Non-Human Primate Evaluation of an Engineered AAV Capsid for Retinal Cell-Specific and Biofactory-Based Ocular Gene Therapies

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The Leading Edge of Retinal Gene Therapy

High transduction efficiency with easy to administer intravitreal (IVT) injection
- The Dyno eCap 1 capsid transduces the retina 2-3X better than an external engineered IVT capsid and 80X better than AAV2

Demonstrated improvement as a biofactory-based expression capsid
- The Dyno eCap 1 capsid expresses the secreted protein, Aflibercept, 2-3X higher in ocular fluids compared to an externally engineered IVT capsid, matching histology quantification

Broad delivery to key retinal cell types
- The Dyno eCap 1 capsid consistently transduces cell types broadly across retinal layers, including photoreceptors

Consistent NHP results across experiments
- The Dyno eCap 1 capsid histology and snRNA-seq results closely match across multiple NHP experiments

Therapeutically relevant for gene therapies
- Early stage inherited retinal diseases, using gene-augmentation/editing in rod photoreceptors
- Late stage photoreceptor-associated dystrophies, using optogenetic delivery to bipolar or retinal ganglion cells
- Glaucoma, using neuroprotective payloads in retinal ganglion cells
- Wet AMD and GA, using secreted payloads in a biofactory approach

Inquire about licensing the Dyno eCap 1 capsid for your gene therapy program Contact bd@dynotx.com to learn more

Discovery of Dyno eCap 1 by Dyno's Platform

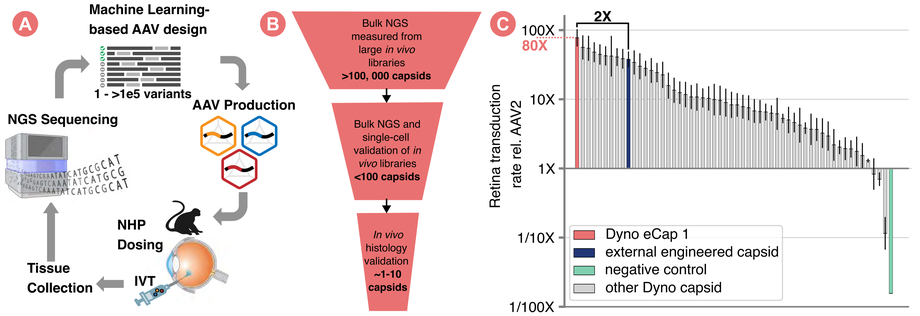


Figure 1. The Dyno eCap 1 capsid was engineered to efficiently transduce cells across the NHP retina using an IVT injection. (A) Dyno's platform combines machine learning and NHP experiments to engineer capsids with transformative properties. (B) Dyno's platform operates at several scales to design capsids with field-leading properties and thoroughly validate them in NHPs. (C) The Dyno eCap 1 capsid transduces major retinal cell types better than leading external engineered IVT capsids and 80x better than AAV2. Error bars show 95% confidence intervals based on SEM across replicates.

Biofactory-Based Expression from Dyno eCap 1

A

Animal	Right Eye	Left Eye
1	Dyno eCap 1- Aflibercept (2.18e11vg)	ext. eng. Aflibercept (3.57e11vg)
2	ext. eng- Aflibercept (3.57e11vg)	Dyno eCap 1- Aflibercept (2.18e11vg)
3	Dyno eCap 1- Aflibercept (2.18e11vg)	AAV2- Aflibercept (3.15e11vg)

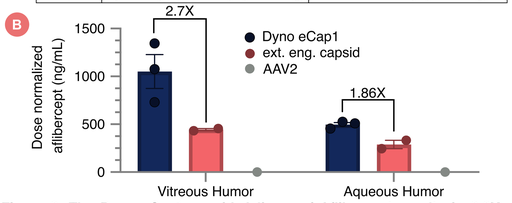
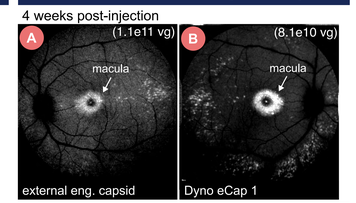


Figure 2. The Dyno eCap1 capsid delivery of Aflibercept results in 2-3X higher Aflibercept concentration in ocular fluids than an ext. eng. capsid. (A) Dosing scheme to compare Dyno eCap 1, ext. eng. capsid and AAV2 biofactory-based potential. (B) Dose normalized ocular fluid aflibercept measurements in the different groups. 1 point is representative of the average measurement quantified in each eye; error bars show SEM. Values below detection threshold are represented as zero value.

