SUMMARY

The disclosure provides materials and methods useful for control of organ function to prevent, inhibit or treat disease. In one example, the method provides for delivery of viral vectors to organs which are then taken up by the axons of nerves which regulate function of those organs. In one example, the viral vector is an adeno-associated virus (AAV) vector. In one example, a retrograde form of adeno-associated virus (AAV), when injected into the wall of the stomach, is specifically taken up into a subset of vagus nerve sensory neurons which respond to distention of the stomach and cause satiety. Molecules that provide for retrograde forms of vectors are known to the art and include but are not limited to native viral proteins, such as HSV protein, rabies virus G, glycoprotein type C, VSV G, B19G, pseudorabies virus protein, AAV capsid protein, and dynein. This represents a specific subset of neurons emanating from the nodose ganglion, while not affecting other nodose neurons which provide sensation to other visceral organs. The viral vector can also be other forms of retrograde vectors, including but not limited to retrograde lentiviral (LV) vectors, herpes simplex virus (HSV) vectors or canine adenovirus (CAV) vectors.

In one aspect, the present disclosure refers to use of a viral vector in the manufacture of a medicament for preventing, inhibiting or treating a cough in a mammal, wherein the mammal has a parasympathetic nerve fiber that innervates the lung of the mammal; the viral vector expresses a gene encoding a designer receptor exclusively activated by designer drugs (DREADD), wherein the DREADD inhibits neuronal activity in the presence of an agent that binds to the DREADD; and the parasympathetic nerve fiber is to be infected with the viral vector.

In another aspect, the present disclosure refers to use of a viral vector in the manufacture of a first medicament and use of an agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to prevent, inhibit or treat a cough in a mammal, wherein the mammal has a parasympathetic nerve fiber that innervates the lung of the mammal; the viral vector expresses a gene encoding a DREADD, wherein the DREADD inhibits neuronal activity in the presence of an agent that binds to the DREADD; the parasympathetic nerve fiber is to be infected with the viral vector; and the agent is to be administered to the mammal in an amount effective to inhibit the activity of the protein.

In one example, a method is provided to deliver one or more genes to nerve fibers that control function of an organ, e.g., a visceral organ including but not limited to stomach, small intestine, large intestine, pancreas, liver, spleen, gall bladder, lung, kidney, and heart. In one example, a viral gene therapy vector is delivered into a region of an organ that is innervated by a regulatory nerve such as a vagus nerve, cardiopulmonary nerve, thoracic splanchnic nerve, lumbar splanchnic nerve, sacral splanchnic nerve or pelvic splanchnic nerve. In one example, the organ is a stomach, intestines, pancreas, liver, lung, heart, adrenal, kidney, gonads, bladder, anal sphincter or urinary sphincter. In one example the viral vector is modified for retrograde transport in the central nervous system. In one example, the viral vector is injected into the organ. In one example, the delivery of the vector prevents, inhibits or treats a disease. In one example, the viral vector is injected into the stomach and the expression of the gene controls food intake. In one example, the viral vector is delivered to the lung, e.g., via inhalation, and the expression of the gene controls cough. In one example, expression of the gene activates the regulatory nerve. In one example, expression of the gene inhibits the regulatory nerve.

The disclosure also provides for a viral vector with improved properties for retrograde uptake into target neurons. This vector contains a capsid, which contains a mix of capsid proteins from one serotype of AAV, e.g., AAV serotype 2, with point mutations increasing retrograde uptake (retroAAV) (Tevro, et al., Neuron 92:372-378 (2016), which is incorporated by reference herein) and capsid proteins from a different serotype of AAV, e.g., AAV serotype rh10. This capsid mix creates a viral vector that has dramatically enhanced retrograde uptake and efficiency into afferent neurons compared with capsids that contain protein exclusively from retroAAV. This vector provides for efficient control of organ function.

The disclosure also provides a method for regulated control of organ function. The method generally includes delivery of a gene via a retrograde vector to neurons afferent to the organs, the product of which responds to an external drug or stimulus to control organ function. In one example, this method can be used to induce satiety and reduce food intake in order to control body weight. In this example, retrograde AAV (retroAAV) expressing a Designer Receptor Exclusively Activated by Designer Drugs (DREADD) that activates neurons, is injected into the wall of the stomach and is taken up into vagus sensory neurons, afferent to the stomach, which respond to stomach stretch and induce satiety. Following systemic administration of a DREADD activator, e.g., clozapine-N-oxide (CNO), satiety is induced and food intake is decreased. Other examples include delivery of an excitatory chemogenetic ion channel to these neurons followed by activation with the appropriate drug or delivery of the excitatory optogenetic ion channel ChR2 followed by light delivery to the nerve fibers to activate ChR2. In another example, this method is used to control intractable cough that is not due to an otherwise treatable disease. In one example, retrograde AAV expressing an inhibitory DREADD is aerosolized and inhaled for uptake into vagus sensory neurons of the lung, followed by systemic administration of a DREADD activator, e.g., CNO, to inhibit activity of these sensory neurons to reduce the cough reflex. In one example, retrograde AAV expressing, for instance, an inhibitory DREADD, is injected, e.g., into the vagus verve or nodose ganglion, followed by systemic administration of a DREADD activator, e.g., CNO, to inhibit activity of these sensory neurons to reduce the cough reflex.

