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Presentation Abstract

Program#/Poster#: 403.6

Title: Circuit-specific expression of channelrhodopsin restores visual function in blind rd1, rd16, and rho ^{-/-} mice

Location: Room N228

Authors: ***A. HORSAGER**^{1,2}, J.-W. LIU³, E. S. BOYDEN^{4,1}, A. C. ARMAN², B. C. MATTEO¹, A. P. SAMPATH², W. W. HAUSWIRTH³;
¹Eos Neuroscience, Inc., Los Angeles, CA; ²Zilkha Neurogenetic Inst., USC, Los Angeles, CA; ³Ophthalmology, Univ. of Florida, Gainesville, FL; ⁴Media Lab., MIT, Cambridge, MA

Abstract: Purpose: Channelrhodopsin-2 (ChR2) is a light-sensitive protein that, when expressed in neurons, depolarizes the cell in response to light stimulation. Microelectronic neural prostheses result in broad and indiscriminant stimulation of the neural interface, whereas expression of ChR2 can be genetically-targeted using cell type-specific regulatory sequences (i.e., promoters) such that activation of specific neural circuits can be achieved. Using the GRM6 regulatory sequence in combination with a tyrosine-mutated adeno-associated virus (AAV), we were able to target expression of ChR2 to the ON bipolar cells of the retina using either a subretinal or intravitreal injection, and subsequently restore visual function in multiple mouse models of blindness.
Methods: We evaluated retinal bipolar cell transduction using wild-type and capsid tyrosine-mutated AAV serotypes. Vector, including the ChR2 and green fluorescent protein (GFP) genes, was either subretinally or intravitreally injected in rd1, rd16, and rho ^{-/-} mice under the control of the GRM6 promoter. Expression and localization of the ChR2-GFP fused protein was evaluated using confocal microscopy and immunohistochemistry. Visual function was measured behaviorally and physiologically in wild-type, untreated, and ChR2-treated mice using a water maze and retinal patch clamp recordings, respectively.
Results: Both wild-type and mutated serotypes were effective at transducing retinal bipolar cells. The capsid tyrosine-mutated serotypes were able to increase bipolar cell transduction by as much as 20-fold, even with an intravitreal injection. In the water maze task, the ChR2-treated mice learned the task nearly as well as

the wild-type mice (the untreated mice were unable to learn the task). Additionally, the light intensity necessary to restore this visually-guided behavior was within the normal visual dynamic range of human vision. Bipolar and ganglion cells recordings show that depolarization in these cells can be mediated by ChR2 activation.

Conclusions: Targeted expression of ChR2 in retinal ON bipolar cells restores circuit-specific computation, behavioral, and physiological visual function in all treated mice, suggesting the broad applicability of this gene therapy. Equally as important, we can target ChR2 expression to bipolar cells using a capsid tyrosine-mutated AAV, even with an intravitreal injection. Further research is necessary to evaluate visual acuity and methods of increasing the sensitivity in these treated animals, taking into account new variants of ChR2. Recent bioengineering work from our group in nonhuman primates suggests hope for a translational path.

Disclosures: **A. Horsager**, Eos Neuroscience, Inc., E. Ownership Interest (stock, stock options, patent or other intellectual property); **J. Liu**, None; **E.S. Boyden**, Eos Neuroscience, Inc., E. Ownership Interest (stock, stock options, patent or other intellectual property); **A.C. Arman**, None; **B.C. Matteo**, Eos Neuroscience, Inc., E. Ownership Interest (stock, stock options, patent or other intellectual property); **A.P. Sampath**, None; **W.W. Hauswirth**, AGTC, Inc., E. Ownership Interest (stock, stock options, patent or other intellectual property).

Keyword(s): channelrhodopsin
vision
gene therapy

Support: DP2 OD002002-01
SFN Research Award for Innovation in Neuroscience
EY17606
Karl Kirschgessner Foundation
EY13729

[Authors]. [Abstract Title]. Program No. XXX.XX. 2009 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2009. Online.

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