), and the VH2 and the VL2 form a second ABD. Further, the first ABDs are carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) binding domains and the second ABD is a CD28 binding domain, or the first ABDs are CD28 binding domains and the second ABD is an CEACAM5 binding domain

[0073] In some examples, the scFv comprises, from N-terminal to C-terminal, VH2-scFv linker-VL2. In some examples, the scFv comprises, from N-terminal to C-terminal, VL2-scFv linker-VH2.

[0074] In exemplary examples, the first ABDs are the CEACAM5 binding domains and the second ABD is the CD28 binding domain. In some examples, VH1 and VL1 are selected from the following: 1) a VH and VL of any of the CEACAM5 binding domains from Figure 41 and Figure 45 or a variant thereof. In some examples, VH2 and VL2 are

selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, 21 and 65 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0075] In some examples, the first Fc domain and second Fc domain are each variant Fc domains.

[0076] In some examples, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering.

[0077] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0078] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0079] In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises amino acid variants E233P/L234V/L235A/G236del/S267K/L368D/K370S/N208D/Q295E/N384D/Q418E/N421D, the first Fc domain comprises amino acid variants E233P/L234V/L235A/G236del/S267K/S364K/E357Q, wherein numbering is according to EU numbering. In exemplary examples, the first and second variant Fc domains each further comprise amino acid variants 428L/434S.

[0080] In some examples, the scFv linker is GKPGSGKPGSGKPGSGKPGS.

[0081] In another example, provided herein is a heterodimeric antibody that comprises a) a first monomer, b) a second monomer, c) a first light chain, and d) a second light chain. The first monomer comprises, from N-terminal to C-terminal, a VH1-CH1-domain linker-VH1-CH1-hinge-CH2-CH3, wherein each of the VH1s is a first variable heavy domain, and CH2-CH3

is a first Fc domain. The second monomer comprises, from N-terminal to C-terminal, an scFv-domain linker-CH2-CH3, wherein VH1 is a first variable heavy domain and CH2-CH3 is a second Fc domain. The first common light chain comprises, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The second light chain comprising, from N-terminal to C-terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain. The scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2), wherein the VH1 of the first monomer and the VL1 of the first light chain and the VH1 of the second monomer and the VL1 of the second light chain each form a first antigen binding domain (ABD), and the VH2 and the VL2 form a second ABD.. Further, the first ABDs are carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) binding domains and the second ABD is a CD28 binding domain, or the first ABDs are CD28 binding domains and the second ABD is an CEACAM5 binding domain.

[0082] In some examples, the scFv comprises, from N-terminal to C-terminal, VH2-scFv linker-VL2. In some examples, the scFv comprises, from N-terminal to C-terminal, VL2-scFv linker-VH2.

[0083] In exemplary examples, the first ABDs are the CEACAM5 binding domains and the second ABD is the CD28 binding domain. In some examples, VH1 and VL1 are selected from the following: 1) a VH and VL of any of the CEACAM5 binding domains from Figure 41 and Figure 45 or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, 21 and 65 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0084] In some examples, the first Fc domain and second Fc domain are each variant Fc domains.

[0085] In some examples, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V, wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering.

[0086] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0087] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0088] In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises amino acid variants E233P/L234V/L235A/G236del/S267K/L368D/K370S/N208D/Q295E/N384D/Q418E/N421D, the first Fc domain comprises amino acid variants E233P/L234V/L235A/G236del/S267K/S364K/E357Q, wherein numbering is according to EU numbering. In exemplary examples, the first and second variant Fc domains each further comprise amino acid variants 428L/434S.

[0089] In some examples, the scFv linker is GKPGSGKPGSGKPGSGKPGS.

[0090] In another example, provided herein is a bispecific antibody that comprises: a) a CEACAM5 binding domain comprising i) a first variable heavy domain (VH1), and ii) a first variable light domain (VL1); and b) an anti-CD28 binding domain comprising i) a second variable heavy domain (VH2), and ii) a second variable light domain (VL2). In some examples, VH1 and VL1 are selected from the following: 1) a VH and VL of any of the CEACAM5 binding domains from Figure 41 and Figure 45 or a variant thereof. In some examples, VH2 and VL2 are selected from one of the following: 1) a VH and VL of any of the CD28 binding domains from Figures 15, 18, 21 and 65 or a variant thereof; or 2) (i) a VH from Figure 15 or 16 or a variant thereof; and (ii) a VL from Figures 15, 17 or 82 or a variant thereof.

