CLAIMS

What is claimed is:

1. A bispecific tetravalent antibody, said bispecific tetravalent antibody comprising:

two IgG1 heavy chains;

two kappa light chains; and

two single chain Fv (scFv) domains;

wherein the two IgG1 heavy chains and kappa light chains form an IgG moiety with a binding specificity to a first member of the EGFR family;

wherein the two scFv domains have a binding specificity to a second member of the EGFR family, and each scFv domain is connected to the C-terminus of either of the IgG1 heavy chains by a connector with an amino acid sequence of $(gly\text{-}gly\text{-}gly\text{-}gly\text{-}ser)_n$, to provide a IgG1-connector connection, wherein n is an integral of at least 1; and

wherein each scFv domain has a structure order of N terminus – variable heavy chain – linker – variable light chain – C terminus or N-terminus – variable light chain– linker– variable heavy chain– C-terminus, and wherein the linker is comprised of amino acid sequence of $(gly\text{-}gly\text{-}gly\text{-}gly\text{-}ser)_m$, wherein m is an integral of at least 3.

2. The bispecific tetravalent antibody of Claim 1, wherein at least one of the IgG1 heavy chains is a humanized or human IgG1 heavy chain; or wherein both IgG1 heavy chains are humanized or human IgG1 heavy chains.

3. The bispecific tetravalent antibody of Claim 1, wherein at least one of the kappa light chains is a humanized or human kappa light chain; or wherein both kappa light chains are humanized or human kappa light chains.

4. The bispecific tetravalent antibody of Claim 1, wherein the first or the second member of the EGFR family comprises HER3, EGFR, a fragment or a derivative thereof; or wherein the first or the second member of the EGFR family is independently selected from a group consisting of HER3, EGFR, a fragment or a derivative thereof.

5. The bispecific tetravalent antibody of claim 1, wherein the IgG moiety has a binding specificity for HER3 or EGFR.

6. The bispecific tetravalent antibody of claim 1, wherein the scFv domains have a binding specificity for EGFR or HER3.

7. The bispecific tetravalent antibody of claim 1, wherein the IgG moiety has a binding specificity for HER3 and the scFv domains have a binding specificity for EGFR simultaneously; or wherein the IgG moiety has a binding specificity for EGFR and the scFv domains have a binding specificity for HER3 simultaneously.

8. The bispecific tetravalent antibody of Claim 1, wherein the IgG1-connector connection is resistant to protease activity.

9. The bispecific tetravalent antibody of Claim 1, wherein the IgG1 heavy chain, connector, and scFv domain have an amino acid comprising SEQ ID NO 56, 66, 76, 86, 98, 108, 118, and 136; or wherein at least one of the kappa light chains comprises an amino acid sequence comprising SEQ ID NO 3, 11, 19, 27, 35, 43, 51, 61, 71, 81, 92, 103, 113, 123, and 131.

10. The bispecific tetravalent antibody of claim 1, wherein the IgG moiety has a binding specificity for HER3, and the scFv domains have a binding specificity for EGFR;

wherein the IgG1 heavy chain, connector, and scFv domain have an amino acid sequence of SEQ ID NO 56, and the kappa light chain has an amino acid sequence of SEQ ID NO 51; or wherein the IgG1 heavy chain, connector, and scFv domain have an amino acid sequence of SEQ ID NO 76, and the kappa light chain has an amino acid sequence of SEQ ID NO 71.

11. The bispecific tetravalent antibody of Claim 1, wherein the antibody binds to EGRF and HERS with a Kd less than 50nM; or wherein the antibody simultaneously binds to EGRF with a Kd less than 50nM and binds to HER3 with a Kd less than 50nM.

12. A kappa light chain for the bispecific tetravalent antibody of Claim 1, comprising an amino acid sequence selected from SEQ ID NO 3, 11, 19, 27, 35, 43, 51, 61, 71, 81, 92, 103, 113, 123, and 131.

13. An isolated nucleic acid encoding the antibody of Claim 1, the IgG1 heavy Chain comprising an amino acid sequences selected from SEQ ID NO 7, 15, 23, 31, 39, 47, and 127, the kappa light chain of Claim 12, the variable light chain comprising an amino acid sequence selected from SEQ ID NO 4, 12, 20, 28, 36, 44, 52, 62, 72, 82, 93, 104, 114, 124, and 132, or the variable heavy chain comprising an amino acid sequence selected from SEQ ID NO 8, 16, 24, 32, 40, 48, 57, 67, 77, 87, 99, 109, 119, 128, and 137.

14. An expression vector comprising the isolated nucleic acid of Claim 13; optionallay wherein the vector is expressible in a cell.

15. A host cell comprising the nucleic acid of Claim 13.

16. A host cell comprising the expression vector of Claim 15; optionally wherein the host cell is a prokaryotic cell or a eukaryotic cell.

17. An immunoconjugate comprising the antibody of Claim 1 and a cytotoxic agent.

18. A pharmaceutical composition, comprising the bispecific tetravalent antibody of Claim 1 and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition of Claim 18, further comprising radioisotope, radionuclide, a toxin, a therapeutic agent, a chemotherapeutic agent or a combination thereof.

20. A pharmaceutical composition, comprising the immunoconjugate of Claim 17 and a pharmaceutically acceptable carrier.

21. Use of the bispecific tetravalent antibody of Claim 1 in the manufacture of a medicament for treating a subject with a cancer.

22. The use of Claim 21, wherein the cancer comprises cells expressing at least two members of EGFR family.

23. The use of Claim 21, wherein the cancer comprises breast cancer, colorectal cancer, pancreatic cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, non-small lung cell cancer, glioma, esophageal cancer, nasopharyngeal cancer, anal cancer, rectal cancer, gastric cancer, bladder cancer, cervical cancer, or brain cancer.

24. The use of Claim 21, further comprising co-administration of a therapeutic agent.

25. The use of Claim 24, wherein the therapeutic agent comprises an antibody, a chemotherapy agent, an enzyme, or a combination thereof.

26. The use of Claim 24, wherein the therapeutic agent comprises an anti-estrogen agent, a receptor tyrosine inhibitor, or a combination thereof.

27. The use of Claim 24, wherein the therapeutic agent comprises capecitabine, cisplatin, trastuzumab, fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, letrozole, erlotinib, lafatinib, dasatinib, gefitinib, imatinib, pazopinib, lapatinib, sunitinib, nilotinib, sorafenib, nab-palitaxel, a derivative or a combination thereof.

28. The use of Claim 24, wherein the therapeutic agent comprises a check point inhibitor.

29. The use of Claim 24, wherein the therapeutic agent comprises PD1, PDL1, CTLA4, 4-1BB, OX40, GITR, TIM3, LAG3, TIGIT, CD40, CD27, HVEM, BTLA, VISTA, B7H4, a derivative or a combination thereof.

30. The use of Claim 21, wherein the subject is a human.

31. A solution comprising an effective concentration of the bispecific tetravalent antibody of Claim 1, wherein the solution is blood plasma in a subject.