

[0008] Thus while bispecifics generated from antibody fragments suffer biophysical and pharmacokinetic hurdles, a drawback of those built with full length antibody -like formats is that they engage co-target antigens multivalently in the absence of the primary target antigen, leading to nonspecific activation and potentially toxicity. The present invention solves this problem by introducing a novel bispecific format that enables the co-engagement of distinct target antigens.

SUMMARY OF THE INVENTION

[0009] Accordingly, the present invention provides a heterodimeric antibody comprising: a) a first heavy chain comprising: i) a first Fc domain variant; ii) a single chain Fv region (scFv) that binds CD3; and b) a second heavy chain comprising: i) a second Fc domain variant; and ii) a first variable heavy domain; and c) a first light chain comprising a first variable light domain and a first constant light domain; wherein said first variable heavy domain and said first variable light domain bind to CD38, and wherein said second heavy chain and said first light chain are selected from the pairs consisting of H1 (SEQ ID NO: 473) and L1.24 (SEQ ID NO: 475); H1 (SEQ ID NO: 476) and L1.96 (SEQ ID NO: 478); H1.77 (SEQ ID NO: 479) and L1.96 (SEQ ID NO: 481); H1.77 (SEQ ID NO: 482) and L1.97 (SEQ ID NO: 484); H1.72 (SEQ ID NO: 485) and L1.97 (SEQ ID NO: 487); H1.71 (SEQ ID NO: 488) and L1.96 (SEQ ID NO: 490), and H1.77 (SEQ ID NO: 491) and L1.24 (SEQ ID NO: 493). Also disclosed are heterodimeric antibodies that bind to CD3 and CD38. The heterodimeric antibodies comprise a first heavy chain comprising a first variable Fc domain and a single chain Fv region (scFv) that binds CD3. The heterodimeric antibodies also comprise a second heavy chain comprising a second Fc variable Fc domain and a first variable heavy domain. The heterodimeric antibodies further comprise a first light chain comprising a first variable light domain and a first constant light domain, wherein said first variable heavy domain and said first variable light domain bind to CD38.

[0010] Also disclosed are heterodimeric antibodies selected from the group consisting of XENP13243; XENP13545; XENP13546; XENP13547; XENP13548; XENP13549; XENP13550; XENP13551; XENP13544; XENP13752; XENP13753; XENP13754; XENP13756; XENP13757 and XENP13694.

[0011] In an additional example, the scFv has a sequence comprising a vhCDR1 having the sequence T-Y-A-M-Xaa1, wherein Xaa1 is N, S or H (SEQ ID NO:435), a

vhCDR2 having the sequence R-I-R-S-K-Xaa1-N-Xaa2-Y-A-T-Xaa3-Y-Y-A-Xaa4-S-V-K-G, wherein Xaa1 is Y or A, Xaa2 is N or S, Xaa3 is Y or A and Xaa4 is D or A (SEQ ID NO:436), a vhCDR3 having the sequence H-G-N-F-G-Xaa1-S-Y-V-S-W-F-Xaa2-Y, wherein Xaa1 is N, D or Q and Xaa2 is A or D (SEQ ID NO:437), a vlCDR1 having the sequence Xaa1-S-S-T-G-A-V-T-Xaa2-Xaa3-Xaa4-Y-A-N, wherein Xaa1 is G, R or K, Xaa2 is T or S, Xaa3 is S or G and Xaa4 is N or H, (SEQ ID NO:438), a vlCDR2 having the sequence Xaa1-T-N-Xaa2-R-A-Xaa3, wherein Xaa1 is G or D, Xaa2 is K or N, and Xaa3 is P or S (SEQ ID NO:439) and a vlCDR3 having the sequence Xaa1-L-W-Y-S-N-Xaa2-W-V, wherein Xaa1 is A or L and Xaa2 is L or H (SEQ ID NO:440).

[0012] In a further example, the scFv is selected from the group consisting of H1.30_L1.47, H1.33_L1.47 and H1.31_L1.47.

[0013] In an additional example, the anti-CD3 variable region has a sequence selected from the group consisting of:

[0014] a) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:430;

[0015] b) a sequence comprising a vhCDR1 having SEQ ID NO:412, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:430;

[0016] c) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:414, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:430;

[0017] d) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:417, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:430;

[0018] e) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:418, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:430;

[0019] f) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:421, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:430;

[0020] g) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:422, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:430;

[0021] h) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:427 and a vlCDR3 having SEQ ID NO:430;

[0022] i) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:428 and a vlCDR3 having SEQ ID NO:430;

[0033] t) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:417, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:433;

[0034] u) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:413, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:433 and

[0035] v) a sequence comprising a vhCDR1 having SEQ ID NO:411, a vhCDR2 having SEQ ID NO:434, a vhCDR3 having SEQ ID NO:416, a vlCDR1 having SEQ ID NO:420, a vlCDR2 having SEQ ID NO:425 and a vlCDR3 having SEQ ID NO:430.

