A Multi-Mechanistic Anti-Angiogenic AAV Gene Therapy Product Candidate, 4D-150, for the Treatment of Wet Age-Related Macular Degeneration (Wet AMD) and Diabetic Macular Edema (DME): Intravitreal Biodistribution, Transgene Expression, Safety and Efficacy in Non-Human Primates

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Presenter Disclosures

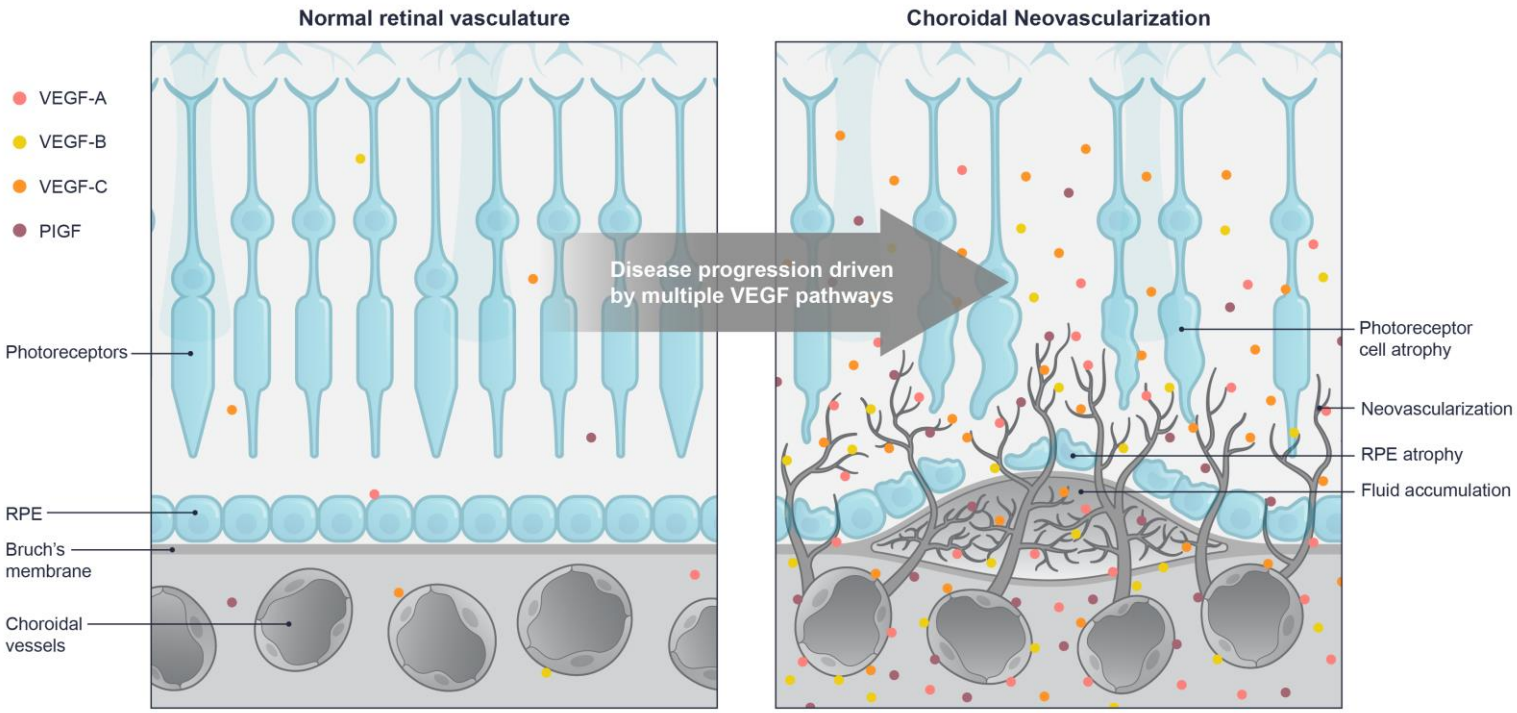
- Chief Scientific Officer & a full-time employee at 4D Molecular Therapeutics, Inc.

- Inventor on patents and pending patent applications related to AAV capsid variants and AAV gene delivery.

Disease Background & Current Treatment

DURABLE EXPRESSION BY AAV GENE THERAPY HOLDS PROMISE

- Wet Age-Related Macular Degeneration (wet AMD)
- Diabetic Macular Edema (DME)
- Both Associated With:
  - Retina swelling & edema
  - Bleeding
  - Reduced visual acuity
- Stimulated by VEGF family members:
  - A, B & C isoforms & PlGF
- Current treatment:
  - IVT injection of anti-VEGF proteins



Abbreviations: VEGF, vascular endothelial growth factor; RPE, retinal pigment epithelium.