In vivo Validation of Dyno eCap 1



C

Animal	Right Eye	Left Eye
#	Capsid 1- Reporter 1 (i.e. GFP) Capsid 2- Reporter 2	Capsid 1- Reporter 2 Capsid 2- Reporter 1 (i.e. GFP)

Figure 3. Transduction of NHP macula and peripheral retina observed by fluorescent fundus imaging. eGFP expression after 4 weeks post-dosing with (A) the external engineered capsid and (B) Dyno eCap 1. (C) Dual capsid dosing scheme to test capsids head to head.

Dyno eCap 1 Transduces NHP Retina 2-3X Better than an External Engineered Capsid, with Greatest Transduction Seen in Photoreceptors, Bipolar Cells and Retinal Ganglion Cells

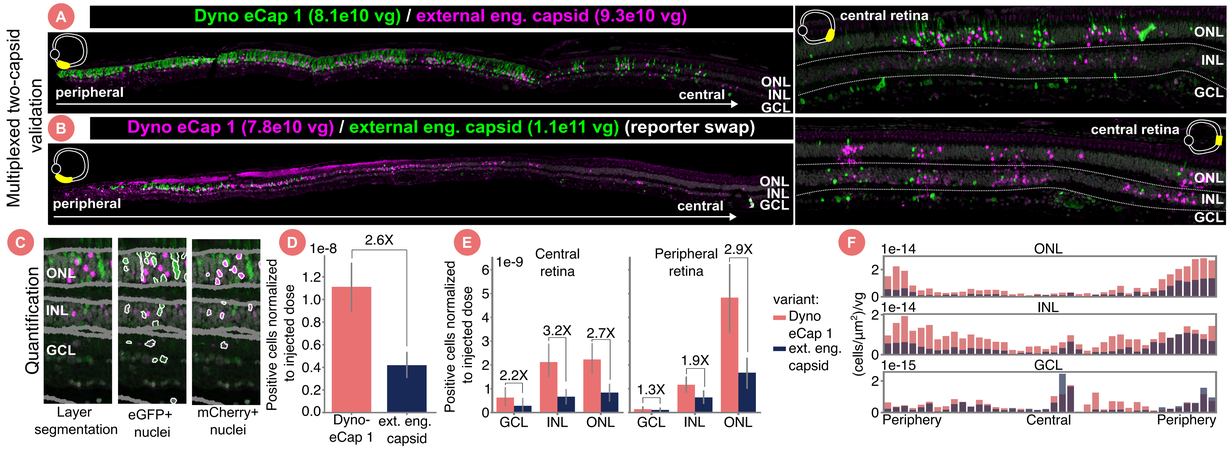


Figure 4. The Dyno eCap 1 capsid transduces up to 3-fold more efficiently than an external engineered capsid across the 3 layers of the NHP neural retina. (A-B) IF staining from co-injection with Dyno eCap 1 and an external eng. capsid with different reporter genes. Reporter genes swapped between (A) and (B). The anatomical location of each image is indicated by the eye schematic. (C-F) Quantification of transduced cells normalized to injected dose across the entire section (D), split by region (E), and plotted as a binned bar graph of transduced cells over area (binned into 40 regions of the same length) across the entire section (F). Pink is Dyno eCap 1 and dark blue is the ext. eng. capsid. Error bars in graphs show SEM.

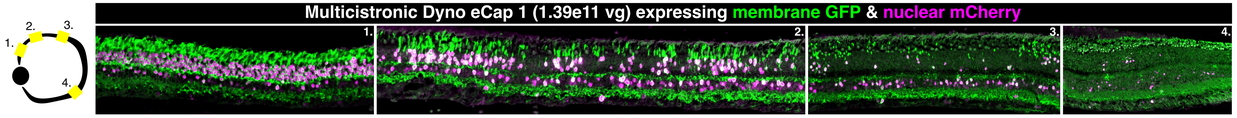


Figure 5. The Dyno eCap 1 capsid transduces the peripheral retina with high efficiency and expands into sparser patches towards the central retina. Eyes were injected with Dyno eCap 1 (1.39e11 vg) packaging a multicistronic reporter expressing membrane localized GFP and nuclear mCherry. The anatomical location of each image is indicated by the eye schematic.