[0036] In an additional example, the anti-CD3 variable region comprises a variable heavy region and a variable light region selected from the group consisting of:

[0037] SEQ ID NOs: 5 and 6; SEQ ID NOs: 9 and 10; SEQ ID NOs: 13 and 14; SEQ ID NOs: 17 and 18; SEQ ID NOs: 21 and 22; SEQ ID NOs: 25 and 26; SEQ ID NOs: 29 and 30; SEQ ID NOs: 33 and 34; SEQ ID NOs: 37 and 38; SEQ ID NOs: 41 and 42; SEQ ID NOs: 45 and 46; SEQ ID NOs: 49 and 50; SEQ ID NOs: 53 and 54; SEQ ID NOs: 57 and 58; SEQ ID NOs: 61 and 62; SEQ ID NOs: 65 and 66; SEQ ID NOs: 69 and 70; SEQ ID NOs: 73 and 74; SEQ ID NOs: 77 and 78; SEQ ID NOs: 81 and 82; SEQ ID NOs: 85 and 86; SEQ ID NOs: 89 and 90; SEQ ID NOs: 93 and 94; SEQ ID NOs: 97 and 98; SEQ ID NOs: 101 and 102; SEQ ID NOs: 105 and 106; SEQ ID NOs: 109 and 110; SEQ ID NOs: 113 and 114; SEQ ID NOs: 117 and 118; SEQ ID NOs: 121 and 122; SEQ ID NOs: 125 and 126; SEQ ID NOs: 129 and 130; SEQ ID NOs: 133 and 134; SEQ ID NOs: 137 and 138; SEQ ID NOs: 141 and 142; SEQ ID NOs: 145 and 146; SEQ ID NOs: 149 and 150; SEQ ID NOs: 153 and 154; SEQ ID NOs: 157 and 158; SEQ ID NOs: 161 and 162; SEQ ID NOs: 165 and 166; SEQ ID NOs: 169 and 170; SEQ ID NOs: 173 and 174; SEQ ID NOs: 177 and 178; SEQ ID NOs: 181 and 182; SEQ ID NOs: 185 and 186; SEQ ID NOs: 189 and 190; SEQ ID NOs: 193 and 194; SEQ ID NOs: 197 and 198; SEQ ID NOs: 201 and 202; SEQ ID NOs: 205 and 206; SEQ ID NOs: 209 and 210; SEQ ID NOs: 213 and 214; SEQ ID NOs: 217 and 218; SEQ ID NOs: 221 and 222; SEQ ID NOs: 225 and 226; SEQ ID NOs: 229 and 230; SEQ ID NOs: 233 and 234; SEQ ID NOs: 237 and 238; SEQ ID NOs: 241 and 242; SEQ ID NOs: 245 and 246; SEQ ID NOs: 249 and 250; SEQ ID NOs: 253 and 254; SEQ ID NOs: 257 and 258; SEQ ID NOs: 261 and 262; SEQ ID NOs: 265 and 266; SEQ ID NOs: 269 and 270; SEQ ID NOs: 273 and 274; SEQ ID NOs: 277 and 278; SEQ ID NOs: 281 and 282; SEQ ID

NOs: 285 and 286; SEQ ID NOs: 289 and 290; SEQ ID NOs: 293 and 294; SEQ ID NOs: 297 and 298; SEQ ID NOs: 301 and 302; SEQ ID NOs: 305 and 306; SEQ ID NOs: 309 and 310; SEQ ID NOs: 313 and 314; SEQ ID NOs: 317 and 318; SEQ ID NOs: 321 and 322; SEQ ID NOs: 325 and 326; SEQ ID NOs: 329 and 330; SEQ ID NOs: 333 and 334; SEQ ID NOs: 337 and 338; SEQ ID NOs: 341 and 342; SEQ ID NOs: 345 and 346; SEQ ID NOs: 349 and 350; SEQ ID NOs: 353 and 354; SEQ ID NOs: 357 and 358; SEQ ID NOs: 361 and 362; SEQ ID NOs: 365 and 366; SEQ ID NOs: 369 and 370; SEQ ID NOs: 373 and 374; SEQ ID NOs: 377 and 378; SEQ ID NOs: 381 and 382; SEQ ID NOs: 385 and 386; SEQ ID NOs: 389 and 390; SEQ ID NOs: 393 and 394; SEQ ID NOs: 397 and 398; SEQ ID NOs: 401 and 402; SEQ ID NOs: 405 and 406; SEQ ID NOs: 409 and 410.