4D-150 for Wet AMD & DME

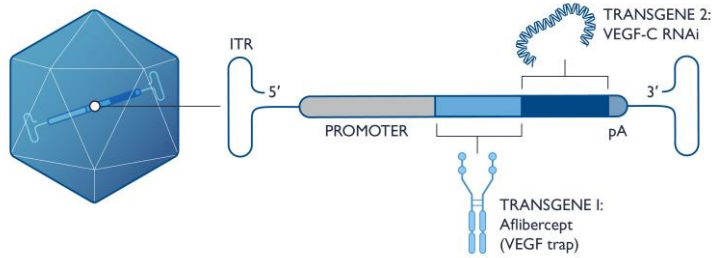
DUAL TRANSGENE, INTRAVITREAL GENE THERAPY INHIBITING FOUR DISTINCT VEGF FAMILY MEMBERS

HIGH UNMET MEDICAL NEED

- Frequent Injections
- Patient / Physician Adherence Issues
- Incomplete Responders

EPIDEMIOLOGY: US

- **Wet AMD: ~200,000/yr** incidence
- **DME: ~1.2M** prevalence



PRODUCT DESIGN

- **Vector:** R100
- **Transgene 1:** Aflibercept
- **Transgene 2:** VEGF-C RNAi
- **Promoter:** Ubiquitous

DIFFERENTIATION

Transduces Entire Retina Surface
Routine & Safe
One-time Intravitreal Administration
Inhibits 4 Targets

STATUS:

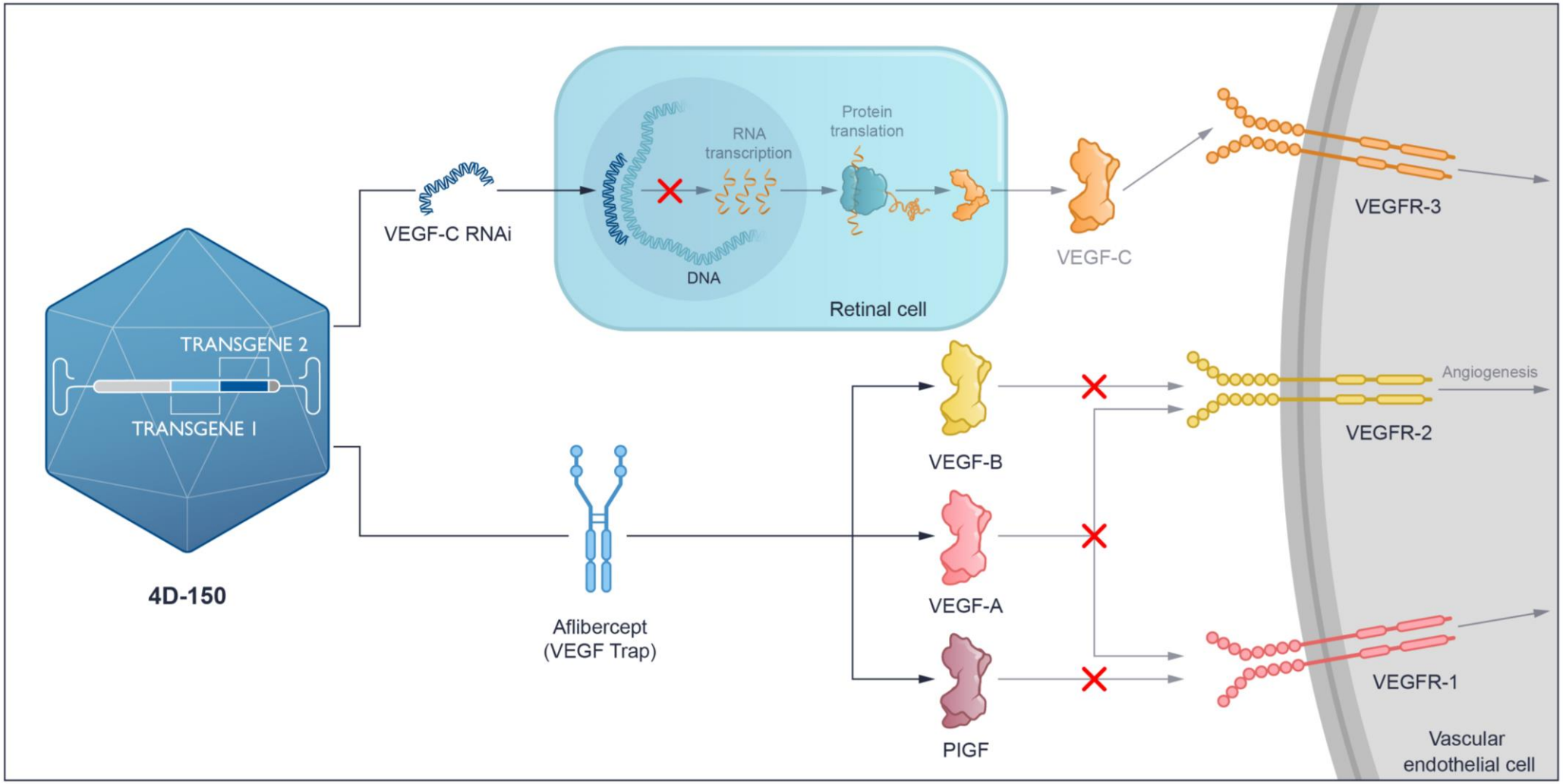
IND-Enabling Studies

EXPECTED MILESTONE:

