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Preclinical Studies Support Intravitreal Gene Therapy for Blue Cone Monochromacy

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Disclosures

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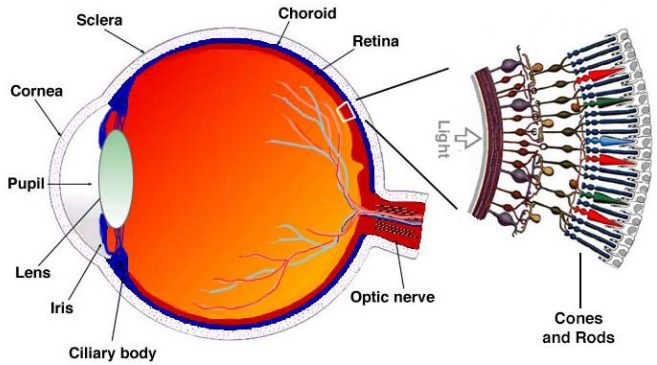
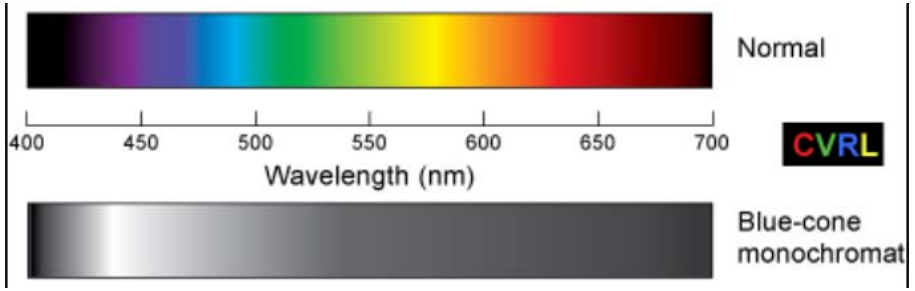
Blue Cone Monochromacy

Retinal Dystrophy

- Rare recessive X-linked inherited condition
- Mutations in genes for M- and L-opsin, proteins required for middle and long-wavelength cone photoreceptor function
- Symptoms:
  - Severe myopia and other refractive errors
  - Photophobia
  - Inability to distinguish colors
  - Involuntary eye twitching (nystagmus) in early childhood
- Onset in infancy, mostly non-progressive, older patients can develop central retinal atrophy
- Gene therapy aimed to restore opsin expression in foveal cones is considered as a potential treatment. However, subfoveal injection of vector poses a risk to the fragile central retinal structure in BCM patients
- **At present, there is no available treatment nor registered clinical trials for treatment of BCM** (clinicaltrials.gov)





