

[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

[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 the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, and YGNWFPU and the first light chain comprises CDR sequences RASQNVDTWVAW, SASYRYS, and QQYDSYPLT; the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, and YGNWFPU and the first light chain comprises CDR sequences RASQNVDTNVA, SASYRYS, and QQYDSYPLT; the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, and YGNWFPU and the first light chain comprises CDR sequences RASQNVDYWVA, AASWRYS, and QQYDVYPLT; the second heavy chain comprises CDR sequences YSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDYWVA, AASWRYS, and QQYDVYPLT; the second heavy chain comprises CDR sequences YSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDYWVA, SASWRYS, and QQYDVYPLT; the second heavy chain comprises CDR sequences YSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDYWVA, AASWRYS, and QQYDVYPLT; or the second heavy chain comprises CDR sequences YSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR

sequences RASQNVDTWVAW, SASYRYS, and QQYDSYPLT. 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.

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 present invention provides methods of producing heterodimeric antibodies of the invention comprising providing a first expression vector comprising a first nucleic acid encoding the second heavy chain comprising the second Fc domain variant; and the first variable heavy domain; and providing a second expression vector comprising a second nucleic acid encoding the first heavy chain comprising the first Fc domain variant and the single chain Fv region (scFv) that binds CD3; providing a third expression vector comprising a third nucleic acid encoding the first light chain; wherein said first variable heavy domain and the variable light domain of the first light chain bind CD38; 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; and 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.

[0043A] In an additional aspect, the present invention provides a pharmaceutical composition comprising the heterodimeric antibody as described herein. In another aspect, the present invention refers to a nucleic acid composition comprising an expression vector comprising a nucleic acid encoding the first heavy chain of the present invention and an expression vector comprising a second nucleic acid encoding the second heavy chain of the present invention and a third nucleic acid encoding the first light chain of the present invention.

[0043] In an additional aspect, the invention provides use of a heterodimeric antibody as described herein in the manufacture of a medicament for treating cancer in 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

[0044] Figure 1A and 1B depict the sequence of human CD38. Figure 1A depicts the full length sequence and Figure 1B depicts the extracellular domain.

CLAIMS

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

the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, and YGNWFPU and the first light chain comprises CDR sequences RASQNVDTWVAW, SASYRYS, and QQYDSYPLT;

the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, and YGNWFPU and the first light chain comprises CDR sequences RASQNVDTNVA, SASYRYS, and QQYDSYPLT;

the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, and YGNWFPU and the first light chain comprises CDR sequences RASQNVDYWVA, AASWRYS, and QQYDVYPLT;

the second heavy chain comprises CDR sequences YSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDYWVA, AASWRYS, and QQYDVYPLT;

the second heavy chain comprises CDR sequences YSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDYWVA, SASWRYS, and QQYDVYPLT;

the second heavy chain comprises CDR sequences YSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDYWVA, SASWRYS, and QQYDVYPLT;

the second heavy chain comprises CDR sequences RSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDYWVA, AASWRYS, and QQYDVYPLT; or

the second heavy chain comprises CDR sequences YSWMN, EINPQSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDTWVAW, SASYRYS, and QQYDSYPLT.

2. A heterodimeric antibody according to claim 1, wherein said second heavy chain and said first light chain are selected from the pairs consisting of

(i) H1 of Figure 20D (EVQLVESGGG LVQPGGSLRLSCAASG FDFSRSWM NWVRQAPG KG LEWVSEIN PDSSTINYATSVKGRFTISRDN SKNTLYLQM NSLRAE DTAVYYCARYGNWFPYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS DIAVEWESDGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEA LHNHYTQKSLSLSPGK)

and L1.24 of Figure 20D (DIVMTQSPSSLSASVGDRVTITCRASQNVDTWVAWYQQKPGQSPKALIYSASYRYS GVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDSYPLTFGGGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC);

(ii) H1 of Figure 20E (EVQLVESGGG LVQPGGSLRLSCAASG FD FS RSWM NWVRQAPGKGLEWVSEINPDSSTINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDT AVYYCARYGNWFPYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI AVEWESDGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALH NHYTQKSLSLSPG) and L1.96 of Figure 20E

(DIVMTQSPSSLSASVGDRVTITCRASQNVDYWVAWYQQKPGQSPKALIYAASWRY SGVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDVYPLTFGGGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYE KH KVYACEVTHQG LSSPVTKSFN RG EC);

(iii) H1.77 of Figure 20F (EVQLVESGGG LVQPGGSLRLSCAASGFTFSYSWM NWVRQAPGKGLEWVSEINPQSSTINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDT AVYYCARYGNWFPYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI AVEWESDGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALH NHYTQKSLSLSPG) and L1.96 of Figure 20F (DIVMTQSPSSLSASVGDRVITICRASQNVDYWVAWYQQKPGQSPKALIYAASWRY SGVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDVYPLTFGGG TKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKH KVYACEVTHQG LSSPVTKSFN RG ECSEQ);

(iv) H1.77 of Figure 20G (EVQLVESGGG LVQPGGSLRLSCAASGFTFSYSWM NWVRQAPGKGLEWVSEINPQSSTINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDT AVYYCARYGNWFPYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI AVEWESDGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALH NHYTQKSLSLSPGKSEQ) and L1.97 of Figure 20G (DIVMTQSPSSLSASVGDRVITICRASQNVDYWVAWYQQKPGQSPKALIYSASWRYSGVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDVYPLTFGGG TKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYLSSTLTLSKADYEKH KVYACEVTHQG LSSPVTKSFN RG ECSEQ);

