increases. Drugs for the treatment of AMD already account for over 1% of the entire drugs budget of the UK's National Health Service. While patients with advanced AMD can be trained to fixate extra-foveally, the low refresh rate and the low bleaching threshold of rod cells limits the quality of resulting vision.

SUMMARY

Using mice with absent cone function, we have demonstrated that AAV-mediated over-expression of Rgs9-anchor protein (R9AP), a critical component of GTPase complex that mediates the deactivation of phototransduction cascade, results in desensitization and "photopic shift" of the rod-driven electroretinogram. The treatment enables the rods to respond to brighter light (up to ~2.0 log) than the untreated cells at the expense of scotopic (lower light level) function. Multi-electrode array measurements using the treated retinas showed that the retinal ganglion cells also reflected the "photopic shift" of the rods, by exhibiting graded responses at photopic light levels. Contrast sensitivity function measured by quantifying the head-tracking movements in response to rotating sinusoidal gratings showed an improvement of the sensitivity by up to 25-fold under room light conditions and faster response to repeated stimuli. Furthermore, biochemical measurement of bleachable rhodopsin levels in these mice indicated that the visual cycle was not limiting rod function.

We have also expressed a fast light-driven proton pump, ArchT (Han et al, 2011) in rod photoreceptors. AAV8 particles carrying ArchT-EGFP under control of the Rhodopsin promoter (Rho) were injected subretinally in adult mice. Expression of Rho-ArchT-EGFP was limited to the membrane of rod photoreceptors. Expression of ArchT allowed extremely rapid light responses, while the intrinsic rod response was preserved and was comparable to that observed in non-transduced rod photoreceptors. Overall, ArchT expression did not alter the ability of rod photoreceptors to respond to scotopic stimuli, but it did confer an additional ability to respond with rapid non-bleaching responses to higher levels of illumination. We also found that the transduced rods were

able reliably to sustain this fast 'cone-like' transmission, in that ArchT-expressing rods drove sustained retinal ganglion cell (RGC) spiking at high light intensities and at frequencies approaching those of cone photoreceptors. Expression of Rho-ArchT-EGFP in CNGA3-/- and PDE6C-/- mice lacking cone-mediated vision also extended the sensitivity of these mice to bright light stimuli and conferred fast vision on these mice. The maximal frequency of stimuli that ArchT-expressing mice could follow was similar to that of cone photoreceptors.

Together, these results show that, after transduction of healthy rod photoreceptors with genes encoding either light sensitive proteins characteristic of cones or genes encoding molecules that increase the speed of the endogenous rod signalling mechanism, rods behave more like cones and hence can compensate for cone dysfunction. This has implications for the treatment of a number of vision disorders in which cone function is reduced, but at least some healthy rods remain. This contrasts with previous approaches (Busskamp et al, 2010; US Patent Publication No. 2012258530) in which the goal was to restore lost function in cones. Altering function in rods in the manner of the present invention is advantageous in that conditions in which cones are dysfunctional but can be repaired (for example in the early stages of retinal degeneration when photoreceptor function is lost but the photoreceptor-to-bipolar synapse may be intact) are rare, whereas conditions in which cone dysfunction is more severe or advanced and cannot be repaired or where cones are lost entirely, but yet at least some healthy rod photoreceptors remain, are common (see above). Furthermore, this invention enables the creation of a 'pseudo-fovea', a small patch of cone-like rods that will improve vision in conditions in which foveal cones have been lost or are dysfunctional.

The invention therefore provides in one aspect the use of a vector comprising a nucleic acid encoding a gene product that is light-sensitive and/or that modulates endogenous light-sensitive signalling in a photoreceptor cell in the manufacture of a medicament for improving vision in a patient with cone photoreceptor dysfunction and/or degeneration, wherein the nucleic acid is to be introduced into healthy rod photoreceptors in the retina of the patient to allow expression of said gene product therein, such that the range of light intensities to which the rod photoreceptor responds is extended and/or the speed at which the rod photoreceptor responds to light is increased, wherein the gene product is ArchT, Jaws (cruxhalorhodopsin), iC1C2, or R9AP. In another aspect, the present invention refers to an expression cassette comprising a nucleic acid as defined in the present invention, operably linked to a rod-specific or rod-preferred promoter as defined in the present invention. In still another aspect, the present invention refers to a vector comprising an expression cassette according to the present invention. In one aspect, the present invention refers to vector comprising a nucleic acid encoding a gene product that is light-sensitive and/or that modulates endogenous light-sensitive signalling in a photoreceptor cell, such that the range of light intensities to which the rod photoreceptor responds is extended and/or the speed at which the rod photoreceptor responds to light is increased, wherein the gene product is ArchT, Jaws (cruxhalorhodopsin), iC1C2, or R9AP, and wherein the nucleic acid is operably linked to a rod photoreceptor-specific or rod photoreceptor-preferred promoter. In one aspect, the present invention refers to a host cell comprising a vector according to the present invention. In another aspect, the present invention refers to of a vector as defined in the present invention in the manufacture of a medicament for the improvement of vision as defined in the present invention. In yet another aspect, the present invention refers to the use of a vector as defined in the present invention in the manufacture of a medicament for the improvement of vision as defined in the present invention, in combination with another therapy to be administered for the treatment or prevention of vision disorders. Also described herein is a vector comprising a nucleic acid encoding a gene product that is light-sensitive and/or that modulates endogenous light-sensitive signalling in a photoreceptor cell, for use in a method of improving vision in a patient with cone photoreceptor dysfunction and/or degeneration by introduction of said

nucleic acid into healthy rod photoreceptors in the retina of the patient and expression of said gene product therein, such that the range of light intensities to which the rod photoreceptor responds is extended and/or the speed at which the rod photoreceptor responds to light is increased.