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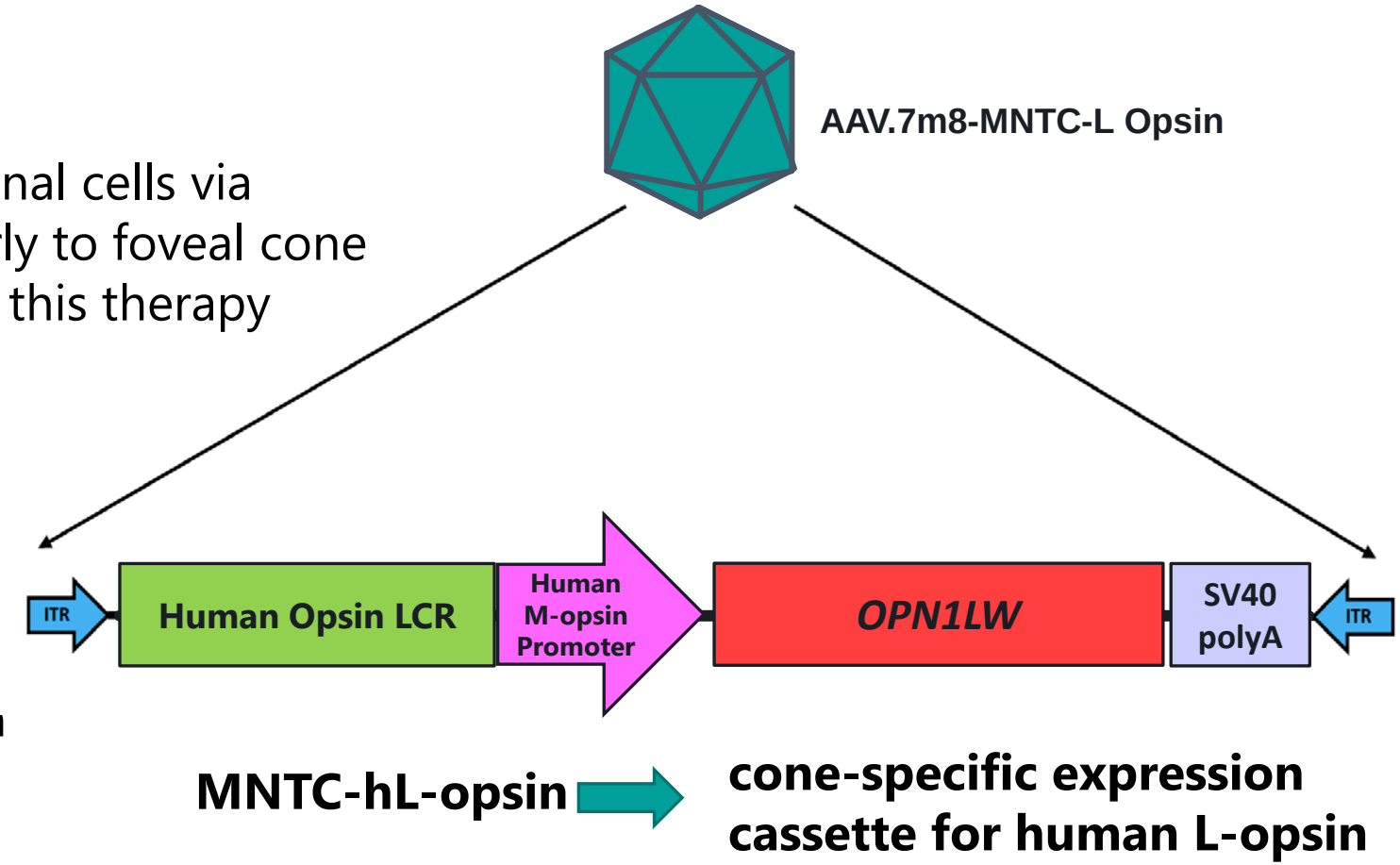
ADVM-062: A Combination of Efficient Tools to Develop a Therapy for BCM

AAV Vector amenable for IVT delivery

AAV.7m8 Capsid:

- AAV.7m8 variant of AAV2
- Exhibits robust tropism for retinal cells via intravitreal injection, particularly to foveal cone photoreceptors, target cells of this therapy



Proprietary cone-specific promoter

MNTC expression cassette:

