WHAT IS CLAIMED IS:

1. Use of an antagonist against a family with sequence similarity 19, member A5 (FAM19A5) protein (FAM19A5 antagonist) in the manufacture of a medicament for treating or preventing a hearing disorder in a subject in need thereof.

2. The use according to claim 1, wherein the hearing disorder comprises a sensorineural hearing loss.

3. The use according to claim 2, wherein:

(a) the sensorineural hearing loss is with tinnitus;

(b) the sensorineural hearing loss is without tinnitus; or

(c) the sensorineural hearing loss comprises an ototoxic drug-induced hearing loss, noise-induced hearing loss, age-related hearing loss, sudden hearing loss, or combinations thereof.

4. Use of an antagonist against a family with sequence similarity 19, member A5 (FAM19A5) protein (FAM19A5 antagonist) in the manufacture of a medicament for (a) reducing or preventing an impairment of ribbon synapses, (b) inducing a formation of ribbon synapses, or (c) improving a function of ribbon synapses within an inner ear of a subject in need thereof.

5. The use according to claim 4, wherein the impairment of ribbon synapses comprises (a) a decrease in the number of ribbon synapses as compared to that of a corresponding subject who does not have an impairment of ribbon synapses within an inner ear; (b) an abnormal function of the ribbon synapses; or (c) both (a) and (b).

6. The use according to claim 4, wherein the function comprises the ability to release one or more neurotransmitters in response to a signal from an inner hair cell.

7. Use of an antagonist against a family with sequence similarity 19, member A5 (FAM19A5) protein (FAM19A5 antagonist) in the manufacture of a medicament for reducing an expression or activity of FAM19A5 protein within a spiral ganglion neuron of a subject in need thereof.

8. The use according to claim 1, wherein the FAM19A5 antagonist comprises: (i) an antisense-oligonucleotide, siRNA, shRNA, miRNA, dsRNA, aptamer, PNA (peptide nucleic acid), or a vector including the same; (ii) an antibody or an antigen-binding fragment thereof that specifically binds to the FAM19A5 protein (anti-FAM19A5 antibody); (iii) a polynucleotide encoding the anti-FAM19A5 antibody; (iv) a leucine rich repeat containing 4 (LRRC4) family mimic molecule; (v) a LRRC4 family peptide; or (vi) any combination of (i) to (v).

9. The use according to claim 8, wherein the anti-FAM19A5 antibody comprises a heavy chain CDR1, CDR2, and CDR3, and a light chain CDR1, CDR2, and CDR3, wherein

(i) the heavy chain CDR1 comprises a CDR1 selected from the group consisting of CDR1s in Table 6;

(ii) the heavy chain CDR2 comprises a CDR2 selected from the group consisting of CDR2s in Table 6;

(iii) the heavy chain CDR3 comprises a CDR3 selected from the group consisting of CDR3s in Table 6;

(iv) the light chain CDR1 comprises a CDR1 selected from the group consisting of CDR1s in Table 7;

(v) the light chain CDR2 comprises a CDR2 selected from the group consisting of CDR2s in Table 7; and/or

(vi) the light chain CDR3 comprises a CDR3 selected from the group consisting of CDR3s in Table 7.

10. The use according to claim 9, wherein: (i) the heavy chain CDR1 comprises the sequence set forth in SEQ ID NO: 220, (ii) the heavy chain CDR2 comprises the sequence set forth in SEQ ID NO: 221, (iii) the heavy chain CDR3 comprises the sequence set forth in SEQ ID NO: 16, (iv) the light chain CDR1 comprises the sequence set forth in SEQ ID NO: 225, (v) the light chain CDR2 comprises the sequence set forth in SEQ ID NO: 228, and (vi) the light chain CDR3 comprises the sequence set forth in SEQ ID NO: 227.

11. The use according to claim 8, wherein the anti-FAM19A5 antibody comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein:

(i) the VH comprises a VH selected from the group consisting of VHs in Table 8; and/or

(ii) the VL comprises a VL selected from the group consisting of VLs in Table 9.

12. The use according to claim 11, wherein the VH comprises the sequence set forth in SEQ ID NO: 235 and the VL comprises the sequence set forth in SEQ ID NO: 240.

