Intravitreal AAV.7m8 delivery of ranibizumab suppresses laser induced choroidal neovascularization in non-human primates

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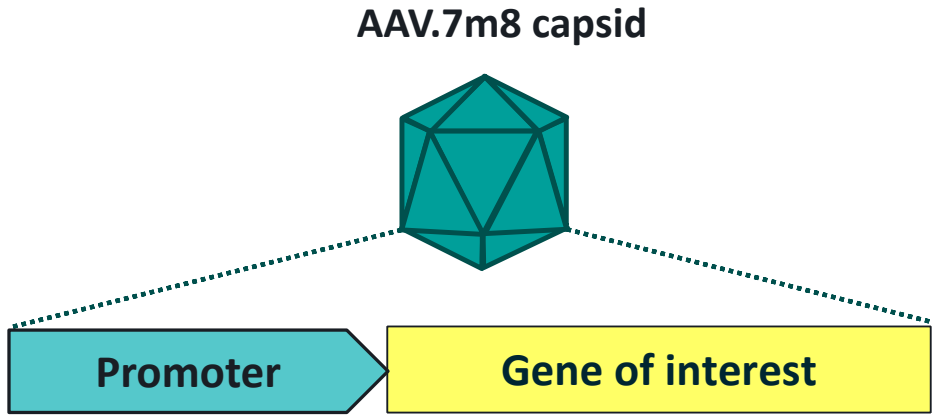
Disclosures

- Kristina Oresic Bender, Ruslan Grishanin, Aivan Nguyen, Pallavi Sharma, Judith Greengard, Claire Gelfman: Employees of Adverum Biotechnologies
- Szilard Kiss and Mehdi Gasmi: Consultants of Adverum Biotechnologies

AAV.7m8: Capsid Engineered for AAV Gene Therapy

- Adverum proprietary AAV.7m8 capsid, a variant of AAV2, discovered by directed evolution (UC Berkeley)
- Screened for highly efficient retinal transduction following intravitreal injection



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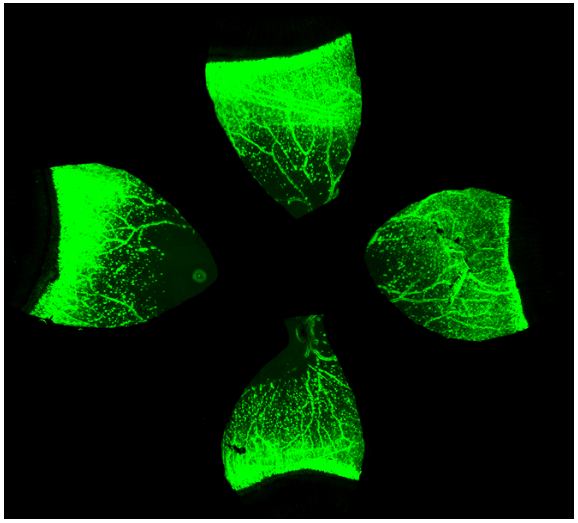
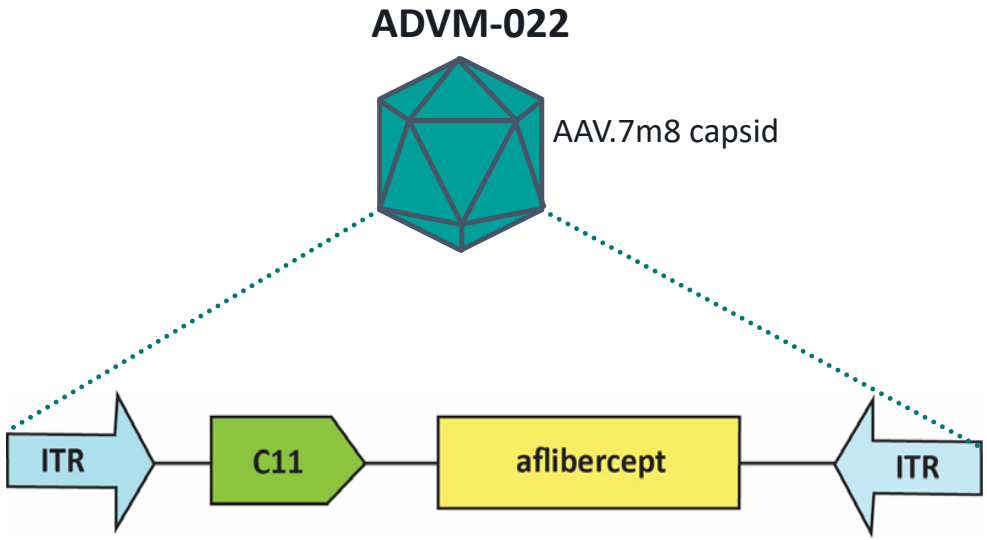
AAV.7m8: Robust Retinal Cell Tropism