- Designed to provide cone-restricted expression of human L-opsin

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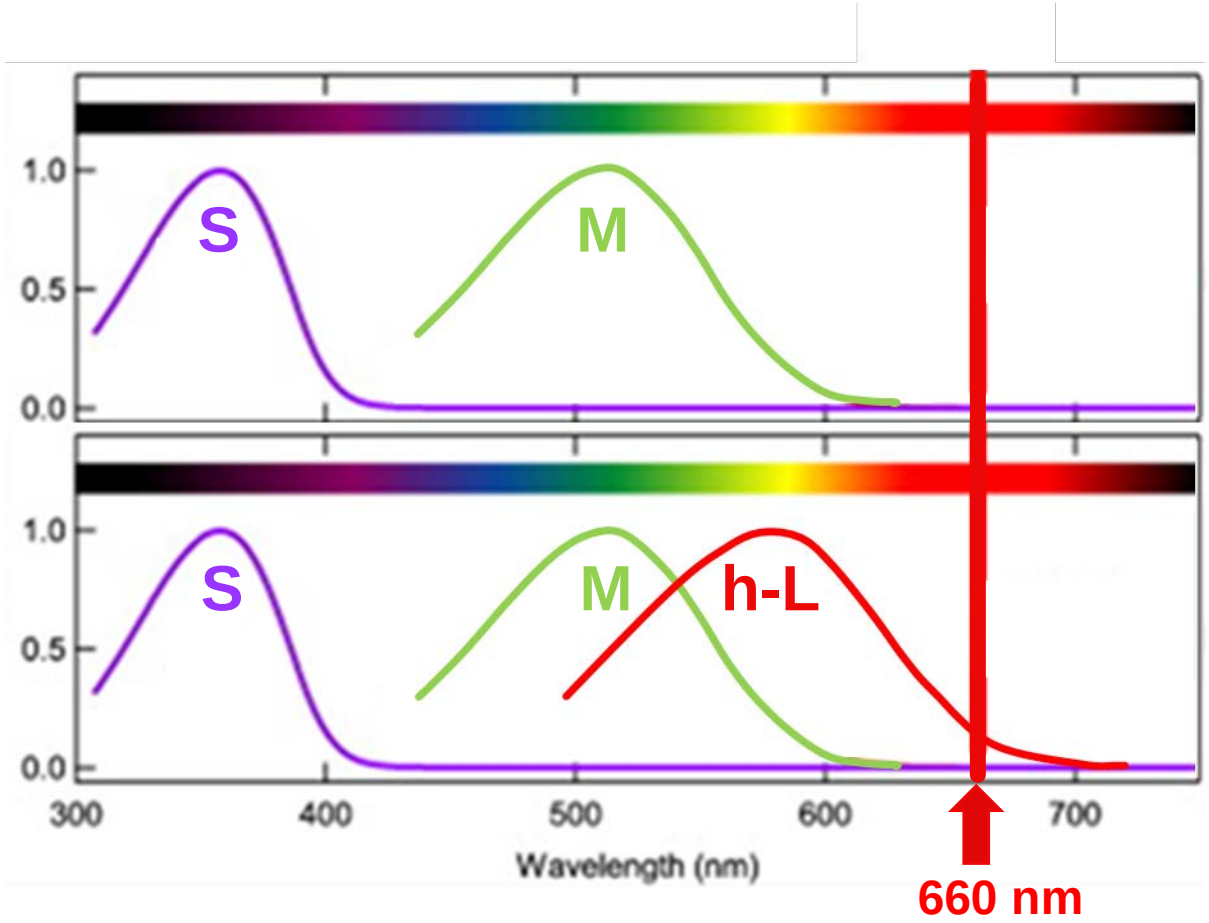
Rationale for Functional Evaluation of ADVM-062 in Dichromatic Rodents



Control mouse retina

ADVM-062

ADVM-062-treated mouse retina

I. Mouse vision is dichromatic, M- and S-cones only

II. Hypothesis: Functional expression of L-opsin from ADVM-062 may expand retinal spectral sensitivity to long wavelength light

III. Color ERG photostimulator was customized with 660 nm LED, to rectify human L-opsin driven responses from native mouse opsins

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Study Protocol

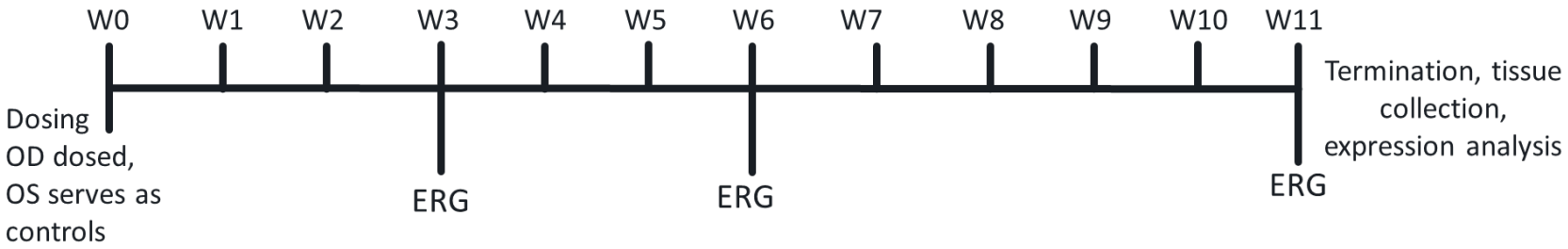
Animal model: C57B/6 mice, males.

Treatment Groups

Groups	Test Article	N. mice /group	Dose (vg/eye)
1	ADVM-062	18	$1.3x10^{11}$, OD only
2	ADVM-062.myc	18	$1x10^{11}$, OD only
3	Vehicle	4	n/a, OD only

Functional assessment by ERG: Stimuli: 660 nm flashes in the presence of a ganzfeld background of 513 nm and varying intensities. Cone-isolating 25 Hz flicker ERG responses to 660 nm flashes were also recorded.

