CLAIMS

What is claimed is:

1. A recombinant fusion protein comprising a fragment of the cardioprotective protein neuregulin-1 (NRG-1) fused to a monoclonal antibody (mAb) backbone.

2. The recombinant fusion protein of claim 1, wherein the NRG-1 fragment comprises an active fragment.

3. The recombinant fusion protein of claim 2, wherein the active protein fragment of NRG-1 comprises the active domain of NRG-1.

4. The recombinant fusion protein of any one of claims 1-3, wherein the mAb is monospecific for ErbB3 (HER3).

5. The recombinant fusion protein of any one of claims 1-4, wherein the NRG-1 fragment comprises the ERBB3/4 binding domain.

6. The recombinant fusion protein of any one of claims 1-5, wherein the NRG-1 fragment binds to and induces signaling through ErbB4 (HER4).

7. The recombinant fusion protein of claim 6, wherein the mAb inhibits NRG-1 signaling through ErbB3 (HER3).

8. The recombinant fusion protein of any one of claims 1-7, wherein said NRG-1 fragment comprises the NRG-1 ß2a isoform.

9. The recombinant fusion protein of any one claims 1-8, wherein the NRG-1 fragment is fused via its N-terminal amino acid to the C-terminus of the antibody heavy chain using a linker.

10. The recombinant fusion protein of claim 9, wherein said linker comprises at least one copy of a Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser linker set forth in SEQ ID NO: 5.

11. The recombinant fusion protein of claim 9, wherein the C-terminus of the antibody heavy chain comprises the Fc domain of the antibody.

12. The recombinant fusion protein of any one of claims 1-11, wherein the monoclonal antibody is glycosylated.

13. The recombinant fusion protein of claim 12, wherein the glycosylation is N-glycosylation.

14. The recombinant fusion protein of claim 12, wherein the glycosylation is O-glycosylation.

15. The recombinant fusion protein of any one of claims 1-14, wherein the NRG-1 fragment comprises the amino acid sequence of SEQ ID NO: 4.

16. The recombinant fusion protein of any one of claims 1-15, wherein the mAb comprises a heavy chain represented by the amino acid sequence of SEQ ID NO: 2.

17. The recombinant fusion protein of any one of claims 1-16, wherein the mAb comprises a light chain represented by the amino acid sequence of SEQ ID NO: 3.

18. The recombinant fusion protein of claim 16, wherein the mature mAb comprises a substitution mutation in at least one of amino acids 234, 239 and 434 of SEQ ID NO: 2.

19. The recombinant fusion protein of claim 18, wherein the at least one substitution mutation comprises a L234F mutation, a S239A mutation, a N434A mutation, or a combination thereof.

20. The recombinant fusion protein of any one of claims 1-19, wherein the recombinant fusion protein comprises the amino acid sequences of SEQ ID NO: 3 and SEQ ID NO: 14.

21. The recombinant fusion protein of any one of claims 1-20, wherein the recombinant fusion protein attenuates proliferation of tumor or cancer cells relative to recombinant NRG-1.

22. The recombinant fusion protein of any one of claims 1-21, wherein the recombinant fusion protein promotes cardiomyocyte proliferation, differentiation, and survival.

23. The recombinant fusion protein of any one of claims 1-22, wherein the recombinant fusion protein promotes proliferation, differentiation and survival of cardiac tissue.

24. The recombinant fusion protein of any one of claims 1-23, wherein the recombinant fusion protein promotes proliferation, differentiation and survival of central nervous system (CNS) cells.

25. The recombinant fusion protein of any one of claims 1-24, wherein the recombinant fusion protein has a reduced capacity to induce antibody-dependent cell cytotoxicity (ADCC).

26. The recombinant fusion protein of any one of claims 1-25, wherein the recombinant fusion protein promotes HER2/4 signaling over HER2/3 signaling relative to the signal induction potential of recombinant NRG-1.

27. A recombinant nucleic acid molecule encoding the recombinant fusion protein of any one of claims 1-26.

28. A recombinant vector comprising the nucleic acid molecule of claim 27.

29. A recombinant cell comprising the recombinant vector of claim 28.

30. A pharmaceutical composition comprising the recombinant fusion protein of anyone of claims 1-26.

31. A method of treating a cardiovascular disease or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of the recombinant fusion protein of any one of claims 1-26 or the pharmaceutical composition of claim 30.

32. The method of claim 31, wherein the treatment alleviates a sign or a symptom of the cardiovascular disease or condition in the subject.

33. A method of preventing, inhibiting, suppressing or delaying the onset of a cardiovascular disease or condition in a subject, the method comprising administering an effective amount of the recombinant fusion protein of any one of claims 1-26 or the pharmaceutical composition of claim 30.

34. A method of treating a CNS-related disease or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of the recombinant fusion protein of any one of claims 1-26 or the pharmaceutical composition of claim 30.

35. The method of claim 34, wherein the treatment alleviates a sign or a symptom of the CNS-related disease or condition in the subject.

36. A method of preventing, inhibiting, suppressing or delaying the onset of a CNS-related disease or condition in a subject, the method comprising administering an effective amount of the recombinant fusion protein of any one of claims 1-26 or the pharmaceutical composition of claim 30.