Also described herein is a vector as defined above, a host cell comprising said vector and methods of treatment carried out with such a vector.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Expression of ArchT in rod photoreceptors leads to fast light-driven currents.

(a), top panels: AAV8-mediated transduction of ArchT-EGFP (green, see left panels) under control of the Rhodopsin promoter. No overlap is observed with cones (purple: Cone arrestin, see middle panels, white: DAPI, see right panels). Lower panels: specificity of expression can also be observed at the level of synapses. (b) ArchT-EGFP is localized to the membrane of rod photoreceptors, including inner and outersegments. (c) Quantification of fluorescence in ArchT-EGFP-expressing rod terminals (green, left peak) and Cone arrestin positive cone terminals (purple, right peak) shows two distinct bands corresponding to the sub-layer where rod and cone synapses localize respectively (n=22). (d) Single-cell recordings from the cell bodies of ArchT-expressing rod photoreceptors. The currents mediated by the intrinsic rod photo-trandsuction (upper trace) in response to 10 ms 530-nm light pulses (green, see vertical bars) were preserved. The ArchT-generated currents were faster (lower trace). Scale bars: (a) upper panels: 50 μm; (a) lower panels and (b): 10 um.

Figure 2: ArchT-expression drives high-frequency responses in rods and fast transmission to Retinal Ganglion Cells.

CLAIMS

1. Use of a vector comprising a nucleic acid encoding a gene product that is light-sensitive and/or that modulates endogenous light-sensitive signalling in a photoreceptor cell in the manufacture of a medicament for improving vision in a patient with cone photoreceptor dysfunction and/or degeneration, wherein the nucleic acid is to be introduced into healthy rod photoreceptors in the retina of the patient to allow expression of said gene product therein, such that the range of light intensities to which the rod photoreceptor responds is extended and/or the speed at which the rod photoreceptor responds to light is increased, wherein the gene product is ArchT, Jaws (cruxhalorhodopsin), iC1C2, or R9AP.

2. The use of a vector according to claim 1, wherein the vector is a viral vector.

3. The use of a vector according to claim 2, wherein the vector is an adeno associated virus (AAV) vector.

4. The use of a vector according to claim 3, wherein the capsid of the AAV vector is derived from AAV8.

5. The use of a vector according to claim 3 or 4, wherein the genome of the AAV vector is derived from AAV2.

6. The use of a vector according to any of the preceding claims, wherein the patient suffers from macular degeneration, achromatopsia or Leber congenital amaurosis.

7. The use of a vector according to claim 6, wherein the macular degeneration is age-related macular degeneration (AMD), an inherited macular degeneration condition or an inherited cone dystrophy.

8. The use of a vector according to claim 7, wherein the AMD is wet or neovascular AMD or geographic atrophy.

9. The use of a vector according to any of the preceding claims, wherein rod photoreceptor signalling is extended into the mesopic and/or photopic illumination range.

10. The use of a vector according to any of the preceding claims, wherein the rods exhibit improved modulation strength and/or faster activation/inactivation kinetics.

11. The use of a vector according to any of the preceding claims, wherein the vector is introduced into rod photoreceptors in vitro, to be followed by transplantation into the retina.

12. The use of a vector according to any of the preceding claims, wherein the mesopic and/or photopic vision of the patient is improved.

13. The use of a vector according to any of the preceding claims, wherein the nucleic acid is expressed under the control of a photoreceptor-specific or photoreceptor-preferred promoter.

14. The use of a vector according to claim 13, wherein said photoreceptor-specific or photoreceptor-preferred promoter is a rod-specific or rod-preferred promoter.

15. The use of a vector according to claim 14, wherein the nucleic acid is expressed under the control of a Rhodopsin (Rho), Neural retina-specific leucine zipper protein (NRL) or Phosphodiesterase 6B (PDE6B) promoter.

16. An expression cassette comprising a nucleic acid as defined in claim 1, operably linked to a rod-specific or rod-preferred promoter as defined in claim 14 or 15.

17. A vector comprising an expression cassette according to claim 16.

18. A vector comprising a nucleic acid encoding a gene product that is light-sensitive and/or that modulates endogenous light-sensitive signalling in a photoreceptor cell, such that the range of light intensities to which the rod photoreceptor responds is extended and/or the speed at which the rod photoreceptor responds to light is increased,

wherein the gene product is ArchT, Jaws (cruxhalorhodopsin), iC1C2, or R9AP, and wherein the nucleic acid is operably linked to a rod photoreceptor-specific or rod photoreceptor-preferred promoter.

19. A vector according to claim 17 or 18, wherein the vector is a viral vector as defined in any one of claims 2 to 5.

20. A host cell comprising a vector according to any one of claims 17 to 19.

21. Use of a vector as defined in any one of claims 1 to 5, 13, 14, 17 or 18 in the manufacture of a medicament for the improvement of vision as defined in any one of claims 1 or 6 to 12.

22. Use of a vector as defined in any one of claims 1 to 5, 13, 14, 17 or 18 in the manufacture of a medicament for the improvement of vision as defined in any one of claims 1 or 6 to 12, in combination with another therapy to be administered for the treatment or prevention of vision disorders.