[0038] In an additional example, the heterodimeric antibodies have the first variable heavy domain and the first variable light domain are selected from the pairs consisting of H1 and L1; H1 and L1.24; H1 and L1.96; H1.77 and L1.96; H1.77 and L1.97; H1.72 and L1.97; H1.71 and L1.96 and H1.77 and L1.24.

[0039] Also disclosed are heterodimeric antibodies as above, wherein the scFv has a charged scFv linker. The charged scFv linker can have a positive charge from 3 to 8 and is selected from the group consisting of SEQ ID NO:s 443 to 451.

[0040] In an additional example, the scFv has a sequence selected from the group consisting of: SEQ ID NO: 4; SEQ ID NO: 8; SEQ ID NO: 12; SEQ ID NO: 16; SEQ ID NO: 20; SEQ ID NO: 24; SEQ ID NO: 28; SEQ ID NO: 32; SEQ ID NO: 36; SEQ ID NO: 40; SEQ ID NO: 44; SEQ ID NO: 48; SEQ ID NO: 52; SEQ ID NO: 56; SEQ ID NO: 60; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 72; SEQ ID NO: 76; SEQ ID NO: 80; SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 92; SEQ ID NO: 96; SEQ ID NO: 100; SEQ ID NO: 104; SEQ ID NO: 108; SEQ ID NO: 112; SEQ ID NO: 116; SEQ ID NO: 120; SEQ ID NO: 124; SEQ ID NO: 128; SEQ ID NO: 132; SEQ ID NO: 136; SEQ ID NO: 140; SEQ ID NO: 144; SEQ ID NO: 148; SEQ ID NO: 152; SEQ ID NO: 156; SEQ ID NO: 160; SEQ ID NO: 164; SEQ ID NO: 168; SEQ ID NO: 172; SEQ ID NO: 176; SEQ ID NO: 180; SEQ ID NO: 184; SEQ ID NO: 188; SEQ ID NO: 192; SEQ ID NO: 196; SEQ ID NO: 200; SEQ ID NO: 204; SEQ ID NO: 208; SEQ ID NO: 212; SEQ ID NO: 216; SEQ ID NO: 220; SEQ ID NO: 224; SEQ ID NO: 228; SEQ ID NO: 232; SEQ ID NO: 236; SEQ ID NO: 240; SEQ ID NO: 244; SEQ ID NO: 248; SEQ ID NO: 252; SEQ ID NO: 256; SEQ ID NO: 260; SEQ ID NO: 264; SEQ ID NO: 268; SEQ ID NO: 272; SEQ ID NO: 276; SEQ ID NO: 280; SEQ ID NO: 284; SEQ ID NO: 288; SEQ ID NO: 292; SEQ ID NO: 296; SEQ ID NO: 300; SEQ ID NO: 304; SEQ

ID NO: 308; SEQ ID NO: 312; SEQ ID NO: 316; SEQ ID NO: 320; SEQ ID NO: 324; SEQ ID NO: 328; SEQ ID NO: 332; SEQ ID NO: 336; SEQ ID NO: 340; SEQ ID NO: 344; SEQ ID NO: 348; SEQ ID NO: 352; SEQ ID NO: 356; SEQ ID NO: 360; SEQ ID NO: 364; SEQ ID NO: 368; SEQ ID NO: 372; SEQ ID NO: 376; SEQ ID NO: 380; SEQ ID NO: 384; SEQ ID NO: 388; SEQ ID NO: 392; SEQ ID NO: 396; SEQ ID NO: 400; SEQ ID NO: 404; SEQ ID NO: 408.

[0041] In a further example, the Fc region of the heavy chains further comprises an FcRn variant, including but not limited to 428L/434S.

[0042] In an additional aspect, the invention provides a nucleic acid composition comprising: a) a first nucleic acid encoding the first heavy chain as described herein; b) a second nucleic acid encoding the second heavy chain as described herein; and c) a third nucleic acid encoding said light chain as described herein. In additional aspect, the invention provides a nucleic acid composition comprising: a) a first expression vector comprising a first nucleic acid encoding the first heavy chain as described herein; b) a second expression vector comprising a second nucleic acid encoding the second heavy chain as described herein; and c) a third expression vector comprising a third nucleic acid encoding the light chain as described herein. Also disclosed are nucleic acid compositions comprising a first nucleic acid encoding a first heavy chain comprising an Fc region and a scFv that binds to CD3, a second nucleic acid encoding a second heavy chain that comprises a heavy constant chain and a heavy variable chain, and a third nucleic acid encoding a light chain, wherein the Fv regions of the second heavy chain and the light chain bind CD38. These nucleic acids can be in different expression vectors or the same. The invention provides host cells comprising the nucleic acid compositions.