- Exhibits robust tropism for retinal cells via intravitreal injection[1, 2, 3]



C11 cassette (with ubiquitous promoter) driving green fluorescent protein expression in non-human primate retina[1]

- AAV.7m8 capsid used in the engineering of ADVM-022 (OPTIC Clinical Trial)



C11=> proprietary, **strong ubiquitous expression cassette**

1. Grishanin, R. et al. Mol Ther 2019;27:118
2. Ramachandran PS, et al. Hum Gene Ther 2017;28:154
3. Dalkara, D. et al. Sci Transl Med 2013; 5:189

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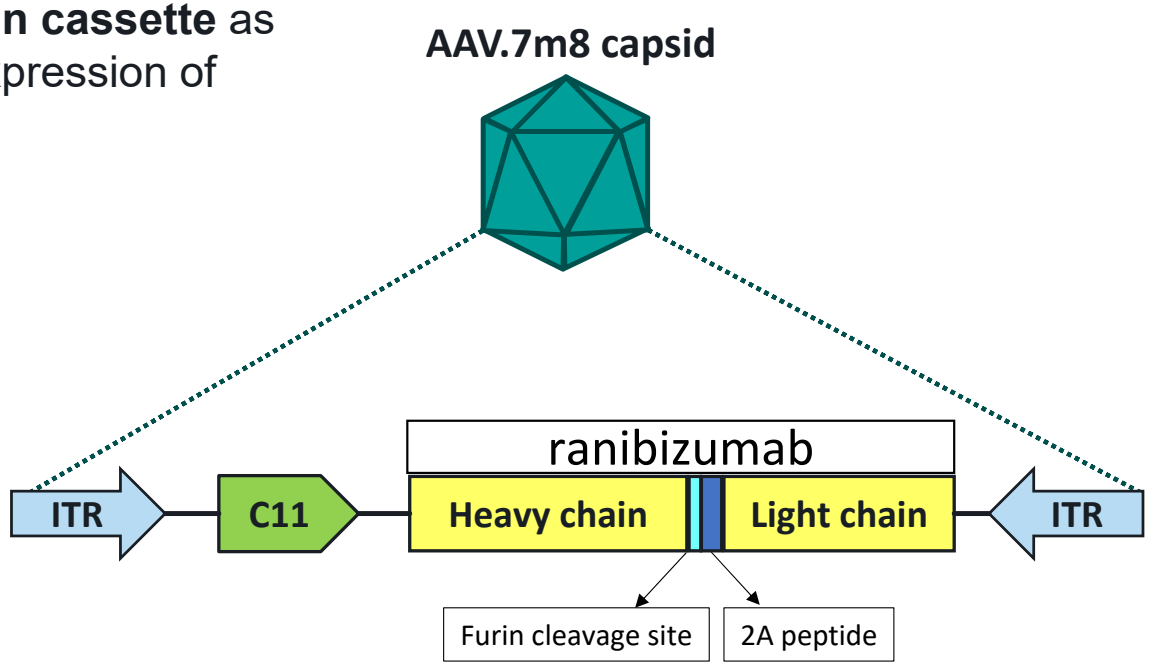
AAV.7m8.ranibizumab

