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Presentation Abstract

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Abstract Title: **AAV- Mediated ON Bipolar Cell Targeting in the *rd1* Mouse Lacking Photoreceptors**

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Abstract Body: **Purpose:** Adeno-associated Viral (AAV) vectors are powerful gene delivery tools for the treatment of retinal disease. The adult *rd1* mouse is a model for studying late stage retinitis pigmentosa when the retina lacks photoreceptors. In this study, we tested whether *in vivo* AAV-mediated transgene expression can target bipolar cells in the adult *rd1* mouse retina.**Methods:** The cDNA encoding a Chr2 with eGFP was cloned downstream of either the mGluR6 enhancer-SV40 minimal promoter (provided by C. Cepko) or the CBA promoter (CMV early enhancer/chicken β actin promoter). These plasmids were transfected into HEK 293 cells. After 48 hours, the cells were examined by fluorescence microscopy to evaluate expression. Then, serotype 5, 7 and 8 single-stranded AAV (ssAAV) and self-complementary AAV (scAAV) vectors were tested *in vivo* for their ability to target bipolar cells in the photoreceptor-less retina of *rd1* mice, by subretinally injection into right eyes of *rd1* mice at 35 days of age; left eyes remained untreated as controls. Levels of transgene expression were measured by GFP expression in retinal sections using GFP and PKC α antibody (against bipolar cells) staining at 3 and 6 weeks post-injection.**Results:** To initially test transgene expression, plasmid DNA constructs regulated by either the mGluR6 promoter or the CBA promoter were transfected into HEK 293 cells *in vitro*. The fraction of cells expressing GFP was approximately 60% for CBA-ChR2-GFP, 40% for sc-mGluR6-ChR2-GFPm and 20% for mGluR6-ChR2-GFP, all of which compare favorably with expression efficiency using our standard plasmid pTR-CBA-GFP. For *in vivo* evaluation, *rd1* mice at PN35 were subretinally injected with scAAV5-CBA-ChR2-GFP, scAAV8-CBA-CHR2-GFP, ssAAV5-mGluR6-CHR2-GFP, ssAAV7-mGluR6-CHR2-GFP, or ssAAV8-

mGluR6-CHR2-GFP. AAV serotype 7 with a CBA promoter and AAV serotype 5 with a mGluR6 promoter supported high expression in bipolar cells and also exhibited only limited expression in Müller cells and retinal ganglion cells.

Conclusions: AAV-mediated transgene expression targeted to bipolar cells was found to be efficient in the retina of adult rd1 mice that lack photoreceptors, suggesting that it may be possible to deliver light activated channels to bipolar cells of a late stage RP retina by subretinal vector administration.

Commercial
Relationships:

J.-W. Liu, None; **A. Horsager**, Eos Neuroscience, Inc., P; **M. Ding**, None; **S. Mani**, None; **V.A. Chiodo**, None; **E.S. Boyden**, Eos Neuroscience, Inc., P; **W.W. Hauswirth**, AGTC Inc, P.

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