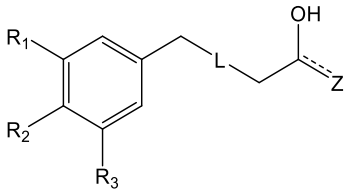
CLAIMS

1. A Leucine Rich Repeat Containing 4 ("LRRC4") family mimic molecule that is capable of inhibiting, reducing, and/or dissociating an interaction between a Family with Sequence Similarity 19, Member A5 ("FAM19A5") protein and a member of a LRRC4 protein family.

2. The LRRC4 family mimic molecule of claim 1, which is not an antibody or an antigen-binding portion thereof.

3. The LRRC4 family mimic molecule of claim 1 or 2, which comprises a polypeptide or a small molecule.

4. The LRRC4 family mimic molecule of claim 3, wherein the small molecule is of formula (I):



(Formula I),

or a pharmaceutically acceptable salt thereof, wherein:

(i) R_1, R_2 and R_3 are independently selected from hydrogen, fluoro, chloro, bromo, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1-fluoroethyl, 2,2-difluoroethyl, 1,2-difluoroethyl, 1,1- difluoroethyl, 2,2,2-trifluoroethyl, methoxy, ethoxy, n-propyloxy, iso-propyloxy, n-butoxy, trifluoromethoxy, difluoromethoxy, fluoromethoxy, acetyl, propionyl, n-butanoyl, iso-butanoyl, n-pentanoyl, nitro, amino, N-methylamino, N-ethylamino, N-n-propylamino, N,N-dimethylamino, N-acetylamino, N-propionylamino, N-(trifluoroacetyl)amino, formyl, hydroxy, methylthio, ethylthio, n-propylthio, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, phenyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, or combinations thereof;

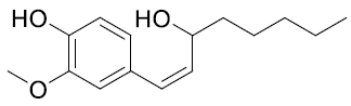
(ii) ---- is a single or double bond;

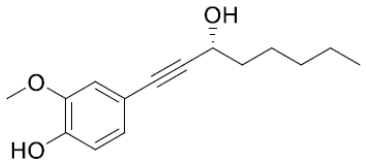
(iii) Z is selected from a straight chain or branched (C_1–C_8)alkyl, a straight chain or branched (C_2-C_8)alkenyl, a straight chain or branched (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_7-C_{14})bicycloalkyl, (C_7-C_{14}) bicycloalkenyl, (7-14 membered) heterobicycloalkyl, (C_6-C_{10}) aryl, (5-10-membered) heteroaryl, and –CH-C(O)-

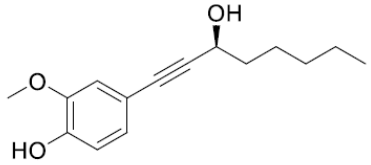
CH=CH-Q, wherein Q is (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (3-8 membered)heterocycloalkyl, (C_6-C_{10})aryl, and (5-6-membered)heteroaryl; wherein each cycloalkyl, cycloalkenyl, heterocyclylalkyl, aryl, and heteroaryl are optionally substituted with one, two, three, four, or five substituents independently selected from (C_1-C_6)alkoxy, (C_1-C_6)alkyl, halo, (C_1-C_6)haloalkoxy, nitro, amino, N-methylamino, N-ethylamino, N-N-propylamino, N,N-dimethylamino, formyl, hydroxy, or combinations thereof; and

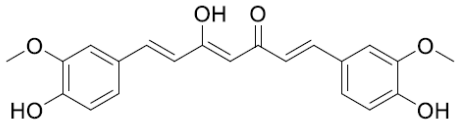
(iv) L is a single, double, or triple bond, and

wherein the LRRC4 family mimic molecule is not a small molecule selected from:

KB 2356  ;

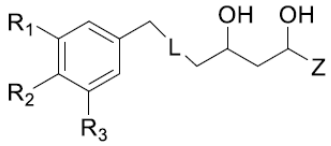
KB 2357  ;

KB 2358  ;

KB 2399 (Curcumin)  ;

or a pharmaceutically acceptable salt thereof.

