ADENOVIRAL VECTOR ENCODING HUMAN ATONAL HOMOLOG-1 (HATH1)

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims the benefit of U.S. Provisional Patent Application No. 62/061,748, filed October 9, 2014.

MATERIAL SUBMITTED ELECTRONICALLY

[0002] A computer-readable nucleotide/amino acid sequence listing is submitted concurrently herewith and identified as follows: One 49,240 Byte ASCII (Text) file named "721767_ST25.TXT," created on September 25, 2015.

BACKGROUND OF THE INVENTION

[0003] A majority of the world's population likely will experience some reduction in hearing capacity or a balance disorder in their lifetime. Approximately 17 percent (36 million) of American adults report some degree of hearing loss, and about 2-3 out of every 1,000 children in the United States are born deaf or hard-of-hearing (statistics from the National Institute on Deafness and Other Communication Disorders (NIDCD)).

[0004] In both hearing and balance, mechanical stimuli are translated into neural signals by sensory hair cells, damage to which is responsible for many types of hearing loss and balance disorders. Mechanical damage by, for example, loud noises, bends cochlear hair cells to the point that the hair cell can no longer transduce signals to the auditory nerves. As mammalian hair cells do not regenerate naturally, permanent hearing loss can occur if hair cells are damaged. Aside from acoustic trauma, which is the predominant cause of hearing impairment, hearing loss also can be caused by hereditary syndromes, bacterial or viral infections, use of prescription drugs, and presbycusis (hearing loss associated with old age). Likewise, balance disorders, especially vestibular disorders, can be caused by infection, head injury, pharmaceutical use, and age.

next cohort. This decision will be made by the SRC. Should notable adverse events or safety concerns be found at one of the planned dose levels, the next planned dose level may be changed.

[0087] For Part C, the safety review described above will be performed as each five subjects complete their first four weeks of study assessments.

[0088] Findings

[0089] The first patients treated with 20 to 40 uL of the composition of the invention under cohorts A, B, and C have reported between 0 and 3 adverse events each - all classified as mild to moderate- over 2-6 months of follow-up. Most adverse events, including all events classified as moderate, were not suspected to be associated with the treatment. In addition, there have been no clinically significant changes in laboratory values following treatment with the composition. These results indicate that the inventive composition invention is safe when administered to a human.

[0090] This example describes a clinical protocol designed to evaluate the safety and efficacy of the inventive adenoviral vector for treating hearing loss in humans.

[0091] The use of the terms "a" and "an" and "the" and "at least one" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term "at least one" followed by a list of one or more items (for example, "at least one of A and B") is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention

and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0092] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIMS:

1. An adenoviral vector comprising:

(a) a serotype 5 adenoviral genome, except that two base pairs are deleted in the VA RNA I region, one or more endogenous nucleotides of the E1 region are deleted to render an endogenous gene in the E1 region functionally deficient, one or more endogenous nucleotides of the E3 region are deleted, and one or more endogenous nucleotides of the E4 region are deleted to render an endogenous gene in the E4 region functionally deficient, wherein a right side inverted terminal repeat (ITR), an E4 region polyadenylation sequence, and an E4 region promoter are retained,

(b) an SV40 early polyadenylation sequence,

(c) a nucleic acid sequence encoding a human atonal homolog-1 (Hath1) protein comprising SEQ ID NO: 1,

(d) a human glial fibrillary acidic protein (GFAP) promoter, and

(e) a transcriptionally inert spacer (TIS), wherein the TIS does not restore the replication-essential function to the deficient region;

wherein elements (b), (c), and (d) are located in sequence from 3' to 5' relative to the adenoviral genome in the E1 region of the adenoviral genome, and wherein element (e) is located in the E4 region of the adenoviral genome between the E4 polyadenylation sequence and the E4 promoter.

2. The adenoviral vector of claim 1, wherein the adenoviral genome does not comprise the endogenous promoters and coding regions of the E1A and E1B genes.

3. The adenoviral vector of claim 2, wherein the adenoviral genome does not comprise endogenous nucleotides 356-3510, inclusive, of the E1 region of the serotype 5 adenoviral genome.

4. The adenoviral vector of any one of claims 1-3, wherein the adenoviral genome does not comprise endogenous nucleotides 28,593-30,471, inclusive, of the E3 region of the serotype 5 adenoviral genome.

5. The adenoviral vector of any one of claims 1-4, wherein the adenoviral genome does not comprise any of the E4 region coding sequences.

6. The adenoviral vector of claim 5, wherein the adenoviral genome does not comprise endogenous nucleotides 32,827-35,563, inclusive, of the E4 region of the serotype 5 adenoviral genome.

7. The adenoviral vector of any one of claims 1-6, wherein the two base-pair deletion in the VA RNA I region is the deletion of endogenous nucleotides 10,594 and 10,595 of the serotype 5 adenoviral genome.

8. The adenoviral vector of any one of claims 1-7, wherein the human glial fibrillary acidic protein (GFAP) promoter comprises SEQ ID NO: 2.

9. The adenoviral vector of any one of claims 1-8, wherein the transcriptionally inert spacer (TIS) comprises in sequence from 5' to 3' relative to the adenoviral genome (i) a polyadenylation (poly(A)) sequence and transcription termination sequence from simian virus 40 (SV40), (ii) a nucleic acid sequence encoding a β-glucuronidase gene, and (iii) a polyadenylation (poly(A)) sequence and transcription termination sequence from the bovine growth hormone (BGH) gene.

10. The adenoviral vector of any one of claims 1-9, which comprises the nucleic acid sequence SEQ ID NO: 3.

11. A composition comprising the adenoviral vector of any one of claims 1-10 and a pharmaceutically acceptable carrier.

12. The composition of claim 11 whereupon the nucleic acid sequence encoding the Hath1 protein is expressed, for use in the generation of sensory cells in the inner ear of a human suffering from hearing loss or a balance disorder.

13. Use of the composition of claim 11 whereupon the nucleic acid sequence encoding the Hath1 protein is expressed, in the manufacture of a medicament for the treatment of

a human suffering from hearing loss or a balance disorder, whereupon sensory cells in the inner ear are to be generated.

14. The composition of claim 12 or the use of claim 13, wherein the composition or medicament is to be administered once to the inner ear of the human.