[0091] In some examples of the bispecific antibodies, the first Fc domain and second Fc domain are each variant Fc domains.

[0092] In some examples of the bispecific antibodies, the first and second Fc domains comprise a set of heterodimerization skew variants selected from the following heterodimerization variants: S364K/E357Q : L368D/K370S; S364K : L368D/K370S; S364K : L368E/K370S; D401K: T411E/K360E/Q362E; and T366W : T366S/L368A/Y407V,

wherein numbering is according to EU numbering. In some examples, the first and second Fc domains comprise heterodimerization skew variants S364K/E357Q : L368D/K370S, wherein numbering is according to EU numbering.

[0093] In certain examples, the first and second Fc domains each comprise one or more ablation variants. In exemplary examples, the one or more ablation variants comprise E233P/L234V/L235A/G236del/S267K, wherein numbering is according to EU numbering.

[0094] In some examples, the one of the first or second monomer further comprises one or more pI variants. In some examples, the CH1-hinge-CH2-CH3 of the second monomer comprises pI variants N208D/Q295E/N384D/Q418E/N421D, wherein numbering is according to EU numbering.

[0095] Also provided herein are nucleic acid compositions comprising nucleic acids encoding the antibodies described herein, expression vector compositions that include such nucleic acids, host cells for making the antibodies that comprise the expression vector compositions, and methods of making the antibodies.

[0096] In another example, provided herein is a method of treating a CEACAM5-cancer in a patient in need thereof, comprising administering to the patient according an anti-CD28 x anti-CEACAM5 bispecific antibody as described herein.

[0097] In another example, provided herein is a method of treating a CEACAM5-associated cancer in a patient in need thereof, comprising administering to the patient an anti-CD28 x anti-CEACAM5 bispecific antibody as described herein; and an anti-CD3 x anti-CEACAM5 bispecific antibody.

[0098] In another example, provided herein is a CEACAM5 antigen binding domain composition that comprises a) a variable heavy domain; and b) a variable light domain. The variable heavy domain comprises the vhCDR1-3 of any of the CEACAM5 binding domain variable heavy domains in Figure 45. The variable light domain comprises the vlCDR1-3 of any of the CEACAM5 binding domain variable light domains in Figure 45. In another example, provided herein is a CEACAM5 antigen binding domain composition that comprises a) a variable heavy domain; and b) a variable light domain. The variable heavy domain comprises at least 85% sequence identity to a CEACAM5 binding domain variable heavy domain in Figure 45. The variable light domain comprises at least 85% sequence identity to a CEACAM5 binding domain variable light domain in Figure 45.

[0099] In some examples, the variable heavy domain has at least 90% sequence identity to a CEACAM5 binding domain variable heavy domain in Figure 45; and the variable light domain has at least 90% sequence identity to a CEACAM5 binding domain variable light domain in Figure 45.

[00100] In some examples, the variable heavy domain has at least 95% sequence identity to a CEACAM5 binding domain variable heavy domain in Figure 45; and the variable light domain has at least 95% sequence identity to a CEACAM5 binding domain variable light domain in Figure 45.

[00101] In some examples, the variable heavy domain has at least 99% sequence identity to a CEACAM5 binding domain variable heavy domain in Figure 45; and the variable light domain has at least 99% sequence identity to a CEACAM5 binding domain variable light domain in Figure 45.

[00102] In some examples, the variable heavy domain has an amino acid sequence of a CEACAM5 binding domain variable heavy domain in Figure 45; and the variable light domain has an amino acid sequence of a CEACAM5 binding domain variable light domain in Figure 45.

[00103] In another example, provided herein is a CD28 antigen binding domain composition that comprises a) a variable heavy domain; and b) a variable light domain. The variable heavy domain comprises the vhCDR1-3 of any of the CD28 binding domain variable heavy domains in Figure 65. The variable light domain comprises the vlCDR1-3 of any of the CD28 binding domain variable light domains in Figure 65.