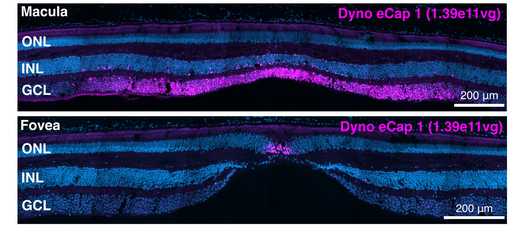


Figure 6. The Dyno eCap 1 capsid transduction in the macula is predominantly in retinal ganglion cells. In the fovea, transduction is seen in photoreceptors indicating differential transduction in different regions of the macula.

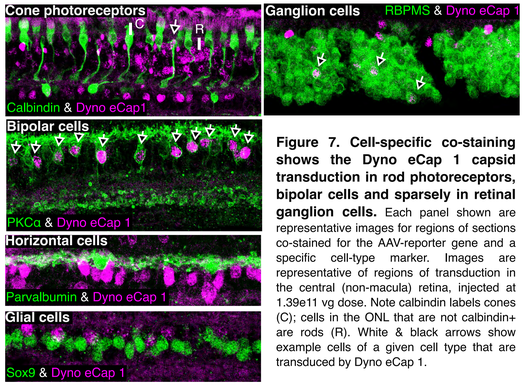


Figure 7. Cell-specific co-staining shows the Dyno eCap 1 capsid transduction in rod photoreceptors, bipolar cells and sparsely in retinal ganglion cells. Each panel shown are representative images for regions of sections co-stained for the AAV-reporter gene and a specific cell-type marker. Images are representative of regions of transduction in the central (non-macula) retina, injected at 1.39e11 vg dose. Note calbindin labels cones (C); cells in the ONL that are not calbindin+ are rods (R). White & black arrows show example cells of a given cell type that are transduced by Dyno eCap 1.

snRNA-seq Highlights Cell Transduction for Dyno eCap 1 is Consistent with Histology

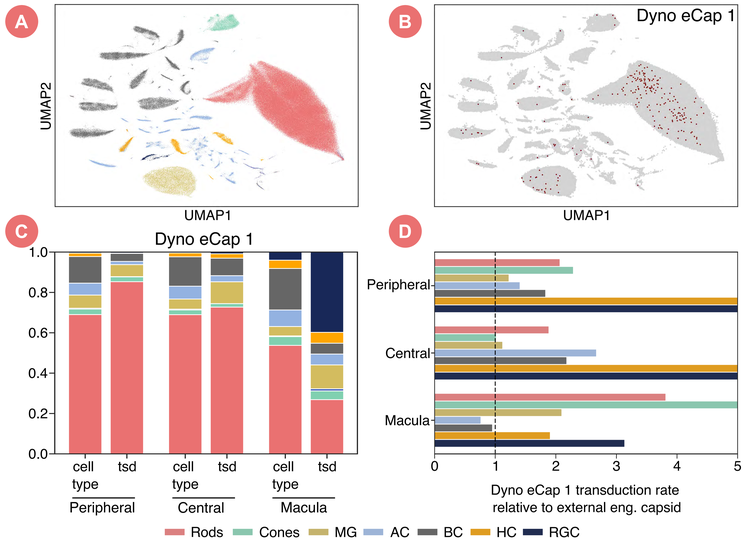


Figure 8. Transduction in NHP retina, measured by snRNA-seq, demonstrates cell type specificity of Dyno eCap1 consistent with histology. Transduction by the Dyno eCap 1 capsid, quantified from snRNA-seq, is 2-3 fold higher than an external engineered capsid across retinal cell-types and regions. (A) UMAP projection of 320,000 retinal cells from central retina and (B) overlay of cells expressing transgene delivered by Dyno eCap 1 capsid. (C) Fraction of cells in each cell type in given retinal regions, compared to the fraction of cells transduced by Dyno eCap 1 (tsd) in those regions. (D) Fold-change improvement in transduction of Dyno eCap 1 capsid to an external eng. capsid for each cell type. Color legend for (A, C and D) is shown below graphs. MG= Müller glia, AC= amacrine cell, BC= bipolar cell, HC= horizontal cell, RGC= retinal ganglion cell.