CLAIMS

1. A method of identifying a modulator of otopetrin-mediated proton translocation activity comprising:

(a) contacting an otopetrin polypeptide, or host cell expressing said polypeptide with a test compound; and

(b) determining a proton translocation activity mediated by the otopetrin polypeptide;

wherein an increase or decrease of at least 1% of the proton translocation activity, compared to an amount of proton translocation activity determined in an absence of the test compound, identifies the test compound as a modulator of the proton translocation activity mediated by the otopetrin polypeptide; and

wherein determining the proton translocation activity comprises: measuring conductivity, current, resistance, voltage potential across a membrane comprising the otopetrin polypeptide; or intracellular pH or intracellular calcium within a host cell expressing an otopetrin polypeptide.

2. The method of claim 1, wherein:

the otopetrin polypeptide comprises a mammalian otopetrin polypeptide, wherein the mammalian otopetrin polypeptide comprises a polypeptide sequence selected from Otop1, Otop2, Otop3;

the otopetrin polypeptide comprises an insect otopetrin polypeptide;

the otopetrin polypeptide is associated with a cell membrane or synthetic membrane; and/or

the otopetrin polypeptide is: ~~at least 80%; at least 85%;~~ at least 90%; at least 95%; at least 96%; at least 97%; at least 98%; at least 99%; or 100%; identical to an otopetrin polypeptide sequence of any one of SEQ ID Nos:1-9.

3. The method of claim 1 or 2, wherein determining the proton translocation activity comprises expressing the otopetrin polypeptide, wherein:

the cell is a mammalian cell;

the cell is an oocyte; and/or

the cell is a HEK-293 cell or a CHO cell.

4. The method of any one of claims 1 to 3, wherein the test compound is selected from the group consisting of a small organic molecule, small inorganic molecule, electrophile, polysaccharide, peptide, protein, antibody, nucleic acid, and an extract, wherein the extract is from a biological material is selected from a bacteria, plant, fungi, animal cell, and animal tissue.

5. A method of identifying a modulator of otopetrin-mediated proton translocation activity comprising:

(a) measuring a proton translocation activity mediated by an otopetrin polypeptide, (i) in the presence of a test compound, and (ii) in the absence of the test compound; and

(b) determining a difference between the proton translocation activity measured in (a)(i) compared to the proton translocation activity measured in (a)(ii), thereby identifying the test compound as a modulator of the proton translocation activity mediated by the otopetrin polypeptide;

wherein measuring the proton translocation activity comprises measuring conductivity, current, voltage potential or resistance across a membrane comprising the otopetrin polypeptide; and/or

wherein measuring the proton translocation activity comprises measuring conductivity, current, intracellular pH, intracellular calcium, or voltage potential or resistance across a membrane comprising the otopetrin polypeptide in response to a change in pH.

6. The method of claim 5, wherein:

the otopetrin polypeptide comprises a mammalian otopetrin polypeptide;

the mammalian otopetrin polypeptide comprises a polypeptide sequence selected from a murine or human Otop1, Otop2, Otop3;

the otopetrin polypeptide comprises an insect otopetrin polypeptide;

the otopetrin polypeptide is associated with, or integrated in a cell membrane or synthetic membrane; and/or

the otopetrin polypeptide is: ~~at least 80%; at least 85%;~~ at least 90%; at least 95%; at least 96%; at least 97%; at least 98%; at least 99%; or 100%; identical to an otopetrin polypeptide sequence of any one of SEQ ID Nos:1-9.

7. The method of claim 5 or 6, the method comprising inducing a change in pH on one side of the otopetrin polypeptide, wherein:

the change in pH is an extracellular change in pH;

the change in pH is an increase in pH;

the change in pH is a decrease in pH; and/or

the change in pH is at least 0.1 pH units.

8. The method of any one of claims 5 to 7, wherein:

the heterologous or homologous cell is a mammalian cell; and/or

the heterologous or homologous cell is an oocyte.

9. The method of any one of claims 5 to 8, wherein the test compound is selected from the group consisting of a small organic molecule, small inorganic molecule, polysaccharide, peptide, protein, antibody, nucleic acid, and an extract, wherein the extract is from a biological material is selected from a bacteria, plant, fungi, animal cell, and animal tissue.

10. The method of claim 1, wherein:

the method comprises comparing the proton translocation activity determined in (b) to a proton translocation activity determined for the otopetrin polypeptide, in the absence of the test compound;

an increase of at least 1% of the proton translocation activity indicates the test compound is an agonist of the proton translocation activity mediated by the otopetrin polypeptide; or

a decrease of at least 1% of the proton translocation activity indicates the test compound is an antagonist of the proton translocation activity mediated by the otopetrin polypeptide.

11. The method of claim 1, wherein:

the conductivity, voltage potential, current, resistance, intracellular pH, intracellular calcium, or the is measured in response to a change in pH;

determining the proton translocation activity comprises a patch clamp technique, voltage clamp technique, measurement of whole cell current, or use of a pH sensitive indicator or calcium-sensitive indicator; or

the pH sensitive indicator comprises pHluorin or pHrodo Red, DFFDA, and BCECF;

the calcium-sensitive indicator comprises Fura-2, ~~Fluo-4, Fluo-3,~~ or a ~~genetically encoded~~fluorescent calcium indicator;

the change in pH is an extracellular change in pH;

the change in pH is a change in intracellular pH;

the change in pH is an increase in pH;

the change in pH is a decrease in pH; and/or

the change in pH is at least 0.1 pH units.

12. The method of claim 4, wherein:

the test compound has a molecular weight in a range of 50 to 500,000 Daltons;

the test compound is at a concentration in a range of: 1 pM to 100 mM; 1 pM to 10 mM; 1 pM to 1 mM; 10 pM to 100 mM; 10 pM to 10 mM; 10 pM to 1 mM; 100 pM to 100 mM; 100 pM to 10 mM; or 100 pM to 1 mM; or

the test compound is at a concentration of: at least 1 pM; at least 10 pM; at least 100 pM; at least 1 nM; at least 10 nM; at least 100 nM; at least 1 μM; at least 10 μM; at least 100 μM; or at least 1 mM.

13. The method of claim 5, wherein:

the difference is at least a difference of 1%;

the proton translocation activity measured in (a)(i) is at least 1% greater than the proton translocation activity measured in (a)(ii) and the test compound is identified in (b) as an agonist of the proton translocation activity mediated by the otopetrin polypeptide;

the proton translocation activity measured in (a)(i) is at least 1% less than the proton translocation activity measured in (a)(ii) and the test compound is identified in (b) as an antagonist of the proton translocation activity mediated by the otopetrin polypeptide;

measuring the proton translocation activity comprises a patch clamp technique, measurement of whole cell currents, two-electrode voltage clamping, or a fluorescence assay using a voltage-sensitive dye; or

measuring the proton translocation activity comprises expressing the otopetrin polypeptide in a heterologous or homologous cell.

14. The method of claim 9, wherein:

the test compound has a molecular weight in a range of 50 to 500,000 Daltons;

the test compound is at a concentration in a range of: 1 pM to 100 mM; 1 pM to 10 mM; 1 pM to 1 mM; 10 pM to 100 mM; 10 pM to 10 mM; 10 pM to 1 mM; 100 pM to 100 mM; 100 pM to 10 mM; or 100 pM to 1 mM; or

the test compound is at a concentration of: at least 1 pM; at least 10 pM; at least 100 pM; at least 1 nM; at least 10 nM; at least 100 nM; at least 1 μM; at least 10 μM; at least 100 μM; or at least 1 mM.