Initiate Clinical Trial in 2H21

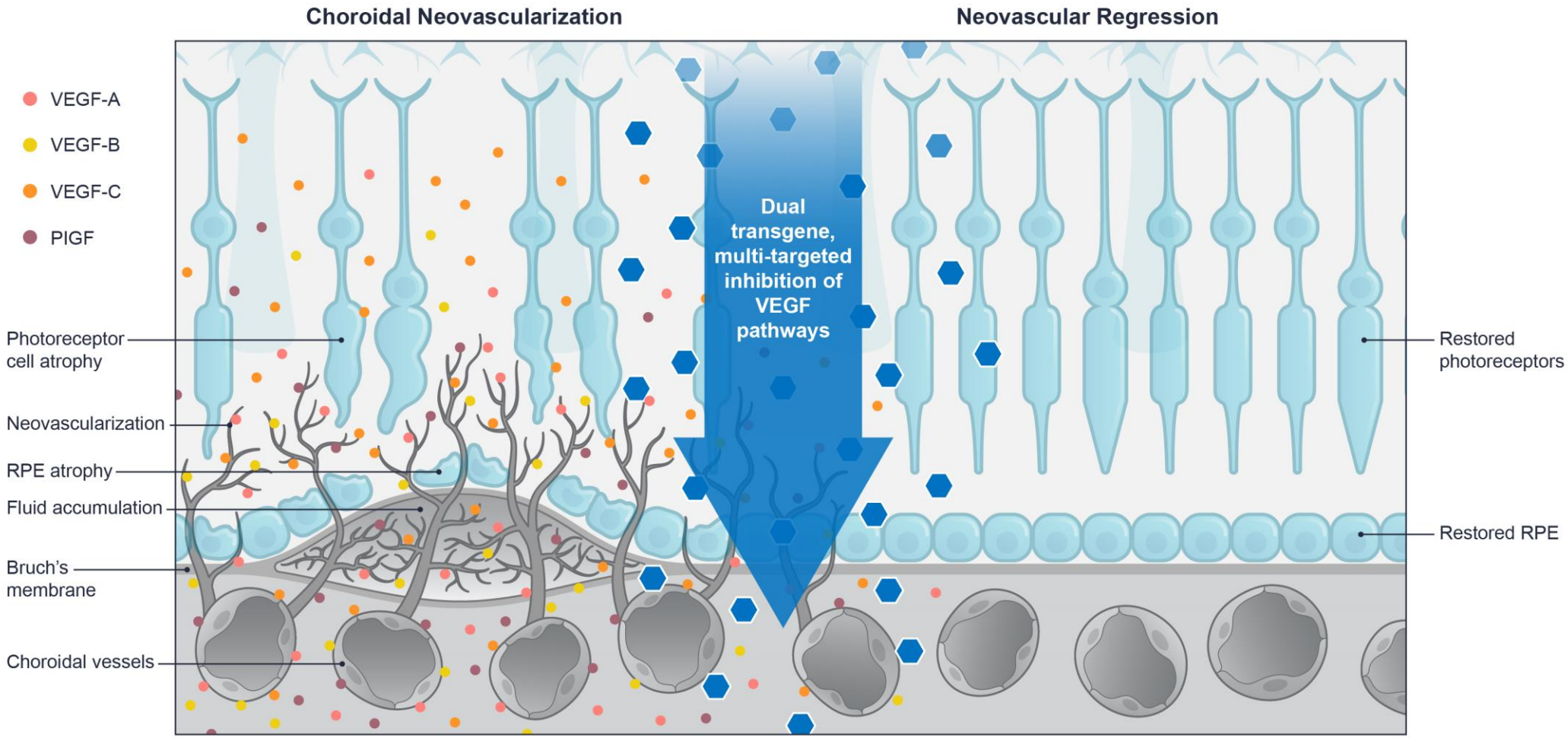
4D-150 Multi-Mechanistic Gene Therapy for Wet AMD & DME

DUAL TRANSGENE, INTRAVITREAL GENE THERAPY INHIBITING FOUR DISTINCT VEGF FAMILY MEMBERS



Abbreviations: VEGF, vascular endothelial growth factor; RPE, retinal pigment epithelium.

