outcomes in cochlear implant results[1]. Specifically, the TMPRSS3 mutant patient has dysfunction of their spiral ganglion[2]. During evaluation of a mouse TMPRSS3 mutant model, it was demonstrated that hair cells degenerated initially and was followed shortly after by the degeneration of spiral ganglion cells[3]. Permanent damage to the hair cells of the inner ear results in sensorineural hearing loss, leading to communication difficulties in a large percentage of the population. Hair cells are the receptor cells that transduce the acoustic stimulus. Regeneration of damaged hair cells would provide an avenue for the treatment of a condition that currently has no therapies other than prosthetic devices.

[0026] During evaluation of human patients with TMPRSS3 mutations, it was demonstrated that cochlear implant function declines with age, which suggests that the delayed degeneration of spiral ganglion cells also occurs in the human population[4]. The foregoing suggests that cochlear implants alone may not be enough to combat hearing loss.

[0027] Opportunities, therefore, exist to provide a combination of molecular therapeutics (e.g., gene therapy) for hearing loss in combination with cochlear implantation.

SUMMARY

[0028] Examples of the present disclosure relate to, among other things, gene therapy systems and methods useful in treating and/or preventing hearing loss. Systems and methods described herein relate to combination gene therapy with cochlear implantation to repair and/or rescue degenerating hair cells and/or degenerating spiral ganglion cells depending on the time of intervention.

[0029] Each of the examples disclosed herein may include one or more of the features described in connection with any of the other disclosed examples.

[0029a] In one aspect, the present disclosure refers to a system for treating hearing loss in hair cells and spiral ganglion cells, comprising: a gene therapeutic construct, wherein the gene therapeutic construct comprises an expression vector for h-TMPRSS3; and a cochlear implant, wherein the cochlear implant comprises a catheter or port for delivering the gene therapy construct.

In another aspect, the present disclosure refers to a system for use in a method of treating or preventing hearing loss in hair cells and spiral ganglion cells in a subject in need thereof, wherein the system comprises a cochlear implant and an expression vector, the method comprising the steps of: implanting the cochlear implant in the subject, wherein the cochlear implant comprises a catheter or port for delivering the expression vector, and administering to the subject an effective amount of the expression vector, wherein the expression vector encodes for h-TMPRSS3 and comprises an initial vector, an enhancer, a promoter, a bGH poly(A) signal, and a closing vector.

In another aspect, the present disclosure refers to a system for treating or preventing hearing loss in hair cells and spiral ganglion cells in a subject in need thereof, wherein the system comprises a cochlear implant and an expression vector; wherein the cochlear implant comprises a catheter or port for delivering the expression vector; and wherein the expression vector encodes for h-TMPRSS3 and comprises an initial vector, an enhancer, a promoter, a bGH poly(A) signal, and a closing vector.

[0030] Disclosed herein is an expression vector including the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2, or a nucleic acid sequence having at least 90% sequence identity to the nucleic acid of SEQ ID NO:1 or SEQ ID NO:2, wherein the nucleic acid sequence is operatively linked to a promoter. Also disclosed herein is a pharmaceutical composition for use in a method for the treatment or prevention of hearing loss that includes an expression vector having the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2, or a nucleic acid sequence having at least 90% sequence identity to the nucleic acid of SEQ ID NO:1 or SEQ ID NO:2, wherein the nucleic acid sequence is operatively linked to a promoter. In some examples, the nucleic acid sequence has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2. In some examples, the expression vector is selected from an adeno-associated viral vector, an adenoviral vector, a herpes simplex viral vector, a vaccinia viral vector, a helper dependent adenoviral vector or a lentiviral vector. In some examples, the vector is an adeno-associated viral vector selected from AAV2, AAV2/Anc80, AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAVrh8, AAVrh10, AAVrh39, AAVrh43AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, Anc80, or a synthetic version of an adeno associated viral vector serotype. In some examples, the adeno-associated viral vector is AAV2, Anc80, or a synthetic version of an adeno associated viral vector serotype. In some examples, the promoter is selected from any hair cell promoter that drives the expression of an operably linked nucleic acid at early development and maintains expression throughout the life, for example, TMPRSS3 promoters, human

cytomegalovirus (HCMV) promoters, cytomegalovirus/chicken beta-actin (CBA) promoters, Myo7a promoters or Pou4f3 promoters.