5. The LRRC4 family mimic molecule of claim 3, wherein the small molecule is of formula (II):



(formula II),

or a pharmaceutically acceptable salt thereof, wherein:

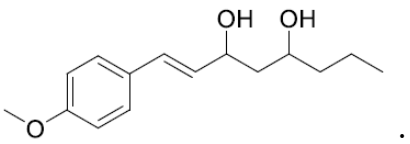
(i) R_1, R_2 and R_3 are independently selected from hydrogen, fluoro, chloro, bromo, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1-fluoroethyl, 2,2-difluoroethyl, 1,2-difluoroethyl, 1,1- difluoroethyl, 2,2,2-trifluoroethyl, methoxy, ethoxy, n-propyloxy, iso-propyloxy, n-butoxy, trifluoromethoxy, difluoromethoxy, fluoromethoxy, acetyl, propionyl, n-butanoyl, iso-butanoyl, n-pentanoyl, nitro, amino, N-methylamino, N-ethylamino, N-n-propylamino, N,N-dimethylamino, N-acetylamino, N-propionylamino, N-(trifluoroacetyl)amino, formyl, hydroxy,

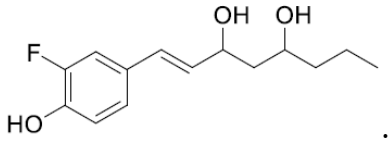
methylthio, ethylthio, n-propylthio, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, phenyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, or combinations thereof;

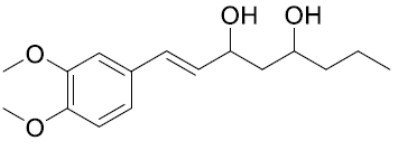
(ii) Z is selected from a straight chain or branched (C_1–C_8)alkyl, a straight chain or branched (C_2-C_8)alkenyl, a straight chain or branched (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_7-C_{14})bicycloalkyl, (C_7-C_{14}) bicycloalkenyl, (7-14 membered) heterobicycloalkyl, (C_6-C_{10}) aryl, (5-10-membered) heteroaryl, and -CH=CH-Q, wherein Q is (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (3-8 membered)heterocycloalkyl, (C_6-C_{10})aryl, and (5-6-membered)heteroaryl; wherein each cycloalkyl, cycloalkenyl, heterocyclylalkyl, aryl, and heteroaryl are optionally substituted with one, two, three, four, or five substituents independently selected from (C_1-C_6)alkoxy, (C_1-C_6)alkyl, halo, (C_1-C_6)haloalkoxy, nitro, amino, N-methylamino, N-ethylamino, N-N-propylamino, N,N-dimethylamino, formyl, hydroxy, or combinations thereof; and

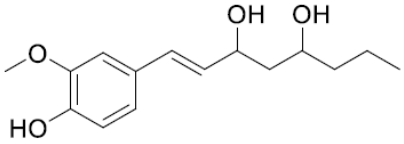
(iii) L is a single, double, or triple bond.

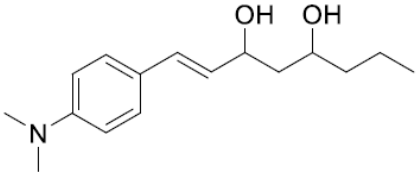
6. The LRRC4 family mimic molecule of claim 5, wherein the small molecule is selected from:

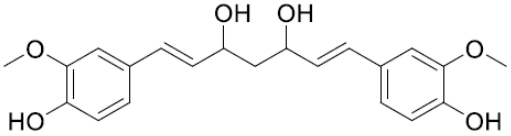


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;


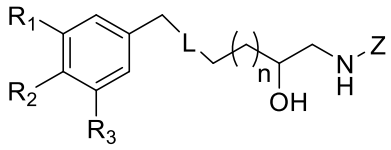
;


;


;

or a pharmaceutically acceptable salt thereof.

7. The LRRC4 family mimic molecule of claim 3, wherein the small molecule is of formula (III):



(formula III),

or a pharmaceutically acceptable salt thereof, wherein:

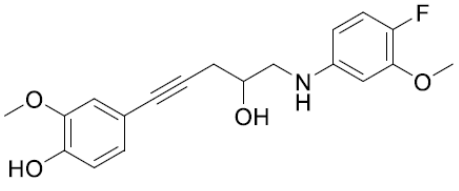
(i) R_1, R_2 and R_3 are independently selected from hydrogen, fluoro, chloro, bromo, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-pentyl, iso-pentyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2-fluoroethyl, 1-fluoroethyl, 2,2-difluoroethyl, 1,2-difluoroethyl, 1,1- difluoroethyl, 2,2,2-trifluoroethyl, methoxy, ethoxy, n-propyloxy, iso-propyloxy, n-butoxy, trifluoromethoxy, difluoromethoxy, fluoromethoxy, acetyl, propionyl, n-butanoyl, iso-butanoyl, n-pentanoyl, nitro, amino, N-methylamino, N-ethylamino, N-n-propylamino, N,N-dimethylamino, N-acetylamino, N-propionylamino, N-(trifluoroacetyl)amino, formyl, hydroxy, methylthio, ethylthio, n-propylthio, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, phenyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, or combinations thereof;