4D-150 Designed to Induce Regression of Neovascularization & For Resolution of Edema

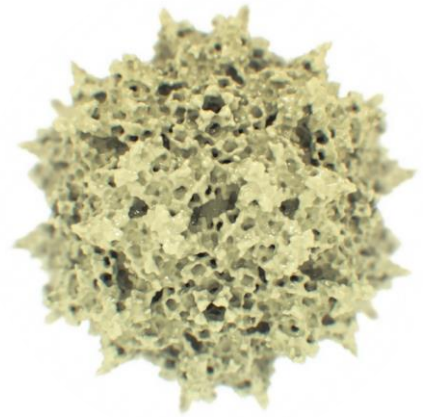


Abbreviations: VEGF, vascular endothelial growth factor; RPE, retinal pigment epithelium.

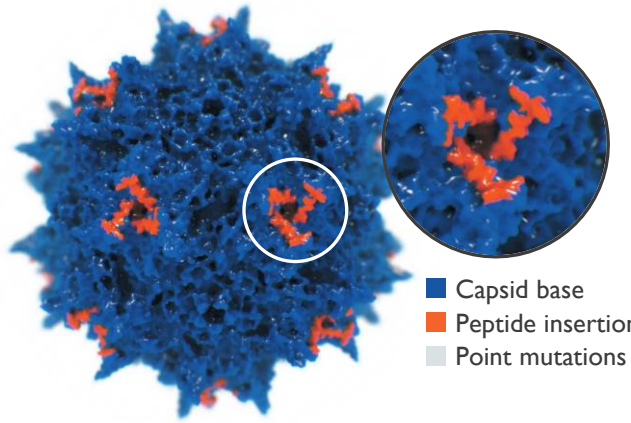
R100 Structure & Target Vector Profile

INTRAVITREAL DELIVERY FOR RETINAL DISEASES

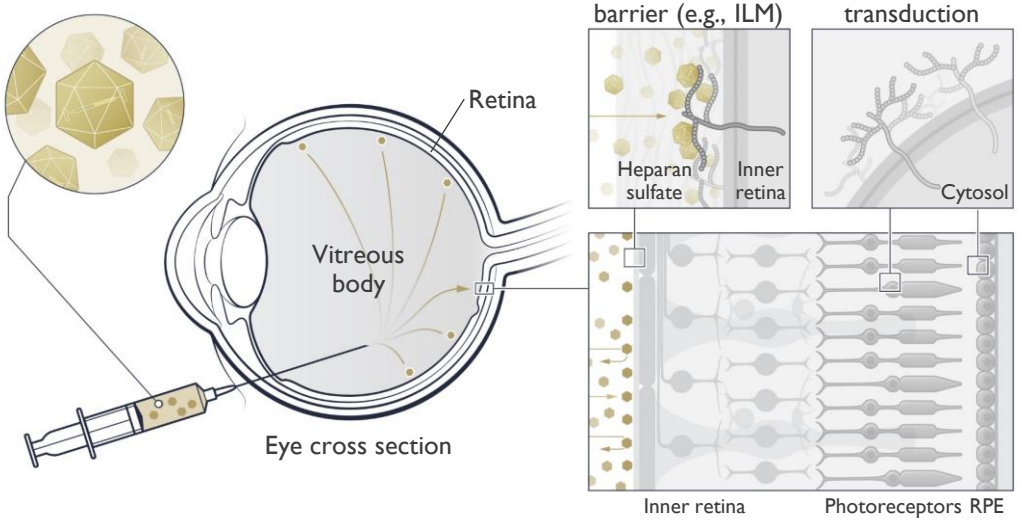
Naturally occurring capsid



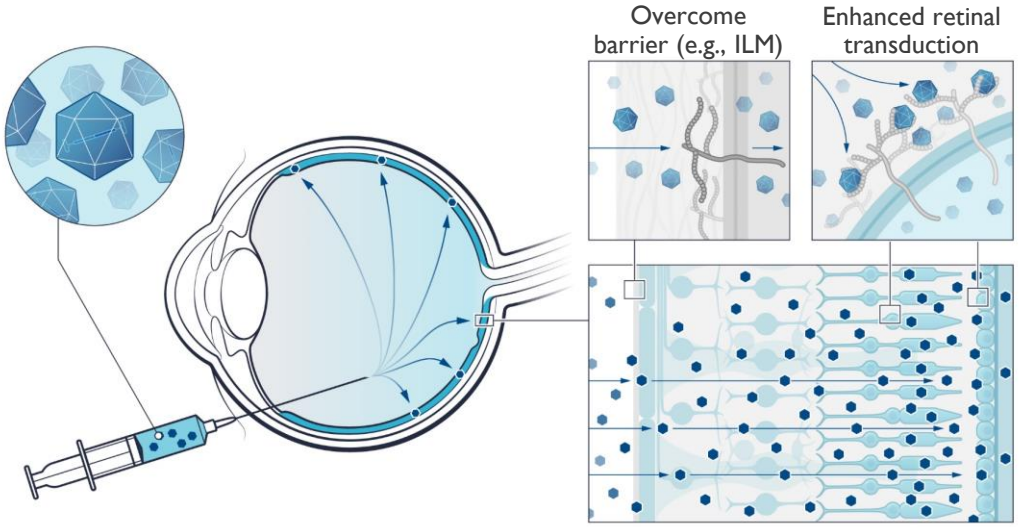
R100



Conventional naturally occurring vectors



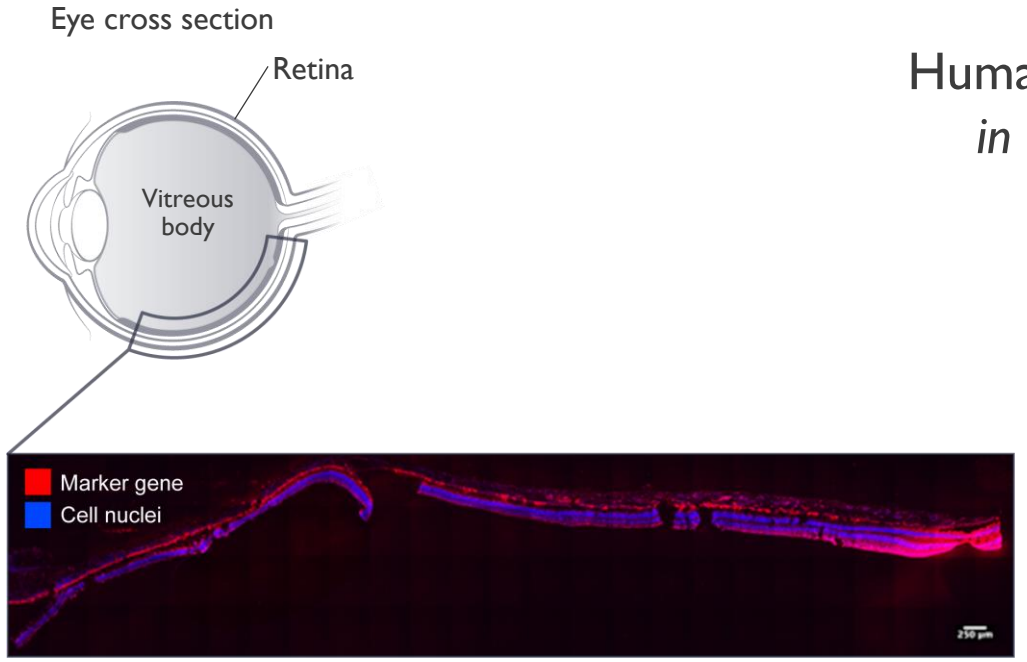
R100



Abbreviations: ILM, inner limiting membrane; RPE, retinal pigment epithelium.