Localization of the transgenic human L-opsin was evaluated using myc-immunofluorescence in the eyes treated with ADVM-062-myc



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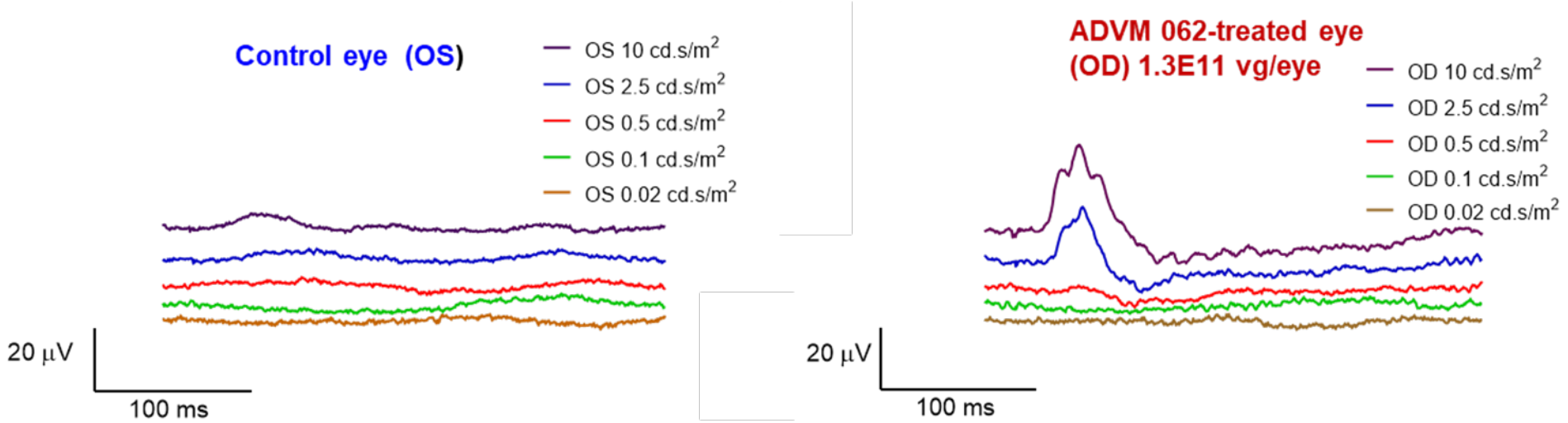
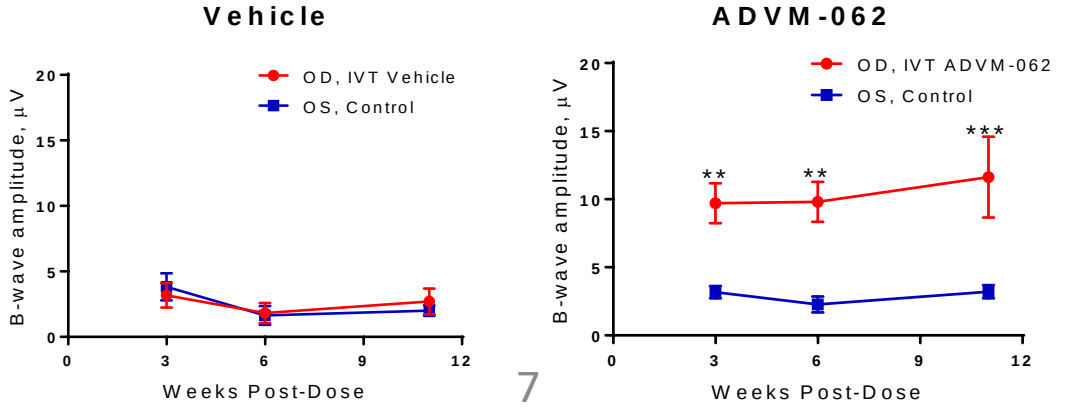
Single IVT Dose of ADVM-062 Significantly Increases Mouse Retina Sensitivity to Long-Wavelength Light

ERG responses to a range of long wavelength light intensities (660 nm)