In one example, the viral vector encodes hM4Di, an engineered version of the M4 muscarinic acetylcholine receptor which, when bound by CNO, clozapine, perlapine, or compound 21 (see Chen et al., ACS Chem. Neurosic., 6:476 (2015)),

WHAT IS CLAIMED IS:

1. Use of a viral vector in the manufacture of a medicament for preventing, inhibiting or treating a cough in a mammal, wherein the mammal has a parasympathetic nerve fiber that innervates the lung of the mammal; the viral vector expresses a gene encoding a designer receptor exclusively activated by designer drugs (DREADD), wherein the DREADD inhibits neuronal activity in the presence of an agent that binds to the DREADD; and the parasympathetic nerve fiber is to be infected with the viral vector.

2. The use of claim 1, wherein the viral vector is to be administered to the mammal via inhalation or injection, or intravenously.

3. The use of claim 1 or 2, wherein the agent is to be administered to the mammal in an amount effective to inhibit the activity of the DREADD.

4. The use of any one of claims 1 to 3, wherein the mammal is a human.

5. The use of any one of claims 1 to 4, wherein the mammal has idiopathic cough or intractable cough.

6. The use of any one of claims 1 to 4, wherein the mammal has chronic obstructive pulmonary disease (COPD) or gastric reflux.

7. The use of any one of claims 1 to 6, wherein the viral vector is an adeno-associated virus, lentivirus, adenovirus, or herpes simplex virus vector.

8. The use of any one of claims 1 to 7, wherein the viral vector is a retrograde form of adeno-associated virus, lentivirus or canine adenovirus.

9. The use of any one of claims 1 to 8, wherein the viral vector is modified for retrograde transport.

10. The use of any one of claims 1 to 9, wherein the DREADD is an engineered M4 muscarinic acetylcholine receptor.

11. The use of claim 10, wherein the DREADD is a hM4Di receptor.

12. The use of any one of claims 1 to 11, wherein the viral vector is a rAAV comprising an adeno-associated viral capsid comprising two or more different AAV capsid serotypes.

13. The use of claim 12, wherein the rAAV comprises capsid proteins from a retro-AAV capsid serotype.

14. The use of any one of claims 12 or 13, wherein the rAAV comprises capsid proteins from a AAVrh10 capsid serotype.

15. The use of claim 14, wherein the rAAV comprises capsid proteins from a retro-AAV capsid serotype and a AAVrh10 capsid serotype.

16. The use of any one of claims 1 to 15, wherein the agent that binds to the DREADD is clozapine-N-oxide (CNO).

17. Use of a viral vector in the manufacture of a first medicament and use of an agent in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to prevent, inhibit or treat a cough in a mammal, wherein the mammal has a parasympathetic nerve fiber that innervates the lung of the mammal; the viral vector expresses a gene encoding a DREADD, wherein the DREADD inhibits neuronal activity in the presence of an agent that binds to the DREADD; the parasympathetic nerve fiber is to be infected with the viral vector; and the agent is to be administered to the mammal in an amount effective to inhibit the activity of the protein.

18. The use of claim 17, wherein the viral vector is to be administered to the mammal via inhalation or injection.

19. The use of claim 17 or 18, wherein the agent is to be intravenously administered.

20. The use of any one of claims 17 to 19, wherein the mammal is a human.

21. The use of any one of claims 17 to 20, wherein the mammal has idiopathic cough or intractable cough.

22. The use of any one of claims 17 to 20, wherein the mammal has chronic obstructive pulmonary disease (COPD) or gastric reflux.

23. The use of any one of claims 17 to 22, wherein the viral vector is an adeno-associated virus, lentivirus, adenovirus, or herpes simplex virus vector.

24. The use of any one of claims 17 to 23, wherein the viral vector is a retrograde form of adeno-associated virus, lentivirus or canine adenovirus.

25. The use of any one of claims 17 to 24, wherein the viral vector is modified for retrograde transport.

26. The use of any one of claims 17 to 25, wherein the DREADD is an engineered M4 muscarinic acetylcholine receptor.

27. The use of claim 26, wherein the DREADD is a hM4Di receptor.

28. The use of any one of claims 17 to 27, wherein the viral vector is a rAAV comprising an adeno-associated viral capsid comprising two or more different AAV capsid serotypes.

29. The use of claim 28, wherein the rAAV comprises capsid proteins from a retro-AAV capsid serotype.

30. The use of claim 28 or 29, wherein the rAAV comprises capsid proteins from a AAVrh10 capsid serotype.

31. The use of claim 30, wherein the rAAV comprises capsid proteins from a retro-AAV capsid serotype and a AAVrh10 capsid serotype.

32. The use of any one of claims 17 to 31, wherein the agent that binds to the DREADD is CNO.