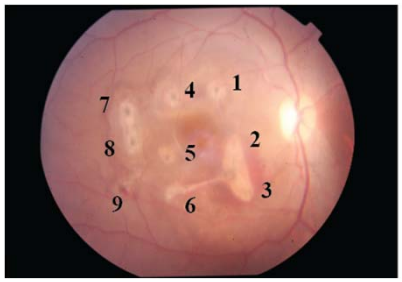
- Uses the same proprietary C11=> **strong ubiquitous expression cassette** as ADVM-022, to drive expression of ranibizumab



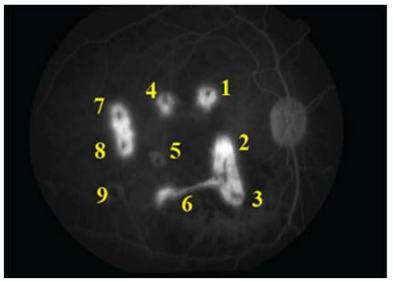
Evaluation of IVT AAV.7m8.ranibizumab in Laser-Induced CNV in Non-human Primates[1]

- Parameters assessed in the study:
  - Efficacy
  - Expression levels and durability
  - Safety

Color fundus photograph



Fluorescent angiogram



A laser-induced in vivo model of CNV uses photocoagulation to disrupt Bruch's membrane, inducing the growth of new choroidal vessels into the subretinal area, and as such mimics certain aspects of neovascular (VEGF-driven) retinopathies.

[1]Goody, RJ et al. Exp Eye Res 2011; 92(6):464

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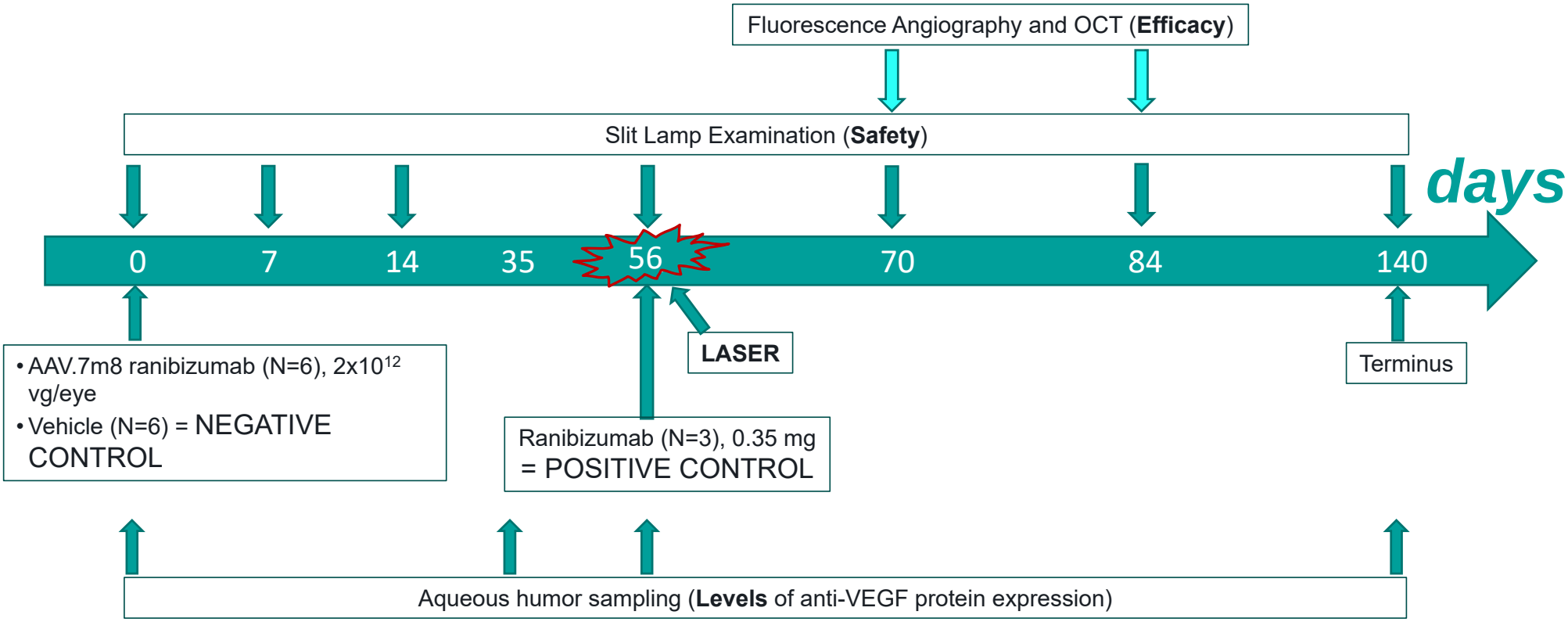
Study Design: IVT AAV.7m8.ranibizumab in Laser-Induced CNV in Non-human Primates