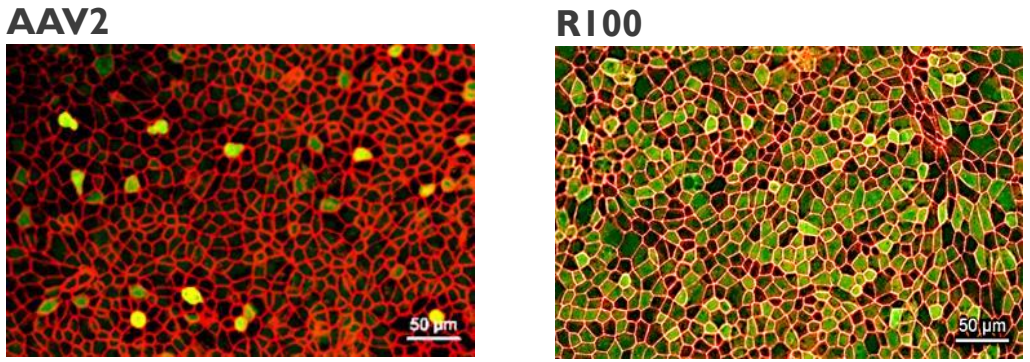
R100 Vector Proof-of-Concept

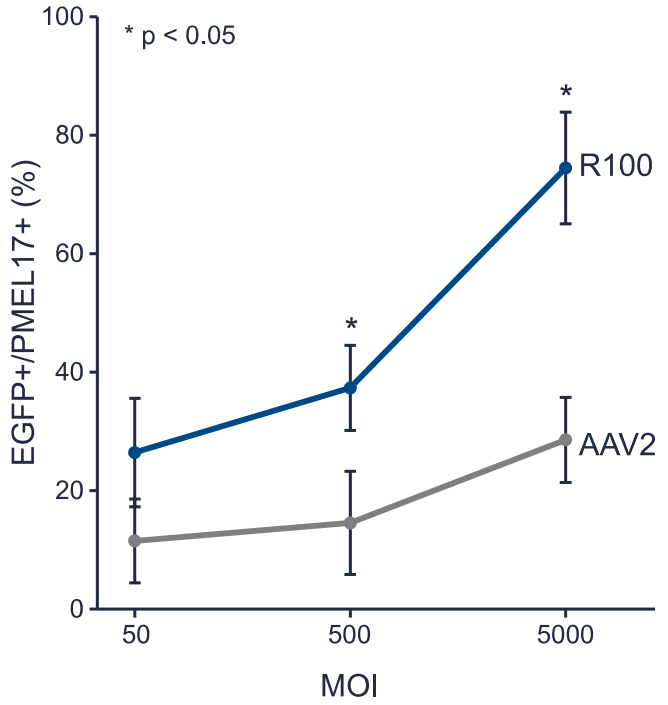
INTRAVITREAL TRANSDUCTION OF NHP RETINA & HUMAN RETINAL RPE CELLS VS AAV2 IN VITRO



