as well as the effect some mutations in those genes have, there is no known treatment for LCA caused by one or more mutations in *RDH12*. Accordingly, a need continues to exist in the art for materials and methods useful in treating retinal dystrophies such as LCA as well as materials and methods useful in correcting genetic anomalies that can lead to such dystrophies.

SUMMARY

[0006] The disclosure provides an adeno-associated virus (AAV) vector comprising a coding region for the gene product of the *RDH12* gene, a gene encoding a retinol dehydrogenase enzyme. The AAV vector comprising *RDH12* is useful in treating retinal dystrophy disorders such as Leber Congenital Amaurosis (LCA) by providing a recombinant construct in which an *RDH12* coding region is placed under the control of a regulable, or controllable, promoter, such as a heterologous promoter, to provide complementing retinol dehydrogenase to subjects lacking wild-type levels of RDH12 activity, such as would result from mutations in *RDH12*. Despite the advantages of relatively small genome size, relatively low tendency to integrate into host DNA, and relatively low immunogenic profile, a surprising finding has been that some AAV serotype combinations, or pseudotypes, yield expression levels for encoded RDH12 product that is not therapeutically effective and/or that exhibits undesirable toxicity in the context of administration to subjects to treat retinal dystrophies. Coincident with that finding is the finding that certain pseudotypes, such as the AAV2/5 pseudotype, demonstrate unexpected and surprisingly effective expression levels and toxicity profiles compatible with therapeutic use to treat retinal dystrophies. Subjects who can be treated by the present methods can include those who have loss of visual function (*e.g.*, impaired response on electroretinogram (ERG) testing), but who retain some photoreceptor cells as determined by optical coherence tomography (OCT). In one aspect, the present disclosure refers to use of an adeno-associated viral vector comprising a nucleic acid in the manufacture of a medicament for treating an ophthalmological condition due to one or more loss-of-function mutations in the gene encoding the Retinol Dehydrogenase 12 (RDH12) protein, wherein the nucleic acid comprises human *RDH12* DNA and wherein the human *RDH12* DNA encodes a protein that is at least 70%, 80%, 90%, 95%, or 99% identical to the full length of SEQ ID NO:2, and wherein the medicament is to be administered to at least one eye of a human subject. Thus, in one example, the disclosure provides a method of treating a human subject who has an ophthalmological condition, such as Leber Congenital Amaurosis, or LCA, or another clinically defined ophthalmological condition, due to one or more loss-of-

function mutations in the gene encoding the Retinol Dehydrogenase12 (RDH12) protein. More particularly, one example of the disclosure provides a method of treating a human subject who has an ophthalmological condition due to one or more loss-of-function mutations in the gene encoding the Retinol Dehydrogenase12 (RDH12) protein, the method comprising administering to at least one eye of the subject an adeno-associated viral vector comprising a nucleic acid, wherein the nucleic acid comprises human *RDH12* DNA, *e.g.*, human *RDH12* cDNA, and wherein the *RDH12* DNA (*e.g.*, human *RDH12* DNA) encodes a protein that is at least 70%, 80%, 90%, 95%, or 99% identical to the full length of SEQ ID NO:2. In some examples, the ophthalmological condition is Leber Congenital Amaurosis (LCA). In some examples noted above, the ophthalmological condition is Leber Congenital Amaurosis (LCA). In some examples, the *RDH12* DNA, *e.g.*, *RDH12* cDNA, is under the expression control of a human rhodopsin kinase 1 (hGRK1) promoter, such as wherein the hGRK1 promoter comprises or consists essentially of SEQ ID NO:3. In some examples, the adeno-associated viral vector is AAV-2, serotype-5 (AAV2/5) or AAV-5. In some examples, the *RDH12* DNA, *e.g.*, *RDH12* cDNA, comprises a sequence that is at least 60% or 70% identical to SEQ ID NO:1. In some examples, the nucleic acid is administered at a titer of about 2 x 10^{10} viral genomes per milliliter (vg/mL) to about 2 x 10^{12} vg/mL, *e.g.*, a titer of about 2 x 10^{10} viral genomes per milliliter (vg/mL) to about 2 x 10^{12} vg/mL, such as about 2 x 10^{11} vg/mL or about 2 x 10^{12} vg/mL. In some examples, the nucleic acid is administered into the subretinal space, *e.g.*, wherein a micro injection cannula is inserted into the subretinal space.

[0007] Another aspect of the disclosure is drawn to a nucleic acid encoding a human *RDH12* DNA, *e.g.*, a human *RDH12* cDNA, wherein the *RDH12* DNA (*e.g.*, human *RDH12* DNA such as cDNA) encodes a protein that is at least 70%, 80%, 90%, 95%, or 99% identical to the full length of SEQ ID NO:2, wherein the *RDH12* DNA is under the control of a human rhodopsin kinase 1 (hGRK1) promoter. In some examples, the hGRK1 promoter comprises or consists essentially of SEQ ID NO:3. In some examples, the human *RDH12* DNA, *e.g.*, human *RDH12* cDNA, encodes a protein comprising SEQ ID NO:2. In some examples, the human *RDH12* DNA, *e.g.*, human *RDH12* cDNA, is at least 60% or 70% identical to the full length of SEQ ID NO: 1.

[0008] Yet another aspect of the disclosure is a nucleic acid as disclosed herein for use in treating a human subject who has an ophthalmological condition due to one or more loss-of-

function mutations in the gene encoding the Retinol Dehydrogenase 12 (RDH12) protein. In some examples, the ophthalmological condition is Leber Congenital Amaurosis (LCA).

