Effect of long-term glaucoma on AAV retinal transduction

Posterboard#: B0089

Abstract Number: 685 - B0089

AuthorBlock: *Shan Fan[1], Chuanxi Xiang[2], Terri L. McGee[2], Chad E. Bigelow[2], Ganesh Prasanna[2], Noel D. Johnson[3], Vikas Gulati[1], Lisa Reid[1], Carol B. Toris[4,1]*

[1]Ophthalmology, University of Nebraska Medical Center, Omaha, Nebraska, United States; [2]Biomedical Research, Ophthalmology, Novartis, Cambridge, Massachusetts, United States; [3]Comparative Medicine, University of Nebraska Medical Center, Omaha, Nebraska, United States; [4]Ophthalmology, The Ohio State University, Columbus, Ohio, United States;

DisclosureBlock: Shan Fan, None; Chuanxi Xiang, Code E (Employment) Novartis, Terri L. McGee, Code E (Employment) Novartis, Chad E. Bigelow, Code E (Employment) Novartis, Ganesh Prasanna, Code E (Employment) Novartis, Noel D. Johnson, None; Vikas Gulati, None; Lisa Reid, None; Carol B. Toris, None;

Purpose

Non-human primates (NHP) have been used to predict AAV tropism of human ocular tissue following intravitreal (IVT) delivery due to the anatomic similarity between human and NHP eyes. Numerous studies have reported the ocular tropism of wild-type and novel AAV serotypes using these models. However, there is a lack of knowledge about how disease state can affect AAV transduction. This study was carried out to gain insight into the effect of long-term induced glaucoma on AAV retinal transduction in NHPs.

Methods

Six female cynomolgus monkeys ranging in age from 15-22 years old were used in this study. Animals had received laser treatment to the trabecular meshwork of one eye 11-19 years prior, to induce monocular, high intra-ocular pressure resulting in long-term glaucoma. Animals received bilateral IVT injections of 1x 10^{11} vg/eye of AAV2.22 CBA-eGFP (N=3) or AAV2.22 hSyn-eGFP (N=3). Four weeks post-injection, animals were euthanized, and eyes were fixed in neutral-buffered formalin and assessed for GFP expression using immunohistochemistry. Comparisons were made between normal and glaucomatous eyes and between expression mediated from the two different promoters.

Results

Eyes that had previously received the laser procedure had fewer RGCs and a thinner nerve fiber layer (NFL) than non-lasered eyes. Retinal expression from both vectors was reduced in the glaucomatous eyes compared to normal eyes consistent with loss of RGCs and NFL. The AAV2.22 CBA-eGFP vector transduced cells of the retina and anterior segment in both normal and glaucomatous eyes. Inner and outer nuclear layer (INL, ONL) transduction in the macula was observed in some glaucomatous eyes with severe NFL thinning, but not in normal eyes. AAV2.22 hSyn-eGFP mediated expression was confined to RGCs, NFL and optic nerve in both normal and glaucomatous eyes.

Conclusions

Retinal ganglion cells were able to be transduced in eyes of aged cynomolgus monkeys with or without long term glaucoma. However, GFP expression was reduced in glaucomatous eyes versus normal eyes due to NFL thinning and RGC loss. Differences in expression patterns mediated from the CBA and hSyn promoters were consistent with expectations from a ubiquitous and RGC-specific promoter. Increased INL and ONL transduction was only observed in glaucomatous eyes after intravitreal AAV2.22 CBA-eGFP. This may have been facilitated by the thinned NFL.