[00104] In another example, provided herein is a CD28 antigen binding domain composition that comprises a) a variable heavy domain; and b) a variable light domain. The variable heavy domain comprises at least 85% sequence identity to a CD28 binding domain variable heavy domain in Figure 65. The variable light domain comprises at least 85% sequence identity to a CD28 binding domain variable light domain in Figure 65.

[00105] In some examples, the variable heavy domain has at least 90% sequence identity to a CD28 binding domain variable heavy domain in Figure 65; and the variable light domain has at least 90% sequence identity to a CD28 binding domain variable light domain in Figure 65.

[00106] In some examples, the variable heavy domain has at least 95% sequence identity to a CD28 binding domain variable heavy domain in Figure 65; and the variable light domain has at least 95% sequence identity to a CD28 binding domain variable light domain in Figure 65.

[00107] In some examples, the variable heavy domain has at least 99% sequence identity to a CD28 binding domain variable heavy domain in Figure 65; and the variable light domain has at least 99% sequence identity to a CD28 binding domain variable light domain in Figure 65.

[00108] In some examples, the variable heavy domain has an amino acid sequence of a CD28 binding domain variable heavy domain in Figure 65; and the variable light domain has an amino acid sequence of a CD28 binding domain variable light domain in Figure 65.

[00109] In some examples, the CD28 binding domain is selected from the following: 1A7[CD28]_H1L1, 1A7[CD28]_H1.1_L1, 1A7[CD28]_H1_L1.71, 1A7[CD28]_H1.1_L1.71, 1A7[CD28]_H1.14_L1, 1A7[CD28]_H1.14_L1.71, CD28.3[CD28]_H0L0, hCD28.3[CD28]_H1L1, 5.11A1[CD28]_H0L0, TGN1412_H1L1, 341VL34[CD28]_H1L1, 341VL36[CD28]_H1L1, 281VL4[CD28]_H1L1, HuTN228[CD28]_H1L1, PV1[CD28]_H0L0, m9.3[CD28]_H0L0, hu9.3[CD28]_H1L1, 9G2[CD28]_H0L0, 9G2[CD28]_H1L1, 2F10A3.140[CD28]_H1L1, TN228[CD28]_H4L2, 1A7[CD28]_H1.1_L1 [S-S], 1A7[CD28]_H1_L1.71 [S-S], 1A7[CD28]_H1.1_L1.71 [S-S], 1A7[CD28]_H1.14_L1 [S-S], 1A7[CD28]_H1.14_L1.71 [S-S], 1A7[CD28]_H1.129_L1.71 [S-S], 1A7[CD28]_H1.106_L1.71 [S-S], 1A7[CD28]_H1.129_L1 [S-S], and 1A7[CD28]_H1.106_L1 [S-S] in Figure 65.

BRIEF DESCRIPTION OF THE DRAWINGS

[00110] Figures 1A and 1B depict the sequences for human, mouse, and cynomolgus CD28. Such CD28 are useful for the development of cross-reactive CD28 antigen binding domains for ease of clinical development.

[00111] Figures 2A and 2B depict STEAP1 and CEACAM5 sequences. Figure 2A depicts the sequences for human, mouse, and cynomolgus STEAP1. Such STEAP1s are useful for the development of cross-reactive STEAP1 antigen binding domains for ease of clinical development. Figure 2B depicts the sequences for human, mouse, and cynomolgus

WHAT IS CLAIMED IS:

1. A heterodimeric antibody comprising:

a) a first monomer comprising:

i) a single chain variable fragment (scFv); and

ii) a first Fc domain, wherein the scFv is covalently attached to the N-terminus of the first Fc domain using a domain linker;

b) a second monomer comprising, from N-terminal to C-terminal, a VH1-CH1-hinge-CH2-CH3, wherein VH1 is a first variable heavy domain and CH2-CH3 is a second Fc domain; and

c) a light chain comprising, from N-terminal to C- terminal, VL1-CL, wherein VL1 is a first variable light domain and CL is a constant light domain,

wherein the scFv comprises a second VH domain (VH2), a scFv linker, and a second variable light domain (VL2),