13. The use according to claim 8, wherein:

(a) the LRRC4 family mimic molecule is not an antibody or an antigen-binding fragment thereof;

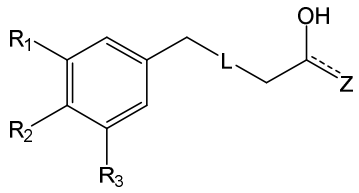
(b) the LRRC4 family mimic molecule comprises a polypeptide;

(c) the LRRC4 family mimic molecule comprises a small molecule; or

(d) any combination of (a) to (c).

14. The use according to claim 13, wherein the LRRC4 family mimic molecule is:

(1) a small molecule 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 and 2-hydroxyethyl;

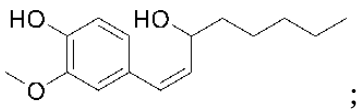
(ii) ---- is a single or double bond;

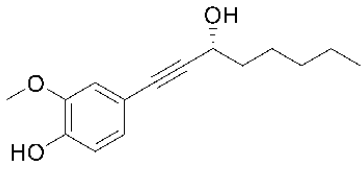
(iii) Z is selected from a straight chain or branched (C_1–C_8)alkyl, a straight chain or branched (C_2-C_8)alkenyl, a straight chain or branched (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_7-C_{14})bicycloalkyl, (C_7-C_{14}) bicycloalkenyl, (7-14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

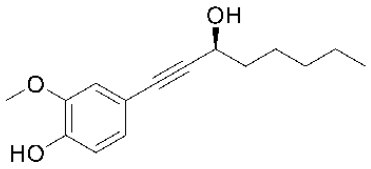
CH=CH-Q, wherein Q is (C_3-C_8)cycloalkyl, (C_5-C_8)cycloalkenyl, (3-8 membered)heterocycloalkyl, (C_6-C_{10})aryl, and (5-6-membered)heteroaryl; wherein each cycloalkyl, cycloalkenyl, heterocyclylalkyl, aryl, and heteroaryl are optionally substituted with one, two, three, four, or five substituents 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, and hydroxy, and

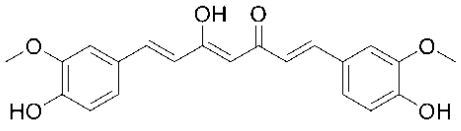
(iv) L is single, double or triple bond, and

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

KB 2356  ;

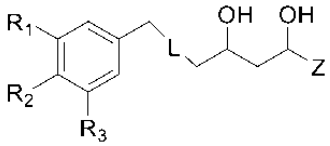
KB 2357  ;

KB 2358  ;

KB 2399 (Curcumin)  ;

or a pharmaceutically acceptable salt thereof;

(2) a small molecule of formula (ii):



(formula II),

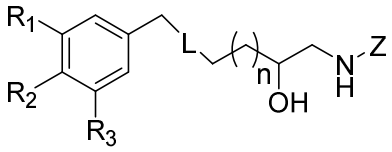
or a pharmaceutically acceptable salt thereof, wherein:

(i) R1, R2 and R3 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 and 2-hydroxyethyl,

(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, and hydroxy, and

(iii) L is single, double or triple bond; or

(3) a small molecule of formula (III):



(formula III),

or a pharmaceutically acceptable salt thereof, wherein:

(i) R1, R2 and R3 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 and 2-hydroxyethyl,