37. The method of any one of claims 31-33, wherein the cardiovascular disease or condition is Chronic heart failure / Congestive heart failure (CHF), Acute heart failure / Myocardial infarction (MI), Left ventricular systolic dysfunction, Reperfusion injury associated with MI, Chemotherapy-induced cardiotoxicity (adult or pediatric),

Radiation-induced cardiotoxicity, Adjunct to surgical intervention in pediatric congenital heart disease.

38. The method of claim 37, wherein the chemotherapy-induced cardiotoxicity results from a subject receiving anthracyclines, alkylating agents, antimicrotubule agents, and antimetabolites agents used as chemotherapy.

39. The method of any one of claims 31-33, wherein the cardiovascular condition is cardiotoxicity as a result of a subject receiving a cancer therapy.

40. The method of claim 39, wherein the cancer therapy is a HER-2 targeted therapy.

41. The method of claim 40, wherein the HER-2 targeted therapy comprises use of trastuzumab, ado-trastuzumab, emtansine, lapatinib, neratinib, and pertuzumab, any anti-HER2 antibody, any anti-HER2 agent or a combination thereof.

42. The method of any one of claims 34-36, wherein the CNS-related disease or condition is Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, Alzheimer's Disease, Bell's Palsy, epilepsy and seizures, Guillain-Barre Syndrome, stroke, traumatic brain injury, multiple sclerosis or a combination.

43. Use of the recombinant fusion protein of any one of claims 1-26 or the pharmaceutical composition of claim 30, for treating a cardiovascular disease or condition in a subject in need thereof, the use comprising administering a therapeutically effective amount of the recombinant fusion protein of or the pharmaceutical composition to the subject.

44. Use of the recombinant fusion protein of any one of claims 1-26 or the pharmaceutical composition of claim 30, for preventing, suppressing, inhibiting or delaying the onset of a cardiovascular disease or condition in a subject, the use comprising administering an effective amount of the recombinant fusion protein of or the pharmaceutical composition to the subject.

45. Use of the recombinant fusion protein of any one of claims 1-26 or the pharmaceutical composition of claim 30, for treating a CNS-related disease or condition in a subject in need thereof, the use comprising administering a therapeutically effective amount of the recombinant fusion protein of or the pharmaceutical composition to the subject.

46. Use of the recombinant fusion protein of any one of claims 1-26 or the pharmaceutical composition of claim 30, for preventing, suppressing, inhibiting or delaying the onset of a CNS-related disease or condition in a subject, the use comprising administering an effective amount of the recombinant fusion protein of or the pharmaceutical composition to the subject.

47. The use of claim 43 or 44, wherein the cardiovascular disease or condition is Chronic heart failure / Congestive heart failure (CHF), Acute heart failure / Myocardial infarction (MI), Left ventricular systolic dysfunction, Reperfusion injury associated with MI, Chemotherapy-induced cardiotoxicity (adult or pediatric), Radiation-induced cardiotoxicity, Adjunct to surgical intervention in pediatric congenital heart disease.

48. The use of claim 47, wherein the chemotherapy-induced cardiotoxicity results from a subject receiving anthracyclines, alkylating agents, antimicrotubule agents, and antimetabolites agents used aschemotherapy.

49. The use of claim 43 or 44, wherein the cardiovascular condition is cardiotoxicity as a result of a subject receiving a cancer therapy.

50. The use of claim 49, wherein the cancer therapy is a HER-2 targeted therapy.

51. The use of claim 50, wherein the HER-2 targeted therapy comprises use of trastuzumab, ado-trastuzumab, emtansine, lapatinib, neratinib, and pertuzumab, any anti-HER2 antibody, any anti-HER2 agent or a combination thereof.

52. The use of claim 45 or 46, wherein the CNS-related disease or condition is Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease, Alzheimer's Disease, Bell's

Palsy, epilepsy and seizures, Guillain-Barre Syndrome, stroke, multiple sclerosis or a combination.

53. A kit, comprising an effective amount of the recombinant protein of any one of claims 1-26 or the pharmaceutical composition of claim 30.

CLAIMS

1. A recombinant fusion protein comprising a fragment of the cardioprotective protein neuregulin-1 (NRG-1) fused to a monospecific ErbB3 (HER3) monoclonal antibody (mAb).

2. The recombinant fusion protein of claim 1, wherein the NRG-1 fragment comprises an active fragment.

3. The recombinant fusion protein of claim 2, wherein the active protein fragment of NRG-1 comprises the active domain of NRG-1.

4. The recombinant fusion protein of any one of claims 1-3, wherein the NRG-1 fragment comprises the ERBB3/4 binding domain.

5. The recombinant fusion protein of any one of claims 1-4, wherein the NRG-1 fragment binds to and induces signaling through ErbB4 (HER4).

6. The recombinant fusion protein of claim 5, wherein the mAb inhibits NRG-1 signaling through ErbB3 (HER3).

7. The recombinant fusion protein of any one of claims 1-6, wherein said NRG-1 fragment comprises the NRG-1 ß2a isoform.

8. The recombinant fusion protein of any one claims 1-7, wherein the NRG-1 fragment is fused via its N-terminal amino acid to the C-terminus of the antibody heavy chain using a linker.