IVT in NHP
in vivo

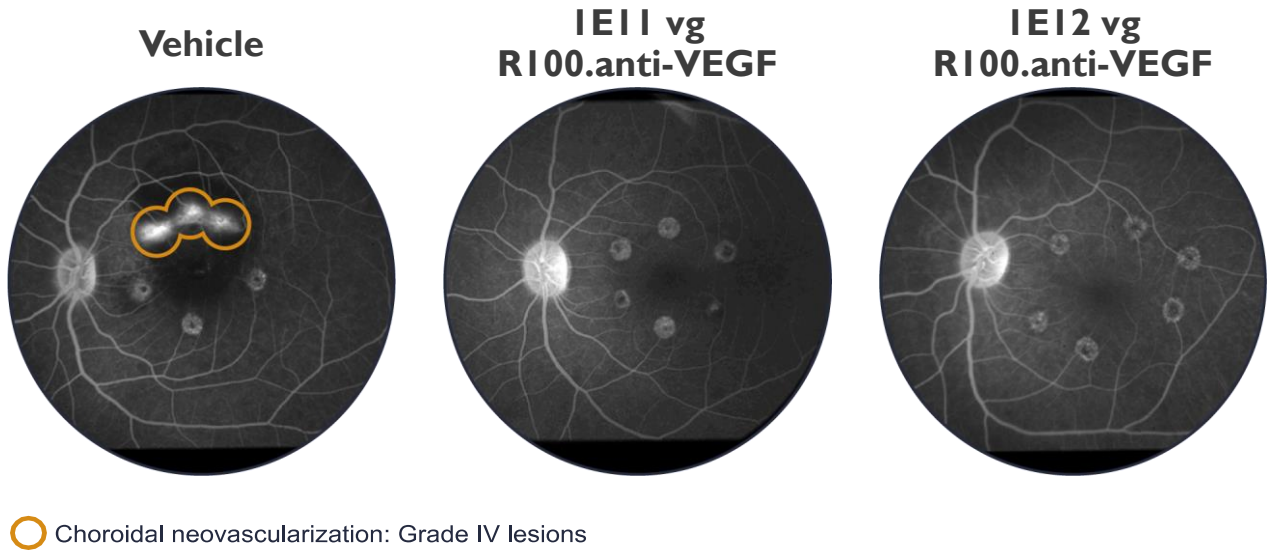
Human RPE
in vitro

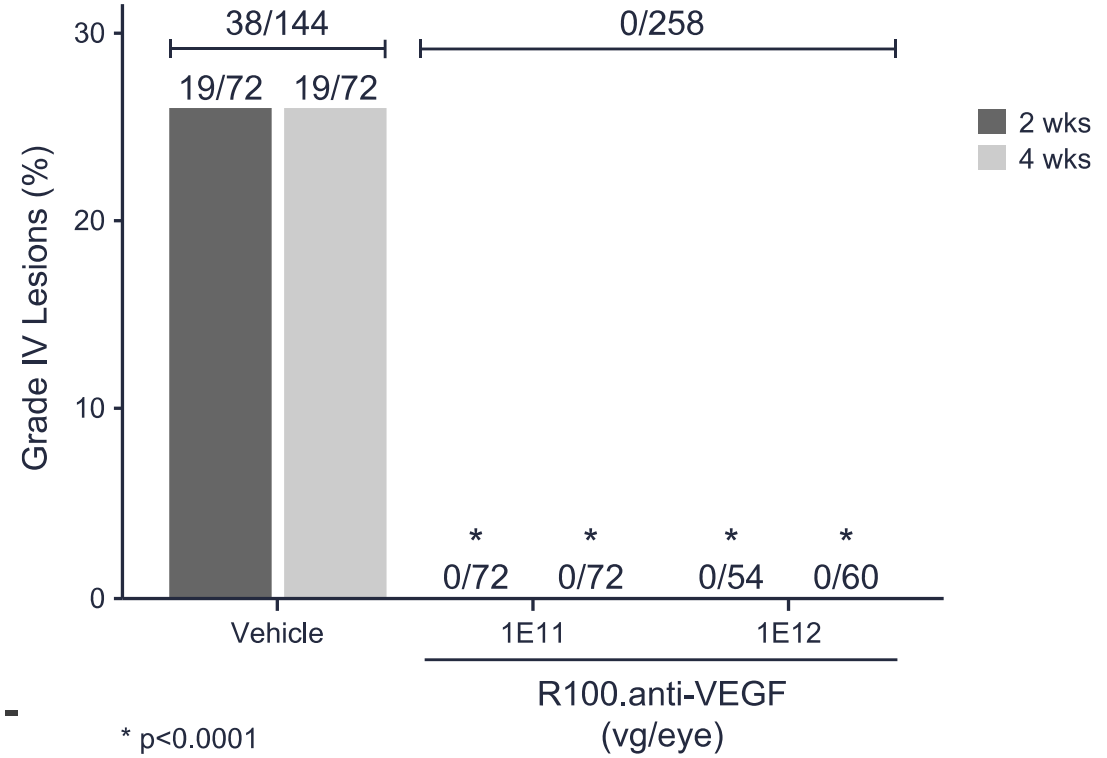




Intravitreal 4D-150 Prototype: Stable Anti-VEGF Expression

R100.ANTI-VEGF EXPRESSION THROUGH 6 AND 12 MONTHS





- Laser-induced CNV 6 weeks after single IVT delivery of 4D-150 prototype*
- Dose-related sustained anti-VEGF expression at 6 and 12 months

*4D-150 Prototype = R100.anti-VEGF

Intravitreal 4D-150: Methods for NHP Preclinical Studies

ACUTE BIODSTRIBUTION & LASER-INDUCED CNV STUDIES

NHP ACUTE BIODISTRIBUTION

- **Eyes (N):** 4 NHP eyes
- **Dose (vg/eye):** 1E12
- **Study Duration:** 28 days
- **Endpoints:**
  - Tolerability
  - Aqueous Aflibercept Expression
  - Retinal miRNA VEGF-C Expression

NHP LASER-INDUCED CNV MODEL

