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# AAVHSCs, a Nuclease-Independent Approach for Editing of Post-Mitotic Neurons in Non-human Primate Retina and Human Organotypic Explants

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## Introduction

We have previously shown that a subset of AAVHSCs (AAVHSC7, 15 and 17) cross the non-human primate (NHP) blood-retinal (BRB) and blood-brain barriers (BBB) following a single-IV delivery. We have now extended this analysis to a total panel of 11 AAVHSC capsids. AAVHSCs are currently used to edit the genomes of dividing cells in a nuclease-independent manner. Here we extend their utility, using in vivo (NHP) and ex vivo (human retina) studies, to the visual pathways of the central nervous system and investigated whether AAVHSCs can induce genome editing in human disease relevant retinal post-mitotic neurons.

## Methods

We intravenously (I.V. @ 4-7E+13 vgs/kg) dosed a gene transfer construct expressing eGFP in a total of 25 juvenile Cynomolgus macaques confirmed negative for neutralizing clade F antibodies with a panel of 11 AAVHSCs or formulation buffer (FB). We harvested brains and eyes at 2 weeks post-dose and monitored vector genomes by ddPCR and eGFP expression by immunohistochemistry. In addition, two macaques were dosed subretinally (SR @ 1E12 vgs/eye) with AAVHSC15-eGFP or FB. Six human organotypic explants (Lion's Eye) were dosed ex vivo (2.5E11vgs/explant) with AAVHSC-15-eGFP or FB, and 12 human organotypic explants (Lion's Eye) were dosed ex vivo (2.5E11vgs/explant) with AAVHSC15-B2M (edit).

## Results

All AAVHSCs cross the BRB and BBB following a single-IV delivery in NHPs. The majority of AAVHSC capsids transduce retinal cells and key relay points along central visual pathways (retinogeniculate and retinotectal), while regional tropism among capsids allows us to rank and select them to best address diseases of the visual pathways according to their clinical presentation. Following a single-SR dose, AAVHSC15 transduces primarily photoreceptors (PRs) and retinal pigment epithelial cells (RPE). Similarly, PR and RPE cells are transduced following ex vivo dosing of human retinal explants. Using next-generation sequencing, we confirm AAVHSC15-mediated editing of human retinal cell genomes by the AAVHSC15.B2M (edit).

## Conclusion

In vivo (NHP) and ex vivo (human), AAVHSCs are suited to target therapeutically relevant retinal cells. In NHP, AAVHSCs exhibit capsid selectivity along key relay points of the visual pathways. In human organotypic retinal explants, we demonstrate editing in disease relevant cells types via a nuclease-independent manner.