

CD38-expressing tumors still have a poor prognosis. Thus, there is a need for improved methods for treating such forms of cancer.

[0007] 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 novel bispecific antibodies directed to CD3 and CD38.

BRIEF SUMMARY

[0008] In a first aspect, the present disclosure refers to a heterodimeric antibody comprising: a) a first monomer comprising: i) a first Fc domain; ii) an anti-CD3 scFv comprising SEQ ID NO: 18; wherein said scFv is covalently attached to the N-terminus of said Fc domain using a domain linker; b) a second monomer comprising a heavy chain comprising: i) a heavy variable domain; and ii) a heavy constant domain comprising a second Fc domain; and c) a light chain comprising a variable light domain and a constant light domain; wherein said heavy variable domain and said variable light domain bind CD38 wherein said variable light domain comprises: a vLCDR1 having the sequence RASQNVDTWVA (SEQ ID NO:69), a vLCDR2 having the sequence SASYRYS (SEQ ID NO:70) and a vLCDR3 having the sequence QQYDSYPLT (SEQ ID NO:71), said variable heavy domain comprises a vhCDR1 having the sequence RSWMN (SEQ ID NO:65), a vhCDR2 having the sequence EINPDSSTINYATSVKG (SEQ ID NO:66) and a vhCDR3 having the sequence YGNWFPY (SEQ ID NO:67). In another aspect, the present disclosure refers to a nucleic acid composition encoding the heterodimeric antibody of the present disclosure, said composition comprising: a) a first nucleic acid encoding said first monomer; b) a second nucleic acid encoding said second monomer; and c) a third nucleic acid encoding said light chain. In yet another aspect, the present disclosure refers to an expression vector composition comprising: a) a first expression vector comprising a nucleic acid encoding said first monomer of the present disclosure; b) a second expression vector comprising a nucleic acid encoding said second monomer of the present disclosure; and c) a third expression vector comprising a nucleic acid encoding said light chain of the present disclosure. In still another aspect, the present disclosure refers to a host cell comprising the nucleic acid

composition of the present disclosure. In another aspect, the present disclosure refers to a host cell comprising the expression vector composition of the present disclosure. In another aspect, the present disclosure refers to a method of making a heterodimeric antibody of the present disclosure comprising culturing the host cell of the present disclosure under conditions wherein said antibody is expressed, and recovering said antibody. In yet another aspect, the present disclosure refers to the use of a heterodimeric antibody of the present disclosure in the preparation of a medicament for treating cancer in a patient in need thereof. In still another aspect, the present disclosure refers to a composition comprising a) a first expression vector comprising a nucleic acid encoding said first monomer of the present disclosure and b) a second expression vector encoding a nucleic acid encoding said second monomer of the present invention and a nucleic acid encoding said light chain of the present disclosure. Also described herein are heterodimeric antibodies directed against CD3 and CD38. In some examples, the heterodimeric antibodies comprise a first monomer comprising SEQ ID NO:91; a second monomer comprising SEQ ID NO:92; and a light chain comprising SEQ ID NO:93. In some examples, the heterodimeric antibodies comprise a first monomer comprising SEQ ID NO:88; a second monomer comprising SEQ ID NO:89; and a light chain comprising SEQ ID NO:90. The disclosure further provides nucleic acid compositions comprising first, second and third nucleic acids that encode the sequences above, as well as expression vectors comprising the nucleic acid compositions, host cells comprising either the nucleic acids or expression vectors, and methods of making and using the heterodimeric antibodies.

[0009] In an additional example, the disclosure provides heterodimeric antibodies comprising: a first monomer comprising: i) a first Fc domain; ii) an anti-CD3 scFv comprising a scFv variable light domain, an scFv linker and a scFv variable heavy domain; wherein said scFv is covalently attached to the N-terminus of said Fc domain using a domain linker; a second monomer comprising a heavy chain comprising: i) a heavy variable domain; and ii) a heavy chain constant domain comprising a second Fc domain; and a light chain comprising a variable light domain and a variable light constant domain. In some examples the scFv variable light domain comprises: a vLCDR1 having SEQ ID NO:15, a vLCDR2 having SEQ ID NO:16 and a vLCDR3 having SEQ ID NO:17, said scFv variable

heavy domain comprises a vhCDR1 having SEQ ID NO:11, a vhCDR2 having SEQ ID NO:12 and a vhCDR3 having SEQ