Durability of ADVM-062 –mediated retina sensitivity to long-wavelength light



** P<0.01
***P<0.001
Two-way ANOVA with Sidak's multiple comparisons test

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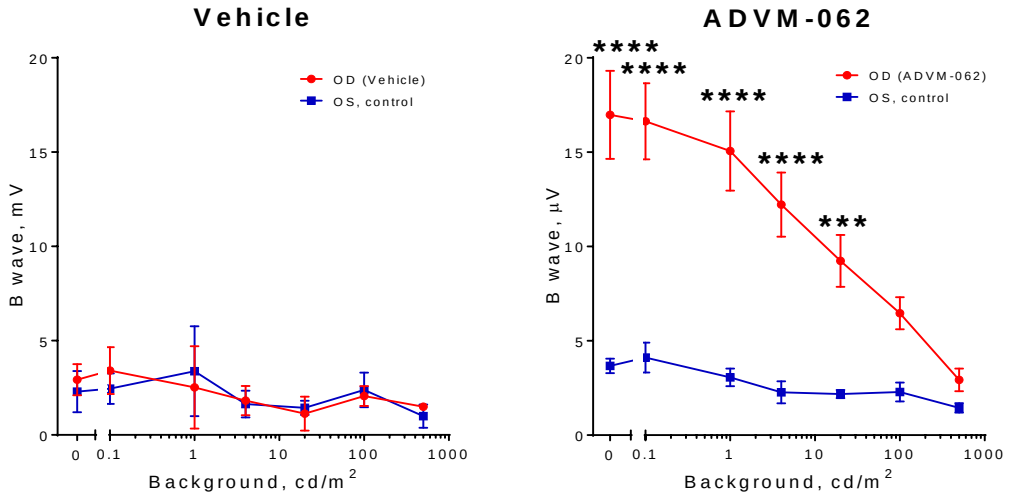
IVT ADVM-062 Sensitizes ERG Responses to Long Wavelength (660 nm) Light Under Cone-Isolating Conditions

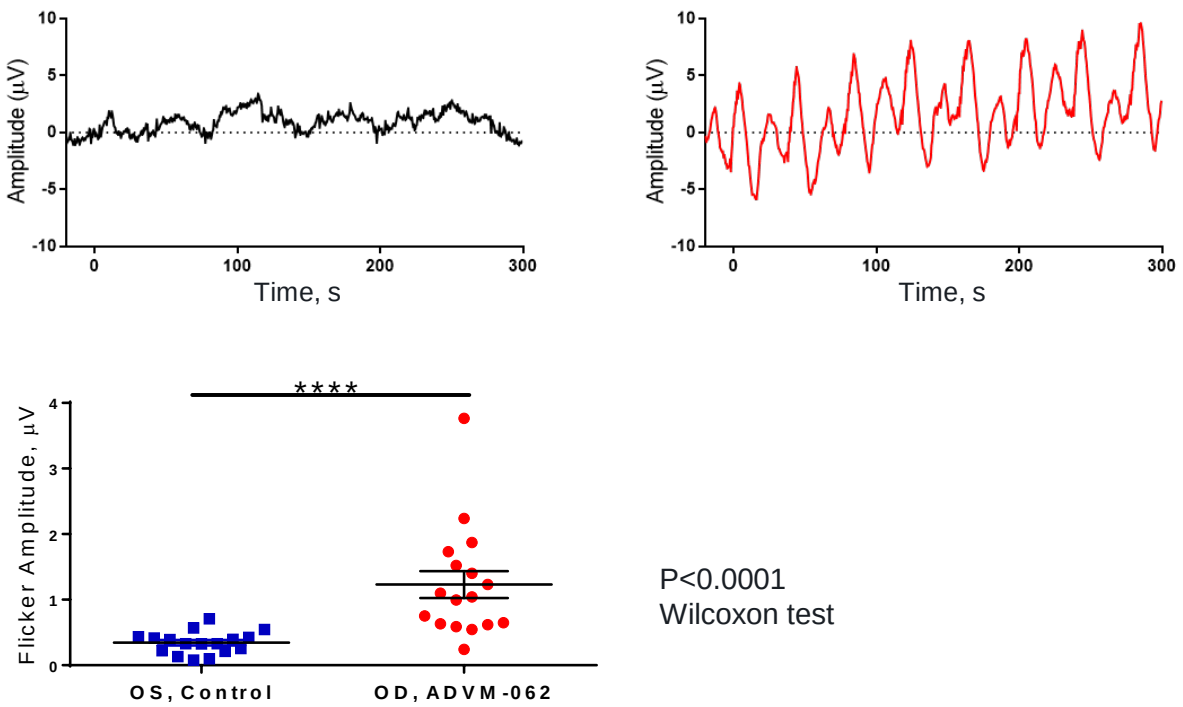
ERG responses to 660 nm light stimulus at 10 cd.s/m^2 measured at different intensities of rod/M-cone desensitizing background (513 nm)



