Claims

1. A compound comprising:

an NK engaging domain comprising:

amino acid residues 1-240 of SEQ ID NO:1, or amino acid residues 19-140 of SEQ ID NO:14;

an NK activating domain comprising:

the amino acid sequence of SEQ ID NO:15, or the amino acid sequence of SEQ ID NO:15 comprising an N72D amino acid substitution or an N72A amino acid substitution;

a first linker linking the NK engaging domain to the NK activating domain;

a targeting domain that selectively binds to a target antigen; and

a second linker linking the NK activating domain to the targeting domain.

2. The compound of claim 1, wherein the NK engaging domain activates an NK cell.

3. The compound of claim 1, wherein the NK engaging domain blocks inhibition of an NK cell.

4. The compound of claim 1 wherein the NK engaging domain moiety comprises an antibody or a binding fragment thereof.

5. The compound of claim 4 wherein the antibody fragment comprises an scFv, a $F(ab)_2$, or a Fab.

6. The compound of claim 1 wherein the targeting domain comprises a moiety that selectively binds to a tumor cell.

7. The compound of claim 6 wherein the targeting domain moiety comprises an antibody or a binding fragment thereof.

8. The compound of claim 7 wherein the antibody fragment comprises an scFv.

9. A composition comprising:
the compound of claim 1; and
a pharmaceutically acceptable carrier.

10. A compound comprising the amino acid sequence set forth in SEQ ID NO:1 or SEQ ID NO:14.

11. The compound of claim 10, wherein the compound comprises two targeting domains.

12. The compound of claim 1, wherein the NK engager domain and the IL-15 sequence are linked by a linker as set forth in SEQ ID NO:3.

13. The compound of claim 1, wherein the IL-15 sequence and the targeting domain are linked by a linker as set forth in SEQ ID NO:4.

14. The compound of claim 5, wherein the antibody, the binding fragment thereof, or the nanobody is human, humanized, or camelid.

15. The compound of claim 1, wherein the first linker comprises:
the amino acids of SEQ ID NO:3;
the amino acids of SEQ ID NO:4;
amino acids 119-133 of SEQ ID NO:5;
amino acids 494-518 of SEQ ID NO:8;
amino acids 241-255 of SEQ ID NO:12;
amino acids 488-506 of SEQ ID:10;
amino acids 277-294 of SEQ ID NO:14; or
amino acids 142-161 of SEQ ID NO:14.

16. The compound of claim 1, wherein the second linker comprises:
the amino acids of SEQ ID NO:3;

the amino acids of SEQ ID NO:4;
amino acids 119-133 of SEQ ID NO:5;
amino acids 494-518 of SEQ ID NO:8;
amino acids 241-255 of SEQ ID NO:12;
amino acids 488-506 of SEQ ID:10;
amino acids 277-294 of SEQ ID NO:14; or
amino acids 142-161 of SEQ ID NO:14.

17. The compound of claim 1, wherein:
the first linker comprises the amino acids of SEQ ID NO:3; and
the second linker comprises the amino acids of SEQ ID NO:4.

18. The compound of claim 1, wherein:
the first linker comprises amino acids 142-161 of SEQ ID NO:14; and
the second linker comprises amino acids 277-294 of SEQ ID NO:14.

19. The compound of claim 1, wherein the targeting domain binds to a target antigen or portion thereof selected from CD133, CD20, H ER2, CEA, EpCAM, VEGF-A, EGFR, CD33, integrin αVβ3, CD51, CD152, CD125, CTAA16.88, MUC1, CD19, CD22, CD38, CD30, CD52, uPAR, LIV-1, CD70, IL-3, IL-4R, mesothelin, ROR1, CSPG4, SS1, IGFR1, HSPG2, IGF-1, epithelial-mesenchymal transition (EMT), TRAIL, CD45, CD74, CD23, HIV, or a cancer antigen.