[0043] In a further aspect, the invention provides methods of producing heterodimeric antibodies of the invention comprising providing a first expression vector comprising a first nucleic acid encoding a first heavy chain comprising a first Fc domain and a first variable heavy chain; providing a second expression vector comprising a second nucleic acid encoding a second heavy chain comprising a first Fc domain and a single chain Fv region (scFv) that binds CD3; and providing a third expression vector comprising nucleic acid comprising a light chain; wherein said first variable heavy chain and the variable light domain of said light chain bind CD38. The first, second and third expression vectors are transfected into host cells at a ratio selected from the group consisting of 1:1.5:1.5, 1:2:1.5, 1:0.667:2, 1:1:2, 1:1.5:2, and 1:2:2. The first, second and third nucleic acids in the host cells

produce a first, second and third amino acid sequence, respectively, such that said first, second and third amino acid sequences form heterodimeric antibody.

[0043A] In an additional aspect, the invention provides s pharmaceutical composition comprising the heterodimeric antibody as described herein.

[0044] In an additional aspect, the invention provides use of a heterodimeric antibody as described herein in the manufacture of a medicament for treating cancer a patient in need thereof. Also disclosed is a methods of treating a patient in need thereof by administering a heterodimeric antibody as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] Figure 1A and 1B depict the sequence of human CD38. Figure 1A depicts the full length sequence and Figure 1B depicts the extracellular domain.

were 2, 5, and 20 µg/kg. Depletion of CD20-CD38⁺ cells was observed in a dose dependent manner (see Fig.). Evidence of the recruitment of T cells was seen in the upregulation of CD69 on CD8⁺ T cells (see Fig.).

CLAIMS

We claim:

1. A heterodimeric antibody comprising:

a) a first heavy chain comprising:

i) a first Fc domain variant;

ii) a single chain Fv region (scFv) that binds CD3; and

b) a second heavy chain comprising:

i) a second Fc domain variant; and

ii) a first variable heavy domain; and

c) a first light chain comprising a first variable light domain and a first constant light domain;

wherein said first variable heavy domain and said first variable light domain bind to CD38, and wherein said second heavy chain and said first light chain are selected from the pairs consisting of H1 (SEQ ID NO: 473) and L1.24 (SEQ ID NO: 475); H1 (SEQ ID NO: 476) and L1.96 (SEQ ID NO: 478); H1.77 (SEQ ID NO: 479) and L1.96 (SEQ ID NO: 481); H1.77 (SEQ ID NO: 482) and L1.97 (SEQ ID NO: 484); H1.72 (SEQ ID NO: 485) and L1.97 (SEQ ID NO: 487); H1.71 (SEQ ID NO: 488) and L1.96 (SEQ ID NO: 490), and H1.77 (SEQ ID NO: 491) and L1.24 (SEQ ID NO: 493).

2. A heterodimeric antibody according to claim 1 wherein said second heavy chain and said first light chain are H1 (SEQ ID NO: 473) and L1.24 (SEQ ID NO: 475).

3. A heterodimeric antibody according to claim 1 or claim 2 wherein said scFv has a charged scFv linker.

4. A heterodimeric antibody according to claim 3 wherein charged scFv linker has a positive charge from 3 to 8 and is selected from the group consisting of SEQ ID NO:s 443 to 451.

5. A heterodimeric antibody according to any of claims 1 to 4 wherein said scFv has a sequence selected from the group consisting of: SEQ ID NO: 4; SEQ ID NO: 8; SEQ ID NO: 12; SEQ ID NO: 16; SEQ ID NO: 20; SEQ ID NO: 24; SEQ ID NO: 28; SEQ ID NO: 32; SEQ ID NO: 36; SEQ ID NO: 40; SEQ ID NO: 44; SEQ ID NO: 48; SEQ ID NO: 52; SEQ ID NO: 56; SEQ ID NO: 60; SEQ ID NO: 64; SEQ ID NO: 68; SEQ ID NO: 72; SEQ ID

