alteration of hemodynamics. There is also a need for better-tolerated therapies, including in particular with respect to treatment in patients with comorbidities such as hypotension, hypokalemia and renal dysfunction. There is also a need for therapies which improve quality of life (QOL) in patients with advanced disease. The present invention seeks to meet one or more of these critical unmet needs.

Summary

In one aspect of the present disclosure, there is provided an NRG4 compound comprising modification of the D residue at position 1 to a G residue and up to five additional modifications as compared to the amino acid sequence of human NRG4 (SEQ ID NO:1).

In another aspect of the present disclosure, there is provided a compound comprising the formula:

X_0GHEEPCGX_8SHKSFCLNGGLCYX_{22}IPTX_{26}PSPFCRCVX_{35}NYTGARCEX_{44}VFL

wherein:

X_0 is selected from the group consisting of T, PT, MPT, S, GS, GGS, GGGS, and $(GGGGX_\lambda)_n$ wherein X_λ is Q, A, E or S and n=1-5 (SEQ ID NO:5), or is absent;

X_8 is E or P;

X_{22} is Q or V;

X_{26} is F or I;

X_{35} is E or A; and

X_{44} is H, K or E

(SEQ ID NO:2).

In a further aspect of the present disclosure, there is provided a compound consisting of the amino acid sequence of SEQ ID NO:18.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein and a pharmaceutically acceptable carrier, diluent, or excipient.

In a further aspect of the present disclosure, there is provided a pump device comprising the compound disclosed herein.

In another aspect of the present disclosure, there is provided an NRG4 compound disclosed herein for use in treating or preventing HFrEF, wherein the NRG4 compound is to be administered for 48-96 hours.

In a further aspect of the present disclosure, there is provided a use of an NRG4 compound disclosed herein in the manufacture of a medicament for treating or preventing HFrEF, wherein the NRG4 compound is to be administered for 48-96 hours.

Description

The present invention provides NRG4 compounds with activity associated with selective binding to HER4. The NRG4 compounds of the present invention have little to no binding to HER3, resulting in reduced risk of toxicity and/or tolerability issues associated with HER3.

The present invention also provides methods of using NRG4 compounds to treat or prevent CVD and related conditions, including in particular HF. Preferred NRG4 compounds and methods of the present invention reduce the risk of CV-related death or HF-related hospitalization, reduce the risk of myocardial infarction (MI) or stroke, reduce the probability of a need for left ventricular assist device (LVAD) or cardiac transplant, improve cardiac function and structure, and/or improve the symptoms and physical limitations associated with HF, leading to improvements in QoL. Preferred NRG4 compounds and methods can be used in combination with standard of care (SoC) without the need for titration or monitoring, and do not increase hypotension, worsen renal function, result in electrolyte imbalance, contribute to liver dysfunction, increase incidence of tumors, and/or lead to persistent hypospermia.

The present invention also provides NRG4 compounds comprising modification of the D residue at position 1 to a G residue and up to five additional modifications as compared to the amino acid sequence of human NRG4 (SEQ ID NO:1).

The present invention also provides NRG4 compounds comprising the formula: X_0GHEEPCGX_8SHKSFCLNGGLCYX_{22}IPTX_{26}PSPFCRCVX_{35}NYTGARCEX_{44}VFL; wherein: X_0 is selected from the group consisting of T, PT, MPT, S, GS, GGS, GGGS, and $(GGGGX_\lambda)_n$ wherein X_λ is Q, A, E or S and n=1-5 (SEQ ID NO:5), or is absent; X_8 is E or P; X_{22} is Q or V; X_{26} is F or I; X_{35} is E or A; and X_{44} is H, K or E (SEQ ID NO:2).

In another aspect, the present invention provides a method of treating or preventing HFrEF in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of an NRG4 compound for 24-96 hours.

WE CLAIM:

1. An NRG4 compound comprising modification of the D residue at position 1 to a G residue and up to five additional modifications as compared to the amino acid sequence of human NRG4 (SEQ ID NO:1).

2. A compound comprising the formula:

X_0GHEEPCGX_8SHKSFCLNGGLCYX_{22}IPTX_{26}PSPFCRCVX_{35}NYTGARCEX_{44}VFL

wherein:

X_0 is selected from the group consisting of T, PT, MPT, S, GS, GGS, GGGS, and $(GGGGX_\lambda)_n$ wherein X_λ is Q, A, E or S and n=1-5 (SEQ ID NO:5), or is absent;

X_8 is E or P;

X_{22} is Q or V;

X_{26} is F or I;

X_{35} is E or A; and

X_{44} is H, K or E

(SEQ ID NO:2).

3. The compound of claim 2 wherein X_8 is P; X_{22} is V; X_{26} is I; X_{35} is E; and X_{44} is E.

4. The compound of claim 2 wherein X_8 is E; X_{22} is V; X_{26} is I; X_{35} is E; and X_{44} is E.

5. The compound of claim 2 wherein X_8 is P; X_{22} is Q; X_{26} is I; X_{35} is E; and X_{44} is E.

6. The compound of claim 2 wherein X_8 is P; X_{22} is V; X_{26} is F; X_{35} is E; and X_{44} is E.

7. The compound of claim 2 wherein X_8 is P; X_{22} is V; X_{26} is I; X_{35} is A; and X_{44} is H or E.

8. The compound of claim 2 wherein X_8 is P; X_{22} is V; X_{26} is F; X_{35} is E; and X_{44} is K.

9. The compound of claim 2 wherein X_8 is P; X_{22} is V; X_{26} is F; X_{35} is E; and X_{44} is H.

10. The compound of claim 2 wherein X_8 is E; X_{22} is V; X_{26} is F; X_{35} is E; and X_{44} is E.

11. The compound of claim 2, wherein X_8 is P; X_{22} is Q; X_{26} is I; X_{35} is E; and X_{44} is K.

12. The compound of any of claims 2-11 further comprising an IgG Fc region.

13. The compound of claim 12, wherein X_0 is SEQ ID NO:5 wherein X_λ is S and n=3, and wherein the IgG Fc region comprises a dimer of SEQ ID NO:6 and SEQ ID NO:7, wherein the N terminal amino acid of X_0 is fused to the C-terminal amino acid of SEQ ID NO:7.

14. The compound of claim 12, wherein X_0 is SEQ ID NO:5 wherein X_λ is S and n=3, and wherein the IgG Fc region comprises a dimer of SEQ ID NO:8 and SEQ ID NO:9, wherein the N terminal amino acid of X_0 is fused to the C-terminal amino acid of SEQ ID NO:9.

15. The compound of any of claims 2-11 wherein X_0 is SEQ ID NO:5 wherein X_λ is S and n=1.

16. The compound of any of claims 2-11 wherein the compound comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:4, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19.

17. A compound consisting of the amino acid sequence of SEQ ID NO:18.

18. The compound of any of claims 1-17, wherein the compound has HER4 binding-related activity which is greater than that of native human NRG4 and at least 70% that of the maximal activity of native human NRG1.

19. The compound of any of claims 1-18, wherein the compound has no HER3 binding-related activity.

20. A pharmaceutical composition comprising the compound of any of claims 1-19 and a pharmaceutically acceptable carrier, diluent, or excipient.

21. A pump device comprising the compound of any of claims 1-19.

22. An NRG4 compound according to any one of claims 1 to 19 for use in treating or preventing HFrEF, wherein the NRG4 compound is to be administered for 48-96 hours.

23. Use of an NRG4 compound according to any one of claims 1 to 19 in the manufacture of a medicament for treating or preventing HFrEF, wherein the NRG4 compound is to be administered for 48-96 hours.