9. The recombinant fusion protein of claim 8, wherein said linker comprises at least one copy of a Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser linker set forth in SEQ ID NO: 5.

10. The recombinant fusion protein of claim 8, wherein the C-terminus of the antibody heavy chain comprises the Fc domain of the antibody.

11. The recombinant fusion protein of any one of claims 1-10, wherein the monoclonal antibody is glycosylated.

12. The recombinant fusion protein of claim 11, wherein the glycosylation is N-glycosylation.

13. The recombinant fusion protein of claim 11, wherein the glycosylation is O-glycosylation.

14. The recombinant fusion protein of any one of claims 1-13, wherein the NRG-1 fragment comprises the amino acid sequence of SEQ ID NO: 4.

15. The recombinant fusion protein of any one of claims 1-14, wherein the mAb comprises a heavy chain represented by the amino acid sequence of SEQ ID NO: 2.

16. The recombinant fusion protein of any one of claims 1-15, wherein the mAb comprises a light chain represented by the amino acid sequence of SEQ ID NO: 3.

17. The recombinant fusion protein of claim 15, wherein the mature mAb comprises a substitution mutation in at least one of amino acids 234, 239 and 434 of SEQ ID NO: 2.

18. The recombinant fusion protein of claim 17, wherein the at least one substitution mutation comprises a L234F mutation, a S239A mutation, a N434A mutation, or a combination thereof.

19. The recombinant fusion protein of any one of claims 1-18, wherein the recombinant fusion protein comprises the amino acid sequences of SEQ ID NO: 3 and SEQ ID NO: 14.

20. The recombinant fusion protein of any one of claims 1-19, wherein the recombinant fusion protein attenuates proliferation of tumor or cancer cells relative to recombinant NRG-1.

21. The recombinant fusion protein of any one of claims 1-20, wherein the recombinant fusion protein promotes cardiomyocyte proliferation, differentiation, and survival.

22. The recombinant fusion protein of any one of claims 1-21, wherein the recombinant fusion protein promotes proliferation, differentiation and survival of cardiac tissue.

23. The recombinant fusion protein of any one of claims 1-22, wherein the recombinant fusion protein promotes proliferation, differentiation and survival of central nervous system (CNS) cells.

24. The recombinant fusion protein of any one of claims 1-23, wherein the recombinant fusion protein has a reduced capacity to induce antibody-dependent cell cytotoxicity (ADCC).

25. The recombinant fusion protein of any one of claims 1-24, wherein the recombinant fusion protein promotes HER2/4 signaling over HER2/3 signaling relative to the signal induction potential of recombinant NRG-1.

26. A recombinant nucleic acid molecule encoding the recombinant fusion protein of any one of claims 1-25.

27. A recombinant vector comprising the nucleic acid molecule of claim 26.

28. A recombinant cell comprising the recombinant vector of claim 27.

29. A pharmaceutical composition comprising the recombinant fusion protein of anyone of claims 1-25.

30. Use of the recombinant fusion protein of any one of claims 1-25 or the pharmaceutical composition of claim 29 in the manufacture of a medicament for treating a cardiovascular disease or condition in a subject in need thereof, the treatment comprising administering a therapeutically effective amount of the recombinant fusion protein of or the pharmaceutical composition to the subject.

31. The use of claim 30, wherein the treatment alleviates a sign or a symptom of the cardiovascular disease or condition in the subject.

32. Use of the recombinant fusion protein of any one of claims 1-25 or the pharmaceutical composition of claim 29 in the manufacture of a medicament for suppressing, inhibiting or delaying the onset of a cardiovascular disease or condition in a subject, the treatment comprising administering an effective amount of the recombinant fusion protein of or the pharmaceutical composition to the subject.

33. The use of any one of claims 30-32, wherein the cardiovascular disease or condition is Chronic heart failure / Congestive heart failure (CHF), Acute heart failure / Myocardial infarction (MI), Left ventricular systolic dysfunction, Reperfusion injury associated with MI, Chemotherapy-induced cardiotoxicity (adult or pediatric), Radiation-induced cardiotoxicity, Adjunct to surgical intervention in pediatric congenital heart disease.

34. The use of claim 33, wherein the chemotherapy-induced cardiotoxicity results from a subject receiving anthracyclines, alkylating agents, antimicrotubule agents, or antimetabolite agents used as chemotherapy.

35. The use of claim any one of claims 30-32, wherein the cardiovascular condition is cardiotoxicity as a result of a subject receiving a cancer therapy.

36. The use of claim 35, wherein the cancer therapy is a HER-2 targeted therapy.

37. The use of claim 36, wherein the HER-2 targeted therapy comprises use of trastuzumab, ado-trastuzumab, emtansine, lapatinib, neratinib, and pertuzumab, any anti-HER2 antibody, any anti-HER2 agent or a combination thereof.

38. A kit, comprising an effective amount of the recombinant protein of any one of claims 1-25 or the pharmaceutical composition of claim 29.