NO: 76; SEQ ID NO: 80; SEQ ID NO: 84; SEQ ID NO: 88; SEQ ID NO: 92; SEQ ID NO: 96; SEQ ID NO: 100; SEQ ID NO: 104; SEQ ID NO: 108; SEQ ID NO: 112; SEQ ID NO: 116; SEQ ID NO: 120; SEQ ID NO: 124; SEQ ID NO: 128; SEQ ID NO: 132; SEQ ID NO: 136; SEQ ID NO: 140; SEQ ID NO: 144; SEQ ID NO: 148; SEQ ID NO: 152; SEQ ID NO: 156; SEQ ID NO: 160; SEQ ID NO: 164; SEQ ID NO: 168; SEQ ID NO: 172; SEQ ID NO: 176; SEQ ID NO: 180; SEQ ID NO: 184; SEQ ID NO: 188; SEQ ID NO: 192; SEQ ID NO: 196; SEQ ID NO: 200; SEQ ID NO: 204; SEQ ID NO: 208; SEQ ID NO: 212; SEQ ID NO: 216; SEQ ID NO: 220; SEQ ID NO: 224; SEQ ID NO: 228; SEQ ID NO: 232; SEQ ID NO: 236; SEQ ID NO: 240; SEQ ID NO: 244; SEQ ID NO: 248; SEQ ID NO: 252; SEQ ID NO: 256; SEQ ID NO: 260; SEQ ID NO: 264; SEQ ID NO: 268; SEQ ID NO: 272; SEQ ID NO: 276; SEQ ID NO: 280; SEQ ID NO: 284; SEQ ID NO: 288; SEQ ID NO: 292; SEQ ID NO: 296; SEQ ID NO: 300; SEQ ID NO: 304; SEQ ID NO: 308; SEQ ID NO: 312; SEQ ID NO: 316; SEQ ID NO: 320; SEQ ID NO: 324; SEQ ID NO: 328; SEQ ID NO: 332; SEQ ID NO: 336; SEQ ID NO: 340; SEQ ID NO: 344; SEQ ID NO: 348; SEQ ID NO: 352; SEQ ID NO: 356; SEQ ID NO: 360; SEQ ID NO: 364; SEQ ID NO: 368; SEQ ID NO: 372; SEQ ID NO: 376; SEQ ID NO: 380; SEQ ID NO: 384; SEQ ID NO: 388; SEQ ID NO: 392; SEQ ID NO: 396; SEQ ID NO: 400; SEQ ID NO: 404; SEQ ID NO: 408.

6. A heterodimeric antibody according to any of claims 1 to 5 wherein the first heavy chain comprises the Fc domain of SEQ ID NO: 520.

7. A heterodimeric antibody according to any one of claims 1 to 5 wherein the first heavy chain comprises amino acids 255-485 of SEQ ID NO: 520.

8. A nucleic acid composition comprising:

a) a first nucleic acid encoding the first heavy chain of any one of claims 1 to 7;

b) a second nucleic acid encoding the second heavy chain of any one of claims 1 to 7;

and

c) a third nucleic acid encoding said light chain of any one of claims 1 to 7.

9. A nucleic acid composition comprising:

a) a first expression vector comprising a first nucleic acid encoding the first heavy chain of any one of claims 1 to 7;

- b) a second expression vector comprising a second nucleic acid encoding the second heavy chain of any one of claims 1 to 7; and
- c) a third expression vector comprising a third nucleic acid encoding the light chain of any one of claims 1 to 7.

10. A host cell comprising the nucleic acid composition of claim 8.

11. A host cell comprising the nucleic acid composition of claim 9.

12. A method of producing a heterodimeric antibody according to any of claims 1 to 7 comprising:

- a) providing a first expression vector comprising a first nucleic acid encoding a first heavy chain comprising:

- i) a first Fc domain;
- ii) a first variable heavy chain; and

- b) providing a second expression vector comprising a second nucleic acid encoding a second heavy chain comprising:

- i) a first Fc domain; and
- ii) a single chain Fv region (scFv) that binds CD3;

and

- c) providing a third expression vector comprising nucleic acid comprising a light chain;

wherein said first variable heavy chain and the variable light domain of said light chain bind CD38;

- d) wherein said first, second and third expression vectors are transfected into host cells at a ratio selected from the group consisting of 1:1.5:1.5, 1:2:1.5, 1:0.667:2, 1:1:2, 1:1.5:2, and 1:2:2 ;

- e) expressing said first, second and third nucleic acids in said host cells to produce a first, second and third amino acid sequence, respectively, such that said first, second and third amino acid sequences form said heterodimeric antibody.

13. The method of claim 12, further comprising (f) formulating the heterodimeric antibody into a pharmaceutical composition.

14. A pharmaceutical composition comprising the heterodimeric antibody of any one of claims 1-7.

15. Use of a heterodimeric antibody according to any of claims 1 to 7 in the manufacture of a medicament for treating cancer a patient in need thereof.