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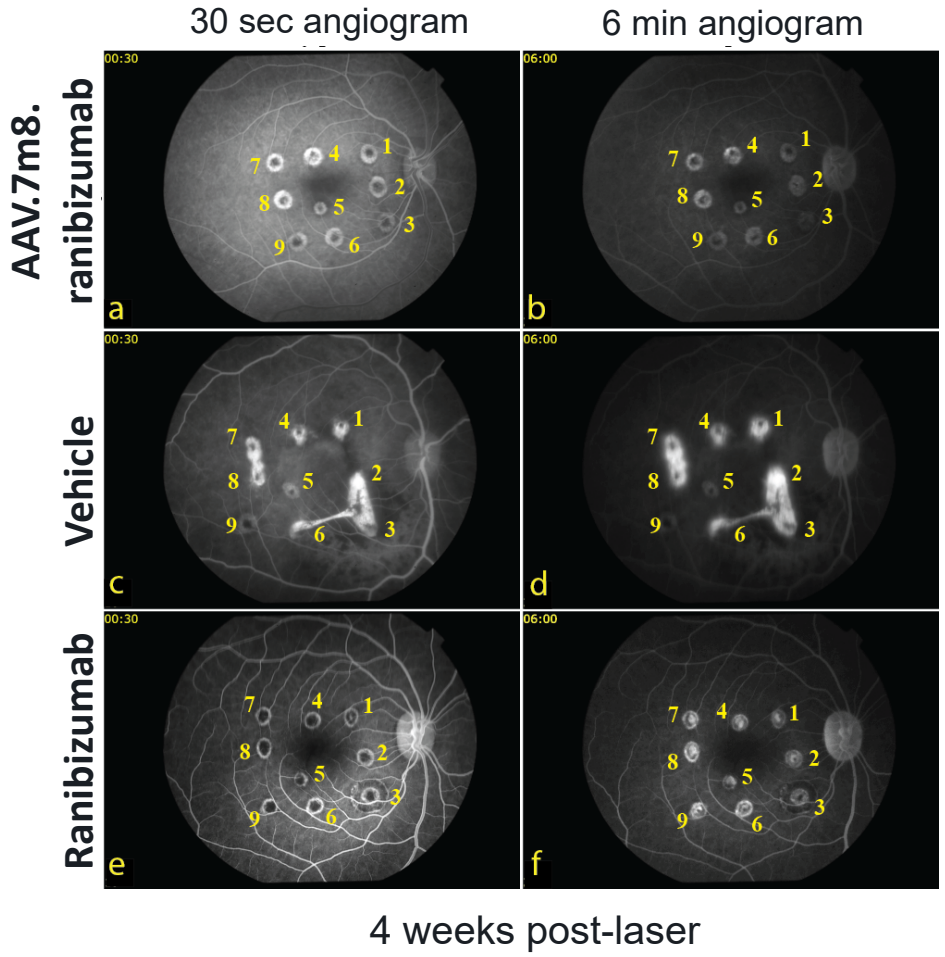
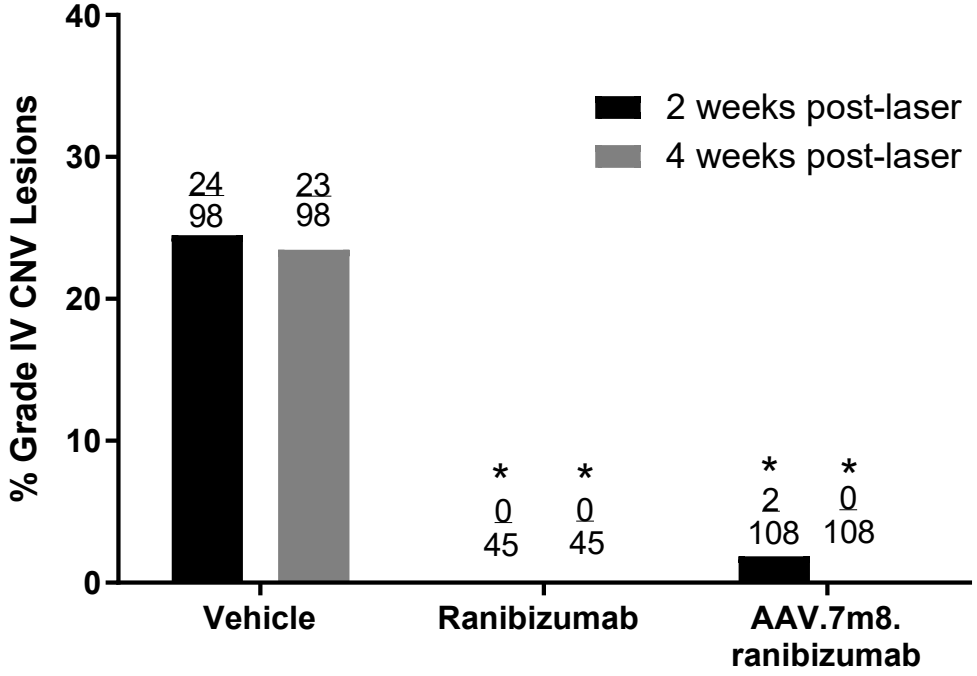
Single Intravitreal Injection of AAV.7m8.ranibizumab Reduces Incidence of Grade IV Lesions