wherein the VH1 and the VL1 together form a first antigen binding domain (ABD) and the VH2 and the VL2 together form a second ABD, and

wherein one of the first ABD and the second ABD is a CD28 binding domain and the other of the first ABD and second ABD is a Six Transmembrane Epithelial Antigen of Prostate 1 (STEAP1) binding domain

wherein VH1 and VL1 are selected from the following:

a) a VH according to the amino acid sequence of SEQ ID NO:1694 and a VL according to the amino acid sequence of SEQ ID NO:1811,

b) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39, or

c) a VH from Figure 31 and a VL from Figure 32; and

wherein VH2 and VL2 are selected from the following:

a) a VH according to the amino acid sequence of SEQ ID NO:2491 and a VL according to the amino acid sequence of SEQ ID NO:110,

b) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant thereof, or

c) a VH from Figures 15 ,16, or 46; and (ii) a VL from Figures 15, 17, or 82.

2. The heterodimeric antibody of claim 1, wherein the first monomer is according to the amino acid sequence of SEQ ID NO:504, the second monomer is according to the amino acid sequence of SEQ ID NO:503, and the light chain is according to the amino acid sequence of SEQ ID NO:505.

3. A bispecific antibody comprising:

a) a Six Transmembrane Epithelial Antigen of Prostate 1 (STEAP1) binding domain comprising i) a first variable heavy domain (VH1), and ii) a first variable light domain (VL1); and

b) an anti-CD28 binding domain comprising i) a second variable heavy domain (VH2), and ii) a second variable light domain (VL2),

wherein VH1 and VL1 are selected from the following:

a) a VH according to the amino acid sequence of SEQ ID NO:1694 and a VL according to the amino acid sequence of SEQ ID NO:1811,

b) a VH and VL of any of the STEAP1 binding domains from Figure 22 or 39, or

c) a VH from Figure 31 and a VL from Figure 32; and

wherein VH2 and VL2 are selected from the following:

a) a VH according to the amino acid sequence of SEQ ID NO:2491 and a VL according to the amino acid sequence of SEQ ID NO:110,

b) a VH and VL of any of the CD28 binding domains from Figures 15, 18, and 21 or a variant thereof, or

c) a VH from Figures 15 ,16, or 46; and (ii) a VL from Figures 15, 17, or 82.

4. A nucleic acid composition comprising:

a) a first nucleic acid encoding the first monomer of any of claims 1 or 2;

b) a second nucleic acid encoding the second monomer of any of claims 1 or 2; and

c) a third nucleic acid encoding the light chain of any of claims 1 or 2.

5. An expression vector composition comprising:

a) a first expression vector comprising the first nucleic acid of claim 4;

b) a second expression vector comprising the second nucleic acid of claim 4; and

c) a third expression vector comprising the third nucleic acid of claim 4; respectively.

6. A host cell comprising the nucleic acid composition of claim 4.

7. A method of making a heterodimeric antibody according to any of claims 1 or 2 comprising culturing the host cell of claim 6 under conditions wherein the heterodimeric antibody is expressed and recovering the heterodimeric antibody.

8. Use of a heterodimeric antibody according to claim 1 or 2 or the bispecific antibody of claim 3 in the manufacture of a medicament for treating a STEAP-associated cancer in a patient in need thereof.

9. Use of a heterodimeric antibody according to claim 1 or 2 or the bispecific antibody of claim 3, and an anti-CD3 x anti-STEAP1 bispecific antibody, in the manufacture of a medicament for treating a STEAP-associated cancer in a patient in need thereof.

10. Use of a heterodimeric antibody according to claim 1 or 2 or the bispecific antibody of claim 3 in the manufacture of a first medicament and use of an anti-CD3 x anti-STEAP1 bispecific antibody in the manufacture of a second medicament, wherein the first and

second medicaments are to be used in combination therapy for treating a STEAP-associated cancer in a patient in need thereof.

11. Use of a heterodimeric antibody according to claim 1 or 2 or the bispecific antibody of claim 3 in the manufacture of a medicament for use in combination therapy for treating a STEAP-associated cancer in a patient in need thereof, wherein the medicament is to be administered in combination with an anti-CD3 x anti-STEAP1 bispecific antibody.