[0031] Disclosed herein is a cell having an expression vector that includes the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2, or a nucleic acid sequence having at least 90% sequence identity to the nucleic acid of SEQ ID NO:1 or SEQ ID NO:2, wherein the nucleic acid sequence is operatively linked to a promoter. In some examples, the nucleic acid sequence has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2. In some examples, the cell is a stem cell. In some examples, the stem cell is an induced pluripotent stem cell.

[0032] Disclosed herein is a method for treating or preventing hearing loss, including administering to a subject in need thereof an effective amount of an expression vector that includes the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2, or a nucleic acid sequence having at least 90% sequence identity to the nucleic acid of SEQ ID NO:1 or SEQ ID NO:2, wherein the nucleic acid sequence is operatively linked to a promoter. In some examples, the nucleic acid sequence has at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:2. In some examples, the expression vector is selected from an adeno-associated viral vector, an adenoviral vector, a herpes simplex viral vector, a vaccinia viral vector, a helper dependent adenoviral vector or a lentiviral vector. In some examples, the vector is an adeno-associated viral vector selected from AAV2, AAV2/Anc80, AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAVrh8, AAVrh10, AAVrh39, AAVrh43, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8

or Anc80, or a synthetic version of an adeno associated viral vector serotype. In some examples, the adeno-associated viral vector is AAV2, Anc80, or a synthetic version of an adeno associated viral vector serotype.s In some examples, the promoter is selected from any hair cell promoter that drives the expression of an operably linked nucleic acid sequence at early development and maintains expression throughout the life, for example, TMPRSS3 promoters, human cytomegalovirus (HCMV) promoters, cytomegalovirus/chicken beta-actin (CBA) promoters, Myo7a promoters or Pou4f3 promoters. In some examples, the expression vector is administered into the inner ear of the subject, for example, by injection. In some examples, the delivery method is selected from cochleostomy, round window membrane, canalostomy or any combination thereof (see, Erin E. Leary Swan, et al. (2008) Inner Ear Drug Delivery for Auditory Applications. Adv Drug Deliv Rev. 60(15):1583–1599). In some examples, the expression vector is delivered into the scala media via the endolymphatic sac (Colletti V, et al. (2010) Evidence of gadolinium distribution from the endolymphatic sac to the endolymphatic compartments of the human inner ear. Audiol Neurootol. 15(6):353-63; Marco Mandalà, MD, et al. (2010) Induced endolymphatic flow from the endolymphatic sac to the cochlea in Ménière's disease. Otolaryngology–Head and Neck Surgery. 143, 673-679; Yamasoba T, et al. (1999) Inner ear transgene expression after adenoviral vector inoculation in the endolymphatic sac. Hum Gene Ther. 10(5):769-74). In some examples, the subject has one or more genetic risk factors associated with hearing loss. In some examples, one of the genetic risk factors is a mutation in the TMPRSS3 gene. In some examples, the mutation in the TMPRSS3 gene is selected from any one or more TMPRSS3 mutations known to cause hearing loss (see, for example, Table 2). In some examples, one of the genetic risk factors is a mutation in the LOXHD1

gene. In some examples, the mutation in the LOXHD1 gene is selected from any one or more LOXHD1 mutations known to cause hearing loss (see, for example, Table 3). In some examples, the subject does not exhibit any clinical indicators of hearing loss.

[0033] In some examples, an expression vector described herein is administered as a combination therapy with one or more expression vectors comprising other nucleic acid sequences and/or with one or more other active pharmaceutical agents for treating hearing loss. For example, a combination therapy may include a first expression vector that has the nucleic acid sequence of SEQ ID NO:1 and a second expression vector that has the nucleic acid sequence of SEQ ID NO:2, wherein both expression vectors are administered to a subject as part of a combination therapy to treat hearing loss.

[0034] Disclosed herein is a transgenic mouse having a human TMPRSS3 gene with a mutation selected from any one or more TMPRSS3 mutation known to cause hearing loss (see, for example, Table 2). Disclosed herein is a transgenic mouse having a human LOXHD1 gene with a mutation selected from any one or more LOXHD1 mutation known to cause hearing loss (see, for example, Table 3).

[0035] It may be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the disclosure, as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate exemplary embodiments of the present disclosure and together with the description, serve to explain the principles of the disclosure.