*p < 0.0001, Fisher's exact test

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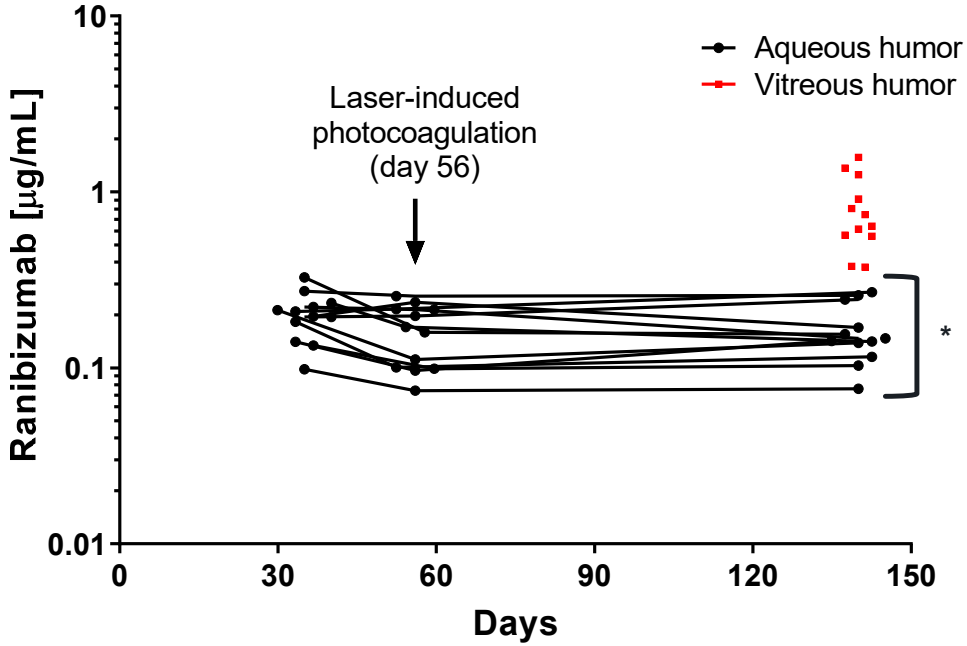
Single Intravitreal Injection of AAV.7m8.ranibizumab Results in Sustained Levels of Ranibizumab Expression in Ocular Fluids