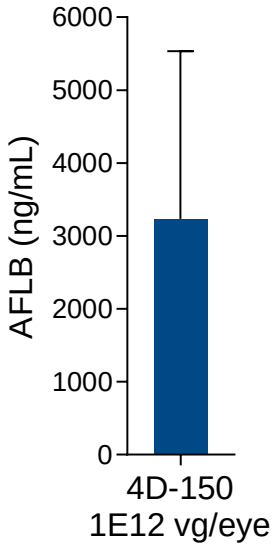
- **Eyes (N):** 42 NHP eyes
  - 14 per dose group
- **Dose (vg/eye):**
  - 1E11
  - 3E11
  - 1E12
- **Study Design:**
  - Day 0: 4D-150 administered
  - Day 28: Steroid taper completed
  - Day 42: Safety assessment followed-up by laser-induced CNV
  - Day 56: 2-week CNV assessment
  - Day 70: 4-week CNV assessment
  - 12-month: End of study *(pending)*
- **Endpoints:**
  - Tolerability
  - Suppression of Grade 4 CNV lesions

Intravitreal 4D-150: NHP Acute Biodistribution Study

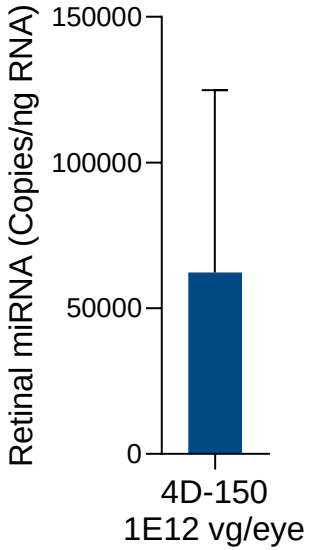
HIGH AFLIBERCEPT AND VEGF-C miRNA EXPRESSION; NO EVIDENCE OF UVEITIS OR RETINAL ABNORMALITY

- 4D-150 resulted in high levels of aqueous aflibercept
- miRNA copies detected across all retinas
- No evidence of uveitis or retinal abnormality

