[0011] US Patent No. 8,088,359 and US Patent Application Publication No. 20120252868 relate to methods of treating hearing loss and phantom hearing.

[0012] US Patent Application Publication No. 20110142917 discloses non-invasive methods of delivering dsRNA molecules to the ear.

[0013] US Patent Application Publication No. 20110034534 relates to, *inter alia*, dsRNA molecules to target CAPNS1.

[0014] US Patent Application Publication No. 20110229557 relates to dsRNA molecules to various gene targets, including CASP2, useful in treating eye diseases.

[0015] PCT Patent Publication No. WO2011/163436 discloses dsRNA to target RHOA.

[0016] Tinnitus and Ménière's disease affects many individuals worldwide and current therapies have not been successful at preventing progression of neuronal degeneration and the attendant hearing loss. A therapeutic treatment, which would protect the inner ear neurons, including hair cells and spiral and vestibular ganglion cells, from damage and cell death (e.g. apoptosis), and thereby attenuate or prevent hearing loss in, for example, Ménière's patients would be highly desirable. It is, accordingly, an aspect to provide methods for neuroprotection of neurons in a subject's ear, including human subjects suffering from tinnitus or Ménière's disease or having similar symtoms, using dsRNA compounds not previously known to have such activity.

SUMMARY

[0017] This disclosure is directed to methods and kits for providing neuroprotection to neurons in subject's ear, for example to spiral ganglion cells and vestibular ganglion cells.

[0017a] In one aspect, there is provided use of a double-stranded RNA (dsRNA) ~~compound~~inhibitor which down regulates expression of a CASP2 gene encoding an mRNA having a sequence set forth in any one of SEQ ID NO:1-3, for the preparation of a medicament for ~~providing neuroprotection of a neuron in the ear of~~treating Ménière's disease in a subject in need thereof, wherein the medicament provides neuroprotection of a neuron in a spiral ganglion or a vestibular ganglion in the subject's ear.

[00 17b] In one embodiment, disclosed herein is a double-stranded RNA (dsRNA) compound which down regulates expression of a CASP2 gene, a NOX3 gene, a CAPNS 1 gene or a RHOA gene encoding an mRNA having a sequence set forth in any one of SEQ ID

CLAIMS

1. Use of a double-stranded RNA (dsRNA) ~~compound~~inhibitor which down regulates expression of a CASP2 gene encoding an mRNA having a sequence set forth in any one of SEQ ID NO:1-3, for the preparation of a medicament for ~~providing neuroprotection of a neuron in the ear of~~treating Ménière's disease in a subject in need thereof, wherein the medicament provides neuroprotection of a neuron in a spiral ganglion or a vestibular ganglion in the subject's ear.

~~1.~~2. The use of claim 1, wherein the double-stranded RNA (dsRNA) inhibitor is an siRNA.

~~2.~~3. The use of any one of claims 1 or 2, wherein the dsRNA compound comprises a sense strand with a nucleotide sequence set forth in SEQ ID NO:8 and an antisense strand with a nucleotide sequence set forth in SEQ ID NO:9.

~~3. The use of any one of claims 1 or 2, wherein the neuron is comprised within a ganglion.~~

~~4. The use of claim 3, wherein the ganglion is a spiral ganglion or a vestibular ganglion.~~

~~5.~~4. The use of any one of claims 1 to 43, wherein the neuroprotection comprises protecting the neuron from cell death.

~~6.~~5. The use of claim ~~5~~4, wherein cell death of the neuron comprises apoptotic cell death.

~~7.~~6. The use of claims ~~5~~4 or ~~6~~5, wherein cell death of the neuron is associated with one or more of: a disease or disorder, ischemia, physical/mechanical trauma, a chemical agent, an infectious agent, an immunologic reaction and a nutritional imbalance.

~~8.~~7. The use of claim ~~7~~6, wherein cell death of the neuron is associated with a disease or disorder.

~~9. The use of claim 1, wherein the subject has or is at risk of developing one or more of a disease or condition associated with pathological abnormalities of an auditory organ or of a vestibular organ.~~

~~10. The use of claim 9, wherein the disease or condition is associated with a symptom selected from the group consisting of: episodic vertigo, hearing loss, tinnitus and aural fullness.~~

~~11. The use of claim 9, wherein the subject is afflicted with or susceptible to Ménière's disease.~~

~~12.~~8. The use of claim 1, wherein the neuroprotection comprises restoration of cochlear function and/or of vestibular function.

~~13.~~9. The use of any of claims 1 to ~~12~~8, wherein the dsRNA ~~compound~~inhibitor down regulates CASP2 expression in a cell in the inner ear of the subject.

~~14.~~10. The use of any of claims 1 to ~~13~~9, wherein the dsRNA ~~compound~~inhibitor has the structure:

5′ z″-GCCAGAAUGUGGAACUCCU-Z′3' (sense strand, SEQ ID NO:24)

3' Z -CGGUCUUACACCUUGAGGA 5'(antisense strand, SEQ ID NO:25)

wherein each A, C, U, and G is an unmodified or modified ribonucleotide or an unconventional moiety and each consecutive ribonucleotide or unconventional moiety is joined to the next ribonucleotide or unconventional moiety by a phosphodiester bond; wherein the sense strand comprises, counting from the 5' terminus, an unmodified ribonucleotide at positions 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 and 19, a L-deoxycytidine at position 18 (set forth in SEQ ID NO:24); wherein the antisense strand comprises at least five alternating unmodified and 2'-O-methyl sugar modified ribonucleotides; and wherein z", Z and Z' are optional.

~~15.~~11. The use of claim ~~14~~10, wherein each Z and Z' is absent; and wherein the antisense strand comprises, counting from the 5' terminus, a 2'O-

Methyl sugar modified ribonucleotide at each of positions 2, 4, 6, 8, 11, 13, 15, 17 and 19 and an unmodified ribonucleotide at each of positions 1, 3, 5, 7, 9, 10, 12, 14, 16 and 18 (set forth in SEQ ID NO:25).

~~16.~~12. The use of claim ~~15~~11, wherein z" is covalently attached to the 5' terminus of the sense strand (SEQ ID NO:26) and comprises an inverted deoxyabasic moiety.

~~17.~~13. The use of any of claims 1 to ~~16~~12, wherein the dsRNA molecule is formulated for transtympanic administration.

~~18.~~14. The use of any of claims 1 to ~~16~~12, wherein the dsRNA molecule is formulated as eardrops.

~~19.~~15. The use of any of claims 1 to ~~18~~14, wherein the subject is a mammal.

~~20~~16. The use of claim ~~19~~15, wherein the subject is a human.