* Same aqueous levels of ranibizumab observed between 2 and 3 weeks post intravitreal injection of recombinant protein in non-human primates (Niwa et al. IOVS. 2015; 56(11):6501)

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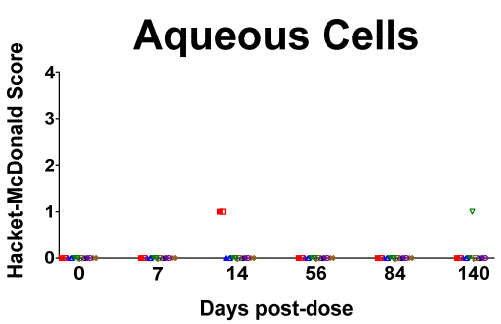
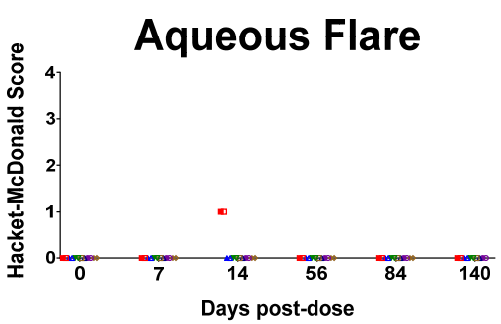
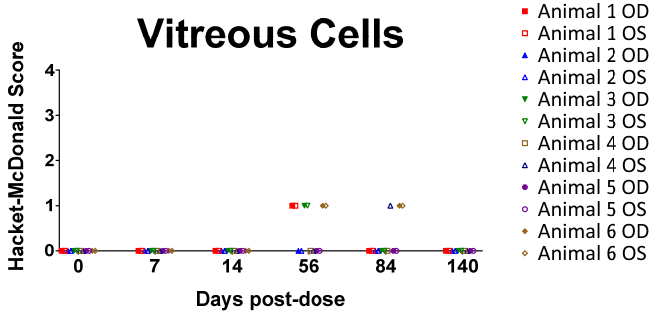
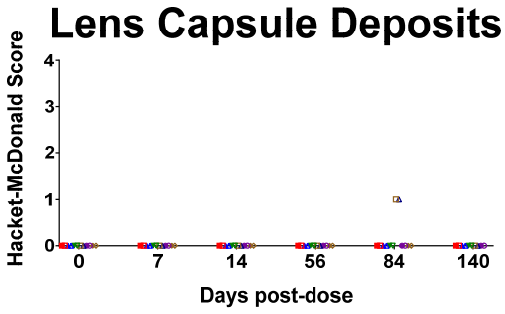
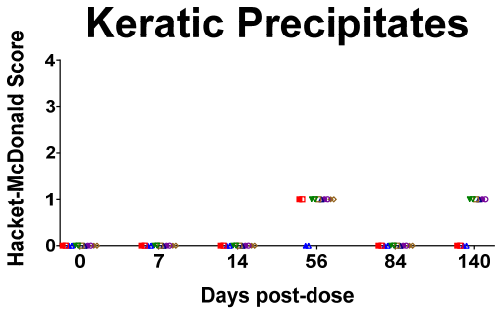
Single Intravitreal Injection of AAV.7m8.ranibizumab is Well-Tolerated in Non-human Primates