Aqueous aflibercept level



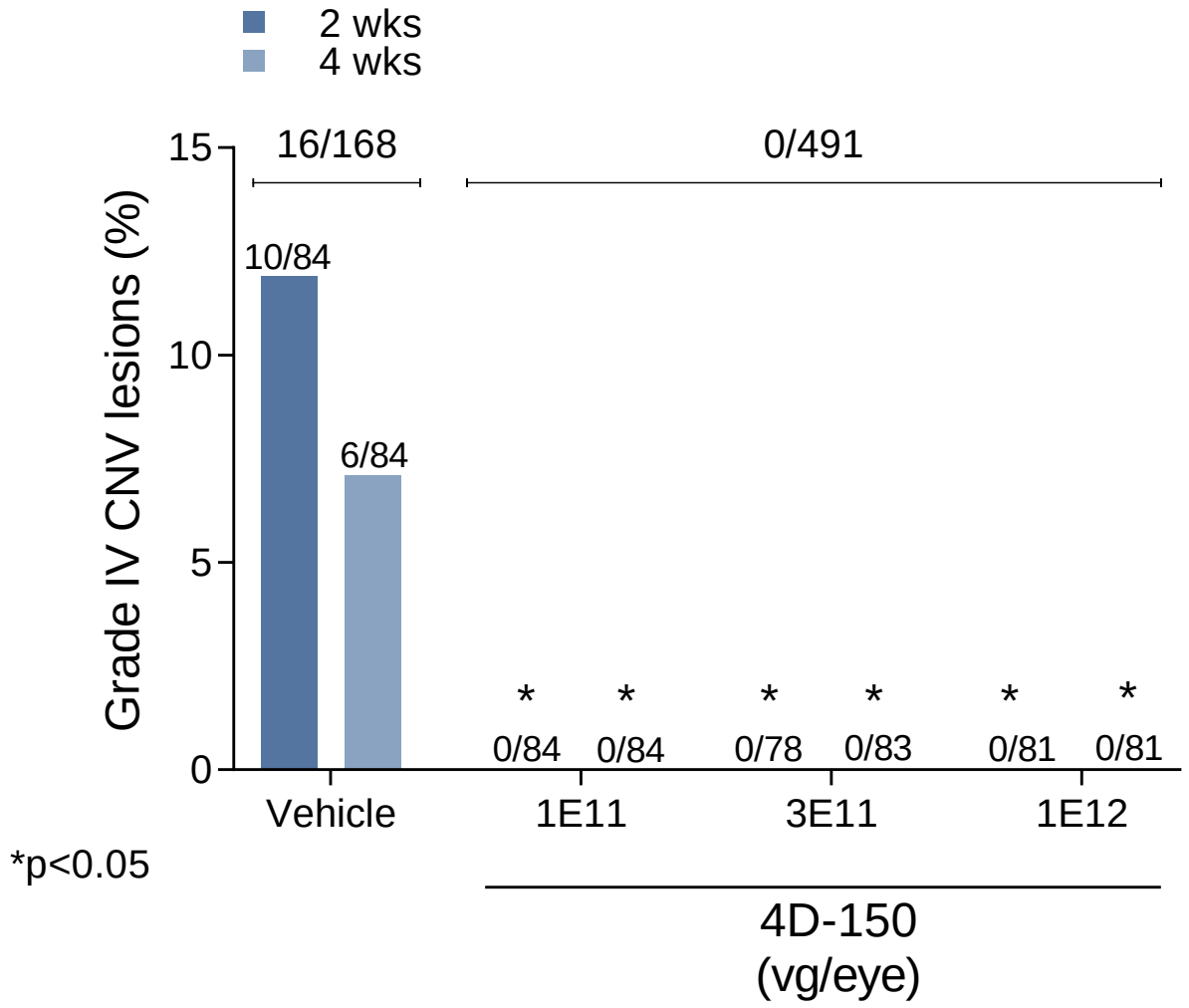
miRNA expression in retina



4 eyes, 2 NHP, 4 weeks in life

Intravitreal 4D-150: Efficacy in NHP CNV Model

100% SUPPRESSION OF CNV INCLUDING AT LOWEST DOSE OF 1E11 VG/EYE



- 100% suppression of CNV (grade IV lesions), including at lowest dose of 1E11 vg/eye
- Day 42 ocular assessments prior to laser:
  - 1E11 vg / eye, no uveitis or retinal abnormalities
  - 3E11 & 1E12 vg / eye, mild to moderate uveitis in a minority of NHP; no retinal abnormalities
  - Tapered 28-day steroid regimen

4D-150 Summary

DUAL-TRANSGENE, INTRAVITREAL GENE THERAPY INHIBITING FOUR DISTINCT VEGF FAMILY MEMBERS FOR WET AMD & DME

- Utilizes 4DMT's targeted & evolved AAV vector R100 - invented for:
  - Routine intravitreal injection
  - Transgene expression across the entire surface area of the retina
  - Transgene expression in all major cell layers of the retina
- Designed for improved efficacy over other approaches:
  - VEGF (A&B) and PlGF (placental growth factor) inhibition via aflibercept expression and secretion
  - VEGF-C inhibition via RNAi
- Efficacy in NHP CNV model: 100% suppression with a single IVT dose, including at the lowest dose of 1E11 vg/eye
- Transgene expression in NHP acute biodistribution study: aflibercept & VEGF-C miRNA
- Clinical trial initiation in wet AMD & DME expected in second half of 2021