

[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 YGNWFPY and the first light chain comprises CDR sequences RASQNVDTWVA, SASYRYS, and QQYDSYPLT; the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, and YGNWFPY and the first light chain comprises CDR sequences RASQNVDTNVA, SASYRYS, and QQYDSYPLT; the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, 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, 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 RASQNVDTWVA, 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.

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 YGNWFPY and the first light chain comprises CDR sequences RASQNVDTWVA, SASYRYS, and QQYDSYPLT;

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

the second heavy chain comprises CDR sequences RSWMN, EINPDSSTINYATSVKG, 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, 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 RASQNVDTWVA, 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 DTAVYYCARYGNWFPYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTPSSSLGTQTYICNVNH KPSDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS DIAVEWESDGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDVFSCSVMHEA LHNHYTQKSLSLSPGK)

and L1.24 of Figure 20D (DIVMTQSPSSLSASVGDRVTITCRASQNVD TWVAWYQQKPGQSPKALIYSASYRYS GVPDRFTGSGSGTDFTLTIS SLQPEDFATYFCQQYDSYPLTFGGG TKLEIKRTVAAPS VFIFPPSDEQLKSGTASV VCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC);

(ii) H1 of Figure 20E (EVQLVESGGG LVQPGGSLRLSCAASG FD FS RSWM NWVRQAPGKGLEWVSEINPDSSTINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDT AVYYCARYGNWFPYWGQGT LVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTPSSSLGTQTYICNVNHKP SDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI AVEWESDGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALH NHYTQKSLSLSPG) and L1.96 of Figure 20E

(DIVMTQSPSSLSASVGDRVTITCRASQNVDY WVAWYQQKPGQSPKALIYAASWRY SGVPDRFTGSGSGTDFTLTIS SLQPEDFATYFCQQYDVYPLTFGGG TKLEIKRTVAAP SVFIFPPSDEQLKSGTASV VCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSLTLSKADYE KH KVYACEVTHQG LSSPVTKSFN RG EC);

(iii) H1.77 of Figure 20F (EVQLVESGGG LVQPGGSLRLSCAASGFTFSYSWM NWVRQAPGKGLEWVSEINPQSSTINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDT AVYYCARYGNWFPYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI AVEWESDQGPNENYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALH NHYTQKSLSLSPG) and L1.96 of Figure 20F (DIVMTQSPSSLSASVGDRVTITCRASQNVDYWVAWYQQKPGQSPKALIYAASWRY SGVPDRFTGSGSGTDFTLTIS SLQPEDFATYFCQQYDVYPLTFGGG TKLEIKRTVAAP SVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYLSSTLTLSKADYEKH K VYACEVTHQG LSSPVTKSFN RG ECSEQ);

(iv) H1.77 of Figure 20G (EVQLVESGGG LVQPGGSLRLSCAASGFTFSYSWM NWVRQAPGKGLEWVSEINPQSSTINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDT AVYYCARYGNWFPYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI AVEWESDQGPNENYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALH NHYTQKSLSLSPGKSEQ) and L1.97 of Figure 20G (DIVMTQSPSSLSASVGDRVTITCRASQNVDYWVAWYQQKPGQSPKALIYSASWRY S GVPDRFTGSGSGTDFTLTIS SLQPEDFATYFCQQYDVYPLTFGGG TKLEIKRTVAAPS VFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYLSSTLTLSKADYEKH K VYACEVTHQG LSSPVTKSFN RG ECSEQ);

(v) H1.72 of Figure 20H (EVQLVESGGG LVQPGGSLRLSCAASG FDFSYSWM NWVRQAPGKGLEWVSEINPQSSTINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDT AVYYCARYGNWFPYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVD VKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDI AVEWESDQGPNENYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDVFSCSVMHEALH

NHYTQKSLSLSPGKSEQ) and L1.97 of Figure 20H (DIVMTQSPSSLSASVGDRVTITCRASQNVDYWVAWYQQKPGQSPKALIYSASWRYS GVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDVYPLTFGGGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFN RG ECSEQ);

(vi) H1.71 of Figure 20I (EVQLVESGGG LVQPG GSLRLSCAASG FTFSRSW M NWVRQAPG KG LEWVSEI NPQSSTINYATSVKG RFTISRDN SKNTLYLQM NS LRAE DTA VYYCARYGNWFPYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN HKPSDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCV VVDVKH E DP EVKFNWYVDGVEVH NAKTKPREEEYNSTYRVVSVLTVLHQDWLN GKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGF YPSDIAVEWES DGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWEQGDVFSCSVM HEALHNHYTQKSLSLSPGK) and L1.96 of Figure 20I (DIVMTQSPSSLSASVGDRVTITCRASQNVDYWVAWYQQKPGQSPKALIYAASWRY SGVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDVYPLTFGGGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSSTLTLSKADYE KH KVYACEVTHQG LSSPVTKSFN RG EC), and

(vii) H1.77 of Figure 20J (EVQLVESGGGLVQPGGSLRLSCAASGFTFSYSWMNWVRQAPGKGLEWVSEINPQS STINYATSVKGRFTISRDN SKNTLYLQMNSLRAEDTA VYYCARYGNWFPYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTF PAVLQSSGLYSLSSVTVPSSSLGTQTYICNVN HKPSDTKVDKKVEPKSCDKTHTCPP CPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVKH EDP EVKFNWYVDGVEVH NAKTKPREEEYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPSDIAVEWESDGQPENNYKTTTPVL DSDGSFFLYSKLTVDKSRWEQGDVFSCSVMH EALHNHYTQKSLSLSPGK) and L1.24 of Figure 20J

(DIVMTQSPSSLSASVGDRVTITCRASQNVDTWVAWYQQKPGQSPKALIYSASYRYS GVPDRFTGSGSGTDFTLTISLQPEDFATYFCQQYDSYPLTFGGGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPPREAKVQWKVDNALQSGNSQESVTEQDSKDS TYSLSSSTLTLSKADYEKH 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 DTA VYYCARYGNWFPYWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTPSSSLGTQTYICNVNH KPSDTKVDKKVEPKSCDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVKHEDPEVKFNWYVDGVEVHNAKTKPREEEYNSTYRVVSVLTVLHQDWLNGK EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCDVSGFYPS DIAVEWESDGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWEQGDVFSCSVMHEA LHNHYTQKSLSLSPGK) and L1.24 (DIVMTQSPSSLSASVGDRVTITCRASQNVD TWVAWYQQKPGQSPKALIYSASYRYS GVPDRFTGSGSGTDFTLTIS SLQPEDFATYFCQQYDSYPLTFGGGT KLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFY PREAKVQWKVDNALQSGNSQESVTEQDSKDS 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 nucleic acid composition comprising:

- a) a first nucleic acid encoding the first heavy chain of any one of claims 1 to 5;
- b) a second nucleic acid encoding the second heavy chain of any one of claims 1 to 5;

and

- c) a third nucleic acid encoding said light chain of any one of claims 1 to 5.

7. 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 5;

- b) a second expression vector comprising a second nucleic acid encoding the second heavy chain of any one of claims 1 to 5; and

- c) a third expression vector comprising a third nucleic acid encoding the light chain of any one of claims 1 to 5.

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

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

10. A method of producing a heterodimeric antibody according to any of claims 1 to 5 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.

11. The method of claim 10, further comprising (f) formulating the heterodimeric antibody into a pharmaceutical composition.

12. A pharmaceutical composition comprising the heterodimeric antibody of any one of claims 1-5.

13. Use of a heterodimeric antibody according to any of claims 1 to 5 in the manufacture of a medicament for treating cancer in a patient in need thereof.

14. 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.