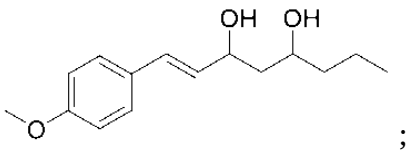
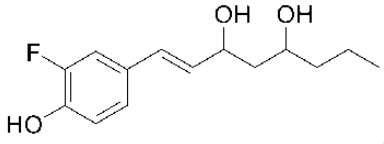
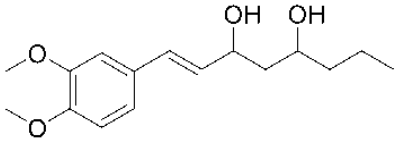
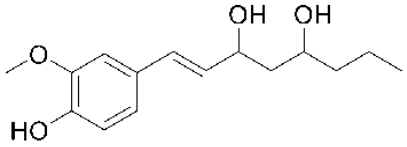
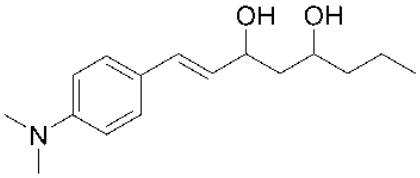
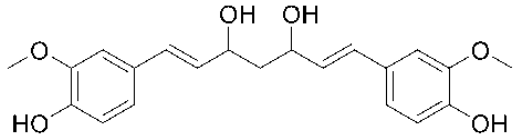
(ii) Z is selected from a straight chain or branched (C_1–C_8)alkyl, a straight chain or branched (C_2-C_8)alkenyl, a straight chain or branched (C_2-C_8)alkynyl, -Y-(C_3-C_8)cycloalkyl, -Y-(C_5-C_8)cycloalkenyl, -Y-(3-8 membered) heterocycloalkyl, -Y-(C_7-C_{14})bicycloalkyl, -Y-(C_7-C_{14}) bicycloalkenyl, -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, and hydroxy,

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

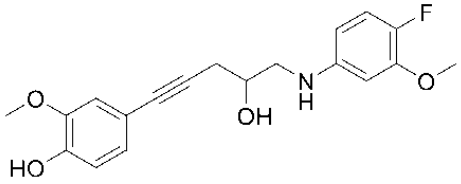
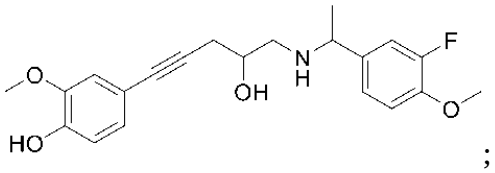
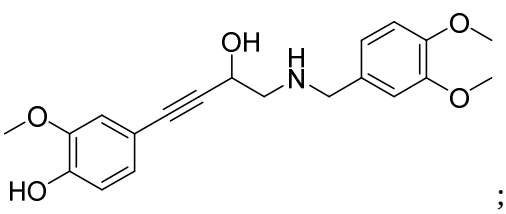
(iv) n is 0 or 1.

15. The use according to claim 14, wherein the LRRC4 family mimic molecule is selected from:


;

;

;

;

;

;

or a pharmaceutically acceptable salt thereof.

16. The use according to claim 14, wherein the LRRC4 family mimic molecule is selected from:


;

;

;

or a pharmaceutically acceptable salt thereof.

17. The use according to claim 13, wherein the LRRC4 family mimic molecule is a polypeptide comprising, consisting of, or consisting essentially of a domain of a LRRC4 protein family member, wherein the domain is capable of binding to the FAM19A5 protein, and wherein the polypeptide is shorter than the corresponding full-length LRRC4 protein family member (SEQ ID NO: 6; SEQ ID NO: 9; or SEQ ID NO: 84).

18. The use according to claim 17, wherein the LRRC4 family mimic molecule comprises:

(1) 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); or

(2) am amino acid sequence having the following formula (from N-terminus to C-terminus):

X1-X2-X3-F-X5-T-X7-T-V-X10 (Formula V) , wherein:

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

X2 is T or S;

X3 is Y or F;

X5 is any amino acid;

X7 is V or I; and/or

X10 is E or V;

(3) 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, e.g., T, S, or Y;

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.

19. The use according to claim 17, wherein the LRRC4 family mimic molecule comprises, consists essentially of, or consists of the amino acid sequence set forth in:

(a) SEQ ID NO: 48 (GYTYFTTVTVETLETQ);

(b) SEQ ID NO: 47 (GYTYFTTVTVETLETQPGEE);

(c) SEQ ID NO: 49 (GYTYFTTVTVETLETQPGEKEPPGPTTD);

(d) SEQ ID NO: 77 (NYSFFTTVTVETTEISPEDTTRK);

(e) SEQ ID NO: 78 (NFSYFSTVTVETMEPSQDERTTR);

(f) SEQ ID NO: 44 (YTYFTTVTVE);

(g) SEQ ID NO: 45 (YSFFTTVTVE); or

(h) SEQ ID NO: 46 (FSYFSTVTVE).

20. The use according to claim 1, wherein the FAM19A5 antagonist is to be administered to the subject via intracochlear injection, intravestibular injection, intravenous administration, or intratympanic administration.