(ii) Z is selected from a straight chain or branched (C_1–C_8)alkyl, a straight chain or branched (C_2-C_8)alkenyl, a straight chain or branched (C_2-C_8)alkynyl, -Y-(C_3-C_8)cycloalkyl, -Y-(C_5-C_8)cycloalkenyl, -Y-(3-8 membered) heterocycloalkyl, -Y-(C_7-C_{14})bicycloalkyl, -Y-(C_7-C_{14}) bicycloalkenyl, -Y-(7-14 membered) heterobicycloalkyl, -Y-(C_6-C_{10})aryl, and –Y-(5-10-membered) heteroaryl, wherein Y is a bond or a C_1-C_3 straight or branched alkylene, and wherein the cycloalkyl, the cycloalkenyl, the heterocyclylalkyl, the aryl, and the heteroaryl are optionally substituted with one, two, three, four, or five substituents independently selected from C_1-C_6alkoxy, C_1-C_6alkyl, halo, C_1-C_6haloalkoxy, nitro, amino, N-methylamino, N-ethylamino, N-N-propylamino, N,N-dimethylamino, formyl, hydroxy, or combinations thereof;

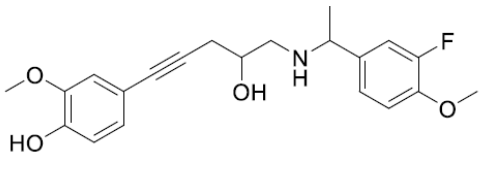
(iii) L is a single, double, or triple bond, and

(iv) n is 0 or 1.

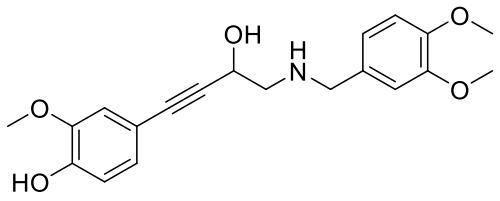
8. The LRRC4 family mimic molecule of claim 7, wherein the small molecule is selected from:



;



;



;

or a pharmaceutically acceptable salt thereof.

9. The LRRC4 family mimic molecule of claim 3, wherein the polypeptidecomprises, consists of, or consists essentially of a domain of a LRRC4 protein family member, wherein the domain is capable of binding to a FAM19A5 protein ("FAM19A5 binding domain"), and wherein the polypeptide is shorter in length than the corresponding full-length LRRC4 protein family member, which comprises the amino acid sequence set forth in SEQ ID NO: 4; SEQ ID NO: 5; or SEQ ID NO: 6.

10. The LRRC4 family mimic molecule of claim 9, wherein the polypeptide comprises an amino acid sequence having the following formula (from N-terminus to C-terminus):

A-(T/S)-B (Formula IV), wherein:

(a) (i) A comprises X1-(T/S)-(Y/F)-F-X5; wherein:

X1 is tyrosine (Y), phenylalanine (F), valine (V), leucine (L), or isoleucine (I);

(T/S) is threonine (T) or serine (S);

(Y/F) is tyrosine (Y) or Phenylalanine (F); and

X5 is any amino acid; and

(ii) B comprises (V/I)-T-V-(E/V); wherein:

(V/I) is valine (V) or isoleucine (I); and

(E/V) is glutamic acid (E) or valine (V); or

(b) (i) A comprises (Y/W/M)-(T/Y)-(Y/W)-(F/Y/W)-(T/Y); wherein:

(Y/W/M) is tyrosine (Y), tryptophan (W), or methionine (M);

(T/Y) is threonine (T) or tyrosine (Y);

(Y/W) is tyrosine (Y) or tryptophan (W); and

(F/Y/W) is phenylalanine (F), tyrosine (Y), or tryptophan (W); and

(ii) B comprises X7-(T/S/Y)-X9-X10; wherein:

X7 is valine (V), tyrosine (Y), phenylalanine (F), leucine (L), tryptophan (W), or methionine (M);

(T/S/Y) is threonine (T), serine (S), or tyrosine (Y);

X9 is valine (V), isoleucine (I), tyrosine (Y), phenylalanine (F), leucine (L), tryptophan (W), or methionine (M); and

X10 is glutamic acid (E), aspartic acid (D), isoleucine (I), tyrosine (Y), phenylalanine (F), methionine (M), or tryptophan (W).