WHAT IS CLAIMED IS:

1. A heterodimeric antibody comprising:

- a) a first monomer comprising:
 - i) a first Fc domain;
 - ii) an anti-CD3 scFv comprising SEQ ID NO: 18; wherein said scFv is covalently attached to the N-terminus of said Fc domain using a domain linker;
- b) a second monomer comprising a heavy chain comprising:
 - i) a heavy variable domain; and
 - ii) a heavy constant domain comprising a second Fc domain; and
- c) a light chain comprising a variable light domain and a constant light domain; wherein said heavy variable domain and said variable light domain bind CD38 wherein said variable light domain comprises: a vLCDR1 having the sequence RASQNVDTWVA (SEQ ID NO:69), a vLCDR2 having the sequence SASYRYS (SEQ ID NO:70) and a vLCDR3 having the sequence QQYDSYPLT (SEQ ID NO:71), said variable heavy domain comprises a vhCDR1 having the sequence RSWMN (SEQ ID NO:65), a vhCDR2 having the sequence EINPDSSTINYATSVKG (SEQ ID NO:66) and a vhCDR3 having the sequence YGNWFPY (SEQ ID NO:67).

2. A heterodimeric antibody according to claim 1 wherein said variable light domain has the sequence
DIVMTQSPSSLSASVGDRVITICRASQNVDTWVAWYQQKPGQSPKALIYSASYRYS GVPD
RFTGSGSGTDFTLTISSLQPEDFATYFCQQYDSYPLTFGGGTKLEIK (SEQ ID NO:68) and
said variable heavy domain has the sequence
EVQLVESGGGLVQPGGSLRLSCAASGFD FSRSWMNWVRQAPGKGLEWVSEINPDSSTIN
YATSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARYGNWFPYWGQGT LTVTSS
(SEQ ID NO:64).

3. A heterodimeric antibody according to claim 1 or claim 2, wherein said first Fc domain and said second Fc domain comprise a set of variants selected from the group consisting of S364K/E357Q : L368D/K370S; L368D/K370S : S364K; L368E/K370S : S364K; T411T/E360E/Q362E : D401K; L368D/K370S : S364K/E357L and K370S : S364K/E357Q.

4. A heterodimeric antibody according to any of claims 1 to 3 wherein said heavy constant domain comprises the amino acid substitutions N208D/Q295E/N384D/Q418E/N421D.

5. A heterodimeric antibody according to any of claims 1 to 4 wherein said first and second Fc domains comprise the amino acid substitutions E233P/L234V/L235A/G236del/S267K.

6. A heterodimeric antibody according to claim 1, wherein the first monomer comprises SEQ ID NO:104; the second monomer comprises SEQ ID NO:109; and the light chain comprises SEQ ID NO:111.

7. A nucleic acid composition encoding the heterodimeric antibody of any of claims 1 to 6, said composition comprising:

- a) a first nucleic acid encoding said first monomer;
- b) a second nucleic acid encoding said second monomer; and
- c) a third nucleic acid encoding said light chain.

8. An expression vector composition comprising:

- a) a first expression vector comprising a nucleic acid encoding said first monomer of any of claims 1-6;
- b) a second expression vector comprising a nucleic acid encoding said second monomer of any of claims 1-6; and
- c) a third expression vector comprising a nucleic acid encoding said light chain of any of claims 1-6.

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

10. A host cell comprising the expression vector composition of claim 8.

11. A method of making a heterodimeric antibody according to any of claims 1 to 6 comprising culturing the host cell of claim 9 or 10 under conditions wherein said antibody is expressed, and recovering said antibody.

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

13. A composition comprising a) a first expression vector comprising a nucleic acid encoding said first monomer of any one of claims 1-6 and b) a second expression vector

encoding a nucleic acid encoding said second monomer of any one of claims 1-6 and a nucleic acid encoding said light chain of any one of claims 1-6.