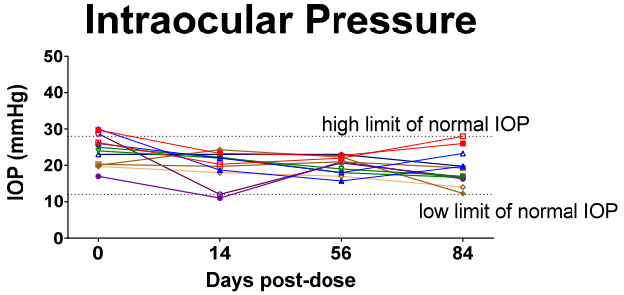








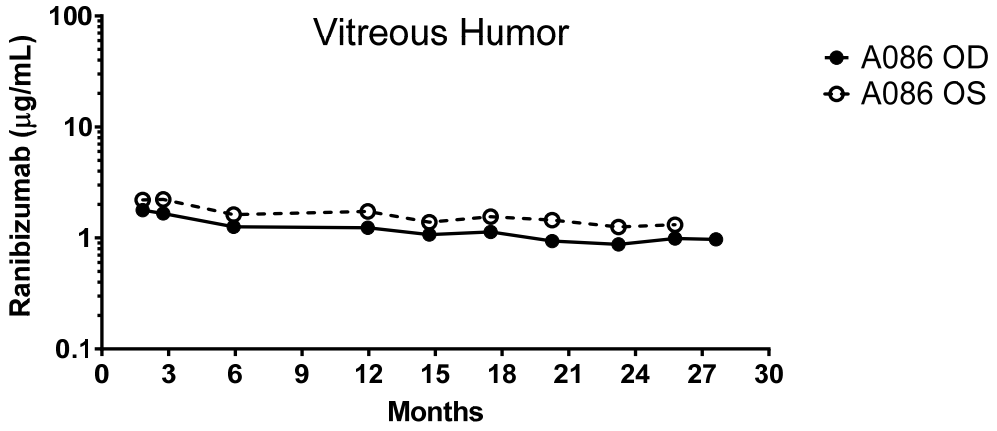


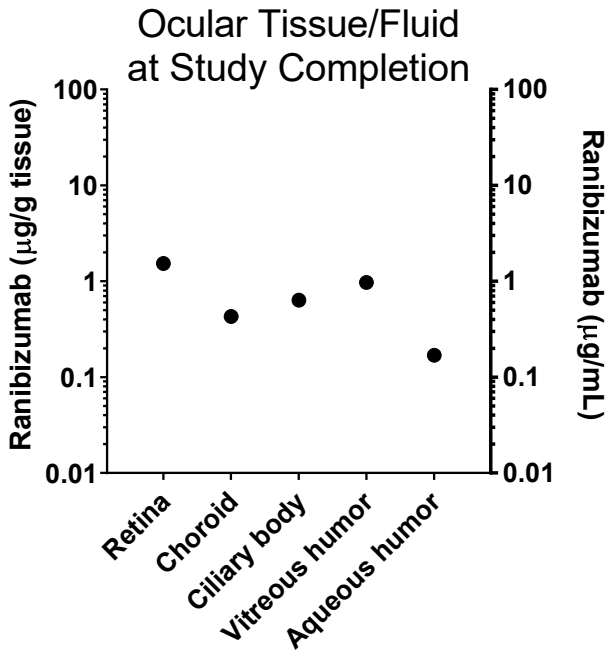


No vitreous haze at any point of the study.

Single Intravitreal Injection of AAV.7m8.ranibizumab Results in Sustained Levels of Ranibizumab Expression

Additional Long Term (28-Month) Study*





* Single animal from a separate study received intravitreal injection of AAV.7m8.ranibizumab ($2x10^{12}$ vg/eye, OU) and followed for 28 months.