11. The LRRC4 family mimic molecule of claim 9, wherein the polypeptide comprises an amino acid sequence having the following formula: (from N-terminus to C-terminus):

X1-X2-X3-X4-X5-X6-X7-X8-X9-X10 (Formula VI) , wherein:

X1 is Y, F, V, L, I, W, or M;

X2 is T, S, or Y;

X3 is Y, F, or W;

X4 is F, Y, or W;

X5 is any amino acids;

X6 is T, S, or Y;

X7 is V, I, Y, F, L, W, or M;

X8 is T, S, or Y;

X9 is V, I, Y, F, L, W, or M; and/or

X10 is E, D, V, I, Y, F, M, or W

.

12. The LRRC4 family mimic molecule of claim 11, wherein:

(a) X1 is Y, F, V, L, or I;

(b) X2 is T or S; (c) X3 is Y or F;

(d) X4 is F;

(e) X5 is T or S;

(f) X6 is T;

(g) X7 is V or I

(h) X8 is T;

(i) X9 is V;

(j) X10 is E or V; or

(k) any combination of (a) to (j).

13. The LRRC4 family mimic molecule of any one of claims 9 to 12, wherein the FAM19A5 binding domain comprises, consists of, or consists essentially of the amino acid sequence set forth in SEQ ID NO: 29, SEQ ID NO: 30, or SEQ ID NO: 31.

14. The LRRC4 family mimic molecule of any one of claims 9 to 13, wherein the polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, or SEQ ID NO: 149.

15. The LRRC4 family mimic molecule of any one of claims 1 to 14, wherein the member of the LRRC4 protein family comprises a LRRC4 protein, LRRC4B protein, LRRC4C protein, or combinations thereof.

16. A nucleic acid encoding the LRRC4 family mimic molecule of any one of claims 9 to 15.

17. A cell comprising the nucleic acid of claim 16.

18. A protein conjugate comprising the LRRC4 family mimic molecule of any one of claims 9 to 15, linked to an agent.

19. A composition comprising the LRRC4 family mimic molecule of any one of claims 1 to 15, the nucleic acid of claim 16, the cell of claim 17, or the protein conjugate of claim 18, wherein optionally the composition further comprises a pharmaceutically acceptable carrier.

20. A kit comprising the LRRC4 family mimic molecule of any one of claims 1 to 15the nucleic acid of claim 16, the cell of claim 17, the protein conjugate of claim 18, or the composition of claim 19, and instructions for use.

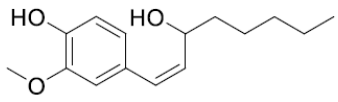
21. A method of producing a molecule that is capable of inhibiting, reducing, and/or dissociating an interaction between a FAM19A5 protein and a member of a LRRC4 protein family,

comprising synthesizing the molecule of any one of claims 1 to 8 or culturing the cell of claim 17 under suitable conditions such that the molecule is produced.

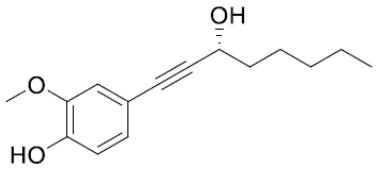
22. The LRRC4 family mimic molecule of any one of claims 1 to 15, the nucleic acid for claim 16, the cell of claim 17, the protein conjugate of claim 18, or the composition of claim 19 for use in a therapy.

23. The LRRC4 family mimic molecule of any one of claims 1 to 15, the nucleic acid of claim 16, the cell of claim 17, the protein conjugate of claim 18, or the composition of claim 19 for use in treating a disease or condition in a subject in need thereof.

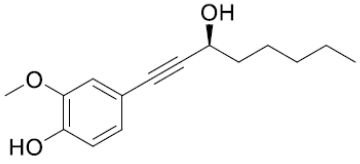
24. A Leucine Rich Repeat Containing 4 ("LRRC4") family mimic molecule for use in treating a disease or condition in a subject in need thereof, wherein the LRRC4 family mimic molecule is a small molecule selected from:

KB 2356 

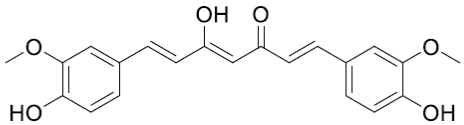
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KB 2357 

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KB 2358 

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KB 2399 (Curcumin) 

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or a pharmaceutically acceptable salt thereof.

25. The LRRC4 family mimic molecule for use of claim 23 or 24, wherein the disease or condition comprises a neurological disease.