(v) H1.72 of Figure 20H (EVQLVESGGG LVQPGGSLRLSCAASG FDFSYSWM NWVRQAPGKGLEWVSEINPQSSTINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDT AVYYCARYGNWFPYWGQGLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI AVEWESDGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALH

NHYTQKSLSLSPGKSEQ) and L1.97 of Figure 20H
 (DIVMTQSPSSLSASVGDRVITICRASQNVQYDVAWYQQKPGQSPKALIYSASWRYS
 GVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDVYPLTFGGGTKLEIKRTVAAPS
 VFIFPPSDEQLKSGTASVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
 TYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFN RG ECSEQ);

(vi) H1.71 of Figure 20I (EVQLVESGGG LVQPG GSLRLSCAASG FTFSRSW M
 NWVRQAPG KG LEWVSEI NPQSSTINYATSVKG RFTISRDN SKNTLYLQM NS LRAE
 DAVYYCARYGNWFPYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
 KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
 HKPSDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV
 VVDVKH E DP EVKFNWYVDGVEVH NAKTKPREEEYNSTYRVVSVLTVLHQDWLN
 GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGF
 YPSDIAVEWES DGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVM
 HEALHNHYTQKSLSLSPGK) and L1.96 of Figure 20I
 (DIVMTQSPSSLSASVGDRVITICRASQNVQYDVAWYQQKPGQSPKALIYAASWRY
 SGVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDVYPLTFGGGTKLEIKRTVAAP
 SVFIFPPSDEQLKSGTASVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDSKD
 STYSLSSTLTLSKADYE KH KVYACEVTHQG LSSPVTKSFN RG EC), and

(vii) H1.77 of Figure 20J
 (EVQLVESGGGLVQPGGSLRLSCAASGFTFSYSWMNWVRQAPGKGLEWVSEINPQS
 STINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYGNWFPYWGQGTLL
 TVTSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
 PAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSDTKVDKKVEPKSCDKTHTCPP
 CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH EDP EVKFNWYVDGVEVH
 NAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
 QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTPPVLD
 DSDGSFFLYSKLTVDKSRWEQGDVFSCSVMH EALHNHYTQKSLSLSPGK) and L1.24
 of Figure 20J
 (DIVMTQSPSSLSASVGDRVITICRASQNVDTWVAWYQQKPGQSPKALIYSASYRYS
 GVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDSYPLTFGGGTKLEIKRTVAAPS
 VFIFPPSDEQLKSGTASVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS
 TYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC).

3. A heterodimeric antibody according to claim 1 wherein said second heavy chain and said first light chain are H1 (EVQLVESGGG LVQPGGSLRLSCAASG FDFSRSWM NWVRQAPG KG LEWVSEIN PDSSTINYATSVKGRFTISRDN SKNTLYLQM NSLRAE DTAVYYCARYGNWFPYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTQTYICNVNH KPSDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS DIAVEWESDGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEA LHNHYTQKSLSLSPGK) and L1.24 (DIVMTQSPSSLSASV GDRVTITCRASQNVD TWVAWYQQKPGQSPKALIYSASYRYS GVPDRFTGSGSGTDFTLTIS SLQPEDFATYFCQQYDSYPLTFGGGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC).

4. A heterodimeric antibody according to any one of claims 1 to 3 wherein said scFv has a charged scFv linker.

5. A heterodimeric antibody according to claim 4 wherein charged scFv linker has a positive charge from 3 to 8 and is selected from the group consisting of SEQ ID NOs: 443 to 451.

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 nucleic acid composition comprising:

- a) a first nucleic acid encoding the first heavy chain of any one of claims 1 to 6;
 - b) a second nucleic acid encoding the second heavy chain of any one of claims 1 to 6;
- and
- c) a third nucleic acid encoding said light chain of any one of claims 1 to 6.

8. 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 6;
- b) a second expression vector comprising a second nucleic acid encoding the second

heavy chain of any one of claims 1 to 6; and

c) a third expression vector comprising a third nucleic acid encoding the light chain of any one of claims 1 to 6.

9. A host cell comprising the nucleic acid composition of claim 7.

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

11. A method of producing a heterodimeric antibody according to any of claims 1 to 6 comprising:

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

- i) the second Fc domain variant; and
- ii) the first variable heavy domain; and

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

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

c) providing a third expression vector comprising a third nucleic acid encoding the first light chain; wherein said first variable heavy domain and the variable light domain of the first 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; and

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.

12. The method of claim 11, further comprising (f) formulating the heterodimeric antibody into a pharmaceutical composition.

13. A pharmaceutical composition comprising the heterodimeric antibody of any one of claims 1-6.

14. Use of a heterodimeric antibody according to any of claims 1 to 6 in the manufacture of a medicament for treating cancer in a patient in need thereof.

15. A nucleic acid composition comprising an expression vector comprising a nucleic acid encoding the first heavy chain of claim 1 and an expression vector comprising a second nucleic acid encoding the second heavy chain of claim 1 and a third nucleic acid encoding the first light chain of claim 1.