CLAIMS

WHAT IS CLAIMED IS:

1. A system for treating hearing loss in hair cells and spiral ganglion cells, comprising:

a gene therapeutic construct, wherein the gene therapeutic construct comprises an expression vector for h-TMPRSS3; and

a cochlear implant, wherein the cochlear implant comprises a catheter or port for delivering the gene therapy construct.

2. The system of claim 1, wherein the expression vector further comprises an initial vector, an enhancer, a promoter, a bGH poly(A) signal, and a closing vector.

3. The system of claim 1, wherein the expression vector is an adeno-associated viral vector or a synthetic version of an adeno associated viral vector serotype.

4. The system of claim 3, wherein the adeno-associated viral vector is selected from the group consisting of AAV2, AAV2/Anc80, AAV5, AAV6, AAV6.2, AAV7, AAV8, AAV9, AAVrh8, AAVrh10, AAVrh39, AAVrh43, AAV1, AAV3, AAV4, or a synthetic version of an adeno associated viral vector serotype

5. The system of claim 2, wherein the promoter is selected from the group consisting of: TMPRSS3 promoters, Myo7a promoters, human cytomegalovirus (HCMV) promoters, cytomegalovirus/chicken beta-actin (CBA) promoters and Pou4f3 promoters.

6. The system of claim 2, wherein the enhancer is selected from the group consisting of: TMPRSS3 enhancers and human cytomegalovirus (HCMV) enhancers.

7. The system of claim 1, wherein the cochlear implant comprises:

a microphone, wherein the microphone is configured to receive sound;

a speech processor, wherein the speech processor is configured to select and/or arrange sounds received up by the microphone;

a transmitter and a receiver/stimulator, wherein the transmitter and the receiver/stimulator are configured to receive signals from the speech processor and convert them into electric impulses; and

an electrode.

8. A system for use in a method of treating or preventing hearing loss in hair cells and spiral ganglion cells in a subject in need thereof, wherein the system comprises a cochlear implant and an expression vector, the method comprising the steps of:

implanting the cochlear implant in the subject, wherein the cochlear implant comprises a catheter or port for delivering the expression vector, and

administering to the subject an effective amount of the expression vector, wherein the expression vector encodes for h-TMPRSS3 and comprises an initial vector, an enhancer, a promoter, a bGH poly(A) signal, and a closing vector.

9. A system for treating or preventing hearing loss in hair cells and spiral ganglion cells in a subject in need thereof, wherein the system comprises a cochlear implant and an expression vector; wherein the cochlear implant comprises a catheter or port for delivering the expression vector; and wherein the expression vector encodes for h-TMPRSS3 and comprises an initial vector, an enhancer, a promoter, a bGH poly(A) signal, and a closing vector.

10. The system of claim 8, wherein the expression vector is to be administered subsequent to the implantation of the cochlear implant.

11. The system of claim 8, wherein the expression vector is to be administered concurrently with the cochlear implant.

12. The system of claim 8 or 9, wherein the expression vector is an adeno-associated viral vector or a synthetic version of an adeno associated viral vector serotype.

13. The system of claim 12, wherein the adeno-associated viral vector is selected from the group consisting of AAV2, AAV2/Anc80, AAV5, AAV6, AAV6.2,

AAV7, AAV8, AAV9, AAVrh8, AAVrh10, AAVrh39, AAVrh43, AAV1, AAV3, or a synthetic version of an adeno associated viral vector serotype

14. The system of claim 8 or 9, wherein the promoter is selected from the group consisting of: TMPRSS3 promoters, Myo7a promoters, human cytomegalovirus (HCMV) promoters, cytomegalovirus/chicken beta-actin (CBA) promoters and Pou4f3 promoters.

15. The system of claim 8 or 9, wherein the expression vector is to be administered by injection into the inner ear of the subject.

16. The system of claim 15, wherein the injection method is selected from the group consisting of cochleostomy, round window membrane, endolymphatic sac, scala media, canalostomy, scala media via the endolymphatic sac, or any combination thereof.

17. The system of claim 8 or 9, wherein the subject has one or more genetic risk factors associated with hearing loss.

18. The system of claim 17, wherein one of the genetic risk factors is a mutation in the TMPRSS3 gene.

19. The system of claim 17, wherein the subject does not exhibit any clinical indicators of hearing loss.