**** P<0.0001; *** P<0.001
RM-2way ANOVA followed by Sidak's post-hoc test

ADVM-062 strongly increases ERG responses to 660 nm 25 Hz flicker

Control, OS **ADVM-062, OD**



P<0.0001
Wilcoxon test

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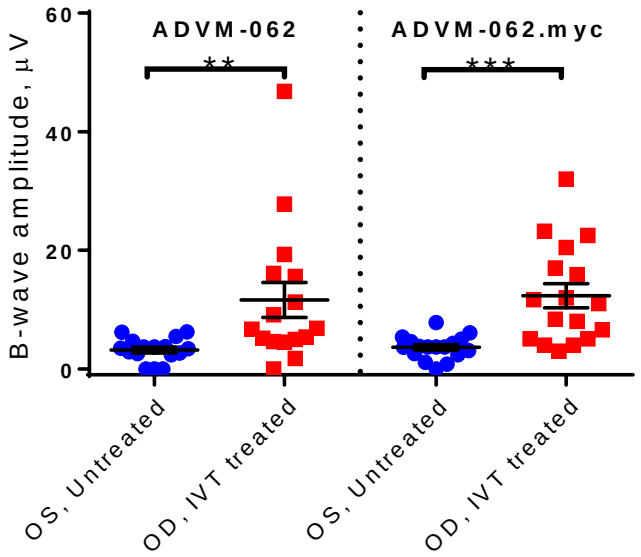
ADVM-062.myc Demonstrates Strong Transduction And Cone-Restricted Expression of Human L-opsin in Mouse Cones

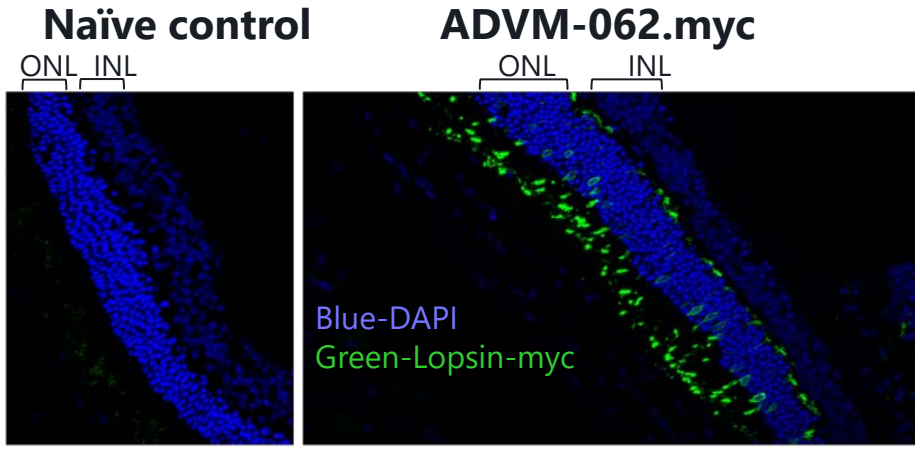
ADVM-062 and ADVM-062.myc similarly augment long wavelength sensitivity of mouse retina



ERG b-wave amplitudes recorded in the eyes IVT treated with ADVM-062 (1.3E11 vg/eye) and ADVM-062.myc (1.0E11 vg/eye)

** P<0.01, ***P<0.001 Wilcoxon test

ADVM-062.myc vector made to detect localization of human L-opsin shows cone-restricted L-opsin expression



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Conclusions

- A single intravitreal dose of ADVM-062 effectively transduces murine cone photoreceptors and produces a *de novo* response to long wavelength stimuli.
- Intravitreal injected ADVM-062 provides expression of human L-opsin in mouse retina exclusively in cones.
- Functional expression was detected 3 weeks after injection and lasted for at least 11 weeks.
- Findings support practicality of AAV7m8 capsid-based vectors for delivery of cone-targeting gene therapy via intravitreal route.
- Findings support further evaluation of ADVM-062 as a potential intravitreally-delivered gene therapy for BCM patients.

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For more information on the AAV.7m8 platform and gene therapy development at Adverum Biotechnologies, please visit the following presentations at ARVO 2020:

- For new data from the ongoing OPTIC Phase 1 trial of ADVM-022 gene therapy in wet AMD, please visit **Dr. Khanani's talk.**
- For the study that demonstrates additional versatility of AAV.7m8 as a platform for intravitreal gene therapy, please see presentation of **Dr. Kristina Oresic Bender.**

THANK YOU

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