[0009] Still another aspect of the disclosure is a viral vector comprising a nucleic acid encoding RDH12 as disclosed herein. In some examples, the viral vector is an adeno-associated viral vector. In some examples, the adeno-associated viral vector is AAV-2, serotype-5 (AAV2/5) or AAV-5.

[0010] Another aspect of the disclosure is a viral vector as disclosed herein for use in treating a human subject who has an ophthalmological condition due to one or more loss-of-function mutations in the gene encoding the Retinol Dehydrogenase 12 (RDH12) protein. In some examples, the ophthalmological condition is Leber Congenital Amaurosis (LCA).

[0011] Another aspect of the disclosure is directed to an isolated host cell comprising a viral vector as disclosed herein, or a nucleic acid as disclosed herein. In some examples, the isolated host cell expresses a human RDH12 protein.

[0012] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0013] Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

BRIEF DESCRIPTION OF THE DRAWING

[0014] Figure 1. RDH activity in the visual cycle and photoreceptor cells. (A) The visual cycle converts vitamin A to 11-*cis* retinal, the chromophore of the visual pigments, and recycles all-*trans* retinal released after bleaching. (B) Retinoid flow shown for a RPE-photoreceptor cell pair. RDH8 in the outer segment can reduce all-*trans* retinal. RDH12 in the inner segment can reduce all-*trans* retinal, 11-*cis* retinal, and other toxic short chain aldehydes. Abbreviations: 11cRAL, 11-*cis* retinal; 11cROL, 11-*cis* retinol; AtRAL, all-*trans* retinal; AtROL, all-*trans*

retinol; RCHO, short-chain aldehyde; RCHOH, short-chain alcohol; Rh, rhodopsin; MRh, metarhodopsin.

[0015] Figure 2. Expression and localization of recombinant RDH12 in *AAV2/5-hGRK1p.hRDH12* injected mice. (A) Schematic of the *AAV2/5-hGRK1p.hRDH12* gene-therapy construct in which a human *RDH12* cDNA is cloned downstream of a human rhodopsin kinase promoter, between inverted terminal repeat sequences derived from the AAV2 genome. (B, C)

What is Claimed Is:

1. Use of an adeno-associated viral vector comprising a nucleic acid in the manufacture of a medicament for treating an ophthalmological condition due to one or more loss-of-function mutations in the gene encoding the Retinol Dehydrogenase 12 (RDH12) protein, wherein the nucleic acid comprises human *RDH12* DNA and wherein the human *RDH12* DNA encodes a protein that is at least 70%, 80%, 90%, 95%, or 99% identical to the full length of SEQ ID NO:2, and wherein the medicament is to be administered to at least one eye of a human subject.

2. The use of claim 1 wherein the ophthalmological condition is Leber Congenital Amaurosis (LCA).

3. The use of claim 1 wherein the *RDH12* DNA is under the expression control of a human rhodopsin kinase 1 (hGRK1) promoter.

4. The use of claim 3 wherein the hGRK1 promoter comprises SEQ ID NO:3.

5. The use of claim 1 wherein the adeno-associated viral vector is AAV-2, serotype-5 (AAV2/5) or AAV-5.

6. The use of claim 1 wherein the RDH12 DNA comprises a sequence that is at least 60% or 70% identical to SEQ ID NO:1.

7. The use of claim 1 comprising administration of the nucleic acid at a titer of about 2 x 10^{10} viral genomes per milliliter (vg/mL) to a titer of about 2 x 10^{12} vg/mL.

8. The use of claim 1 wherein the nucleic acid is to be administered into the subretinal space.

9. The use of claim 8, wherein a micro injection cannula is to be inserted into the subretinal space.

10. A nucleic acid encoding a human *RDH12* DNA, wherein the human *RDH12* DNA encodes a protein that is at least 70%, 80%, 90%, 95%, or 99% identical to the full length of SEQ ID NO:2, wherein the RDH12 DNA is under the control of a human rhodopsin kinase 1 (hGRK1) promoter.

11. The nucleic acid of claim 10, wherein the hGRK1 promoter comprises SEQ ID NO:3.

12. The nucleic acid of claim 10, wherein the human *RDH12* DNA encodes a protein comprising SEQ ID NO:2.

13. The nucleic acid of claim 10, wherein the human *RDH12* DNA is at least 60% or 70% identical to the full length of SEQ ID NO: 1.

14. The nucleic acid of claims 10-13, for use in treating a human subject who has an ophthalmological condition due to one or more loss-of-function mutations in the gene encoding the Retinol Dehydrogenase 12 (RDH12) protein.

15. The nucleic acid of claim 14 wherein the ophthalmological condition is Leber Congenital Amaurosis (LCA).

16. A viral vector comprising the nucleic acid of any of claims 10-15.

17. The viral vector of claim 16, which is an adeno-associated viral vector.

18. The viral vector of claim 17, wherein the adeno-associated viral vector is AAV-2, serotype-5 (AAV2/5) or AAV-5.

19. The viral vector of any one of claims 16 to 18, for use in treating a human subject who has an ophthalmological condition due to one or more loss-of-function mutations in the gene encoding the Retinol Dehydrogenase 12 (RDH12) protein.

20. The viral vector of claim 19 wherein the ophthalmological condition is Leber Congenital Amaurosis (LCA).

21. An isolated host cell comprising the viral vector of any one of claims 16 to 20, or the nucleic acid of any one of claims 10 to 15.

22. The isolated host cell of claim 21, wherein the cell expresses a human RDH12 protein.