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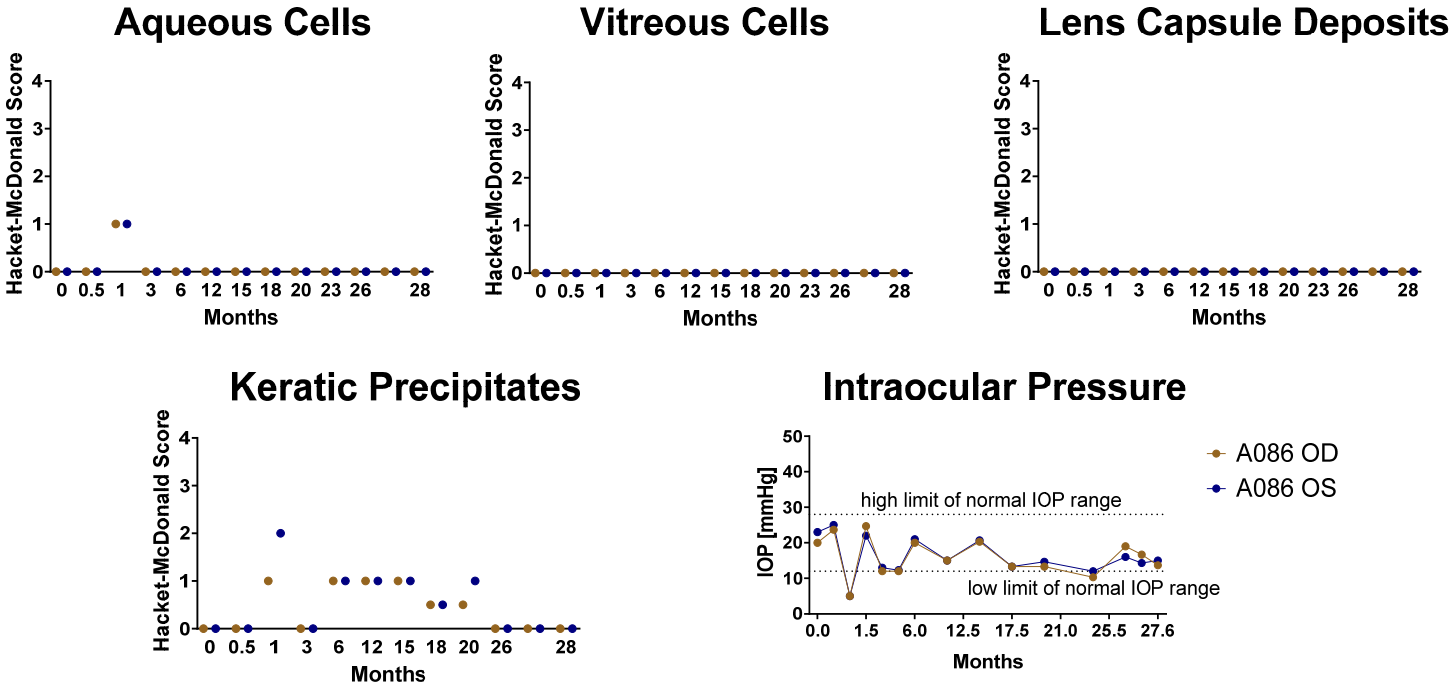
Intravitreal Injection of AAV.7m8.ranibizumab is Well-Tolerated

Additional Long Term (28-Month) Study*



No aqueous flare or vitreous haze at any point of the study.

* Single animal from a separate study received intravitreal injection of AAV.7m8.ranibizumab ($2x10^{12}$ vg/eye, OU) and followed for 28 months.

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Conclusion:

- In this study we have shown that:
  - AAV.7m8 could be used to deliver therapeutically relevant levels of ranibizumab via single intravitreal injection.
  - These levels were sufficient to suppress levels of clinically relevant grade IV lesions in non-human primate model of laser-induced CNV.
  - AAV.7m8.ranibizumab with a strong ubiquitous C11 cassette resulted in durable protein expression and was well tolerated.

This study demonstrates the utility of AAV.7m8 as an effective gene therapy platform for the **intravitreal delivery of therapeutic proteins to the human retina** for the treatment of ocular diseases.

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For more information on how we leverage AAV.7m8 platform:

- To deliver aflibercept protein in patients with nAMD (**ADVM-022**), please visit **Dr. Khanani's Talk;**
- To deliver genes under a cell specific promoter (cone photoreceptor) and drive targeted and cell specific expression of proteins, please visit **Dr. Grishanin's Talk, both at ARVO 2020 website.**

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Gaining momentum in gene therapy

THE END