

Clinical Trial in Age-Related Macular Degeneration

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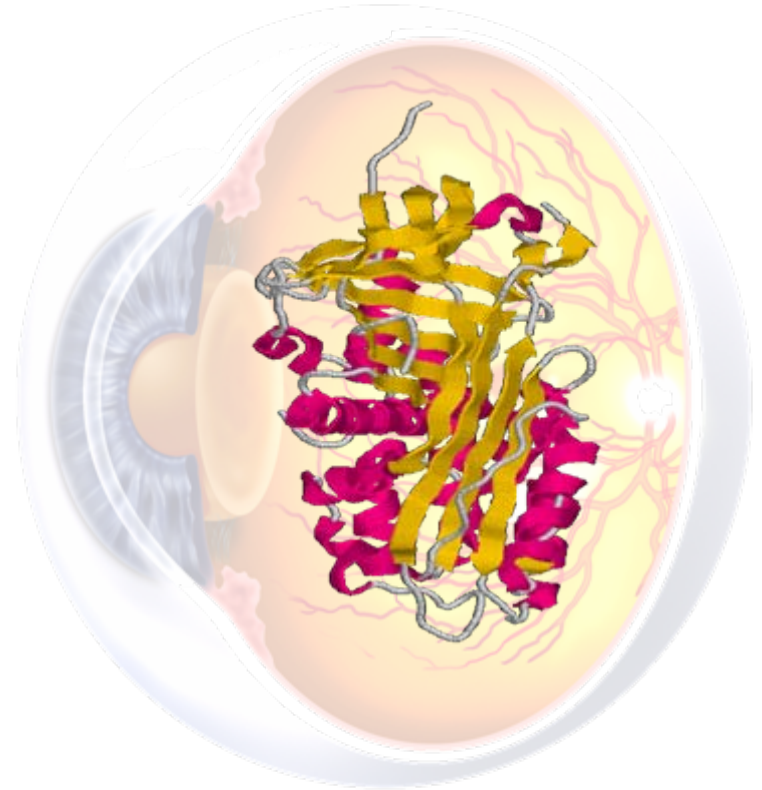
Age-related Macular Degeneration (AMD)

- Leading cause of blindness in US and Europe for persons over age of 50
- Two forms of AMD
 - Dry AMD – 90% of cases
 - Wet AMD – 10% of cases
- Wet AMD results from abnormal blood vessel growth in the back of the eye
- Wet AMD causes central vision loss
- 1.5M sufferers of wet AMD
- 200K new cases annually in US; 500K worldwide



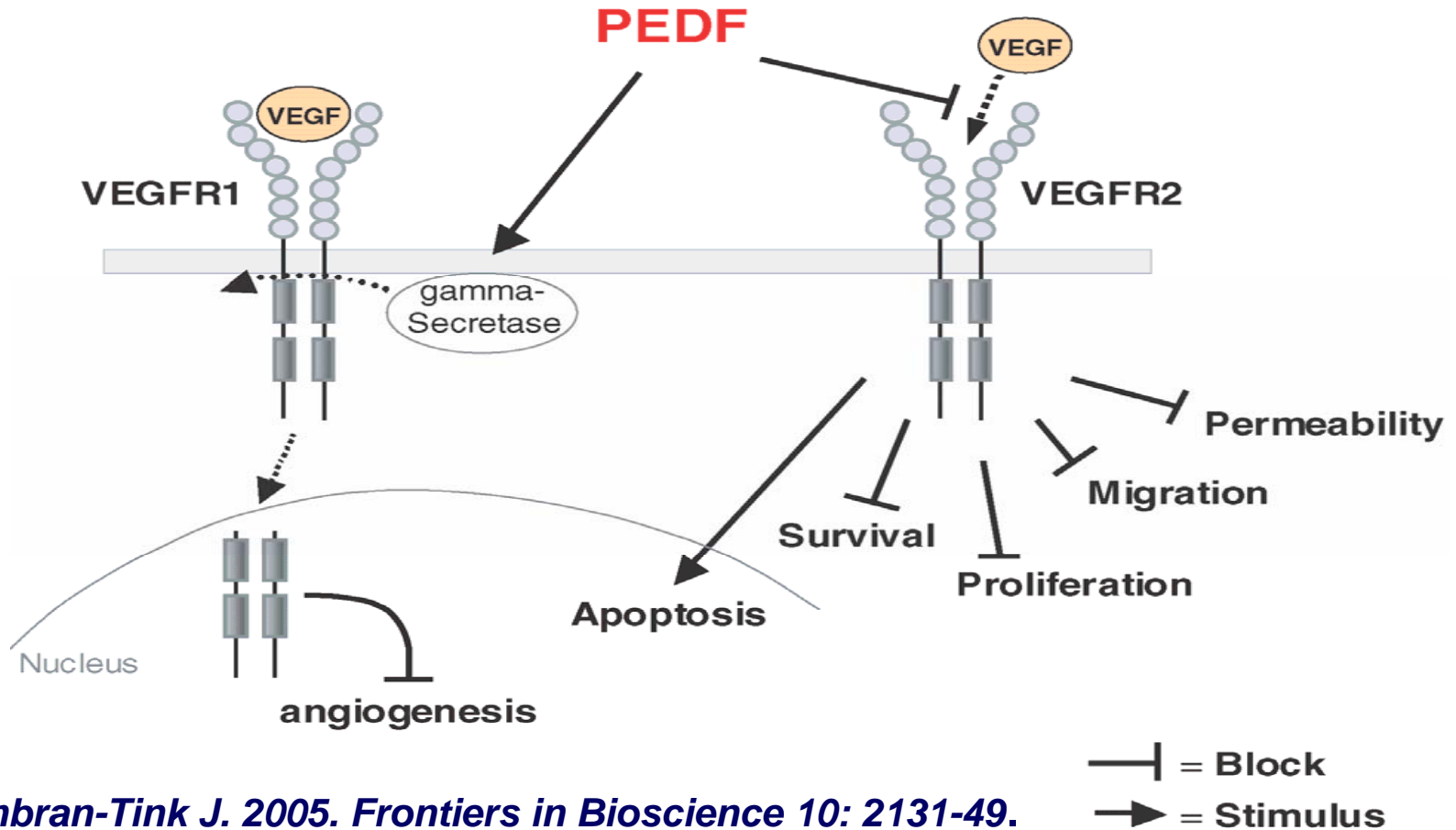
Pigment Epithelium-Derived Factor

- Naturally-occurring potent, secreted anti-angiogenic factor
- Acts on VEGF and other angiogenic pathways
- Regression of existing abnormal blood vessels
- Neuroprotective properties: helps rescue damaged photoreceptors
- Decreased PEDF levels in patients with wet AMD



King GL et al., Engl J Med. 2000 Feb 3;342(5):349-51.

PEDF Stops Abnormal Blood Vessel Growth at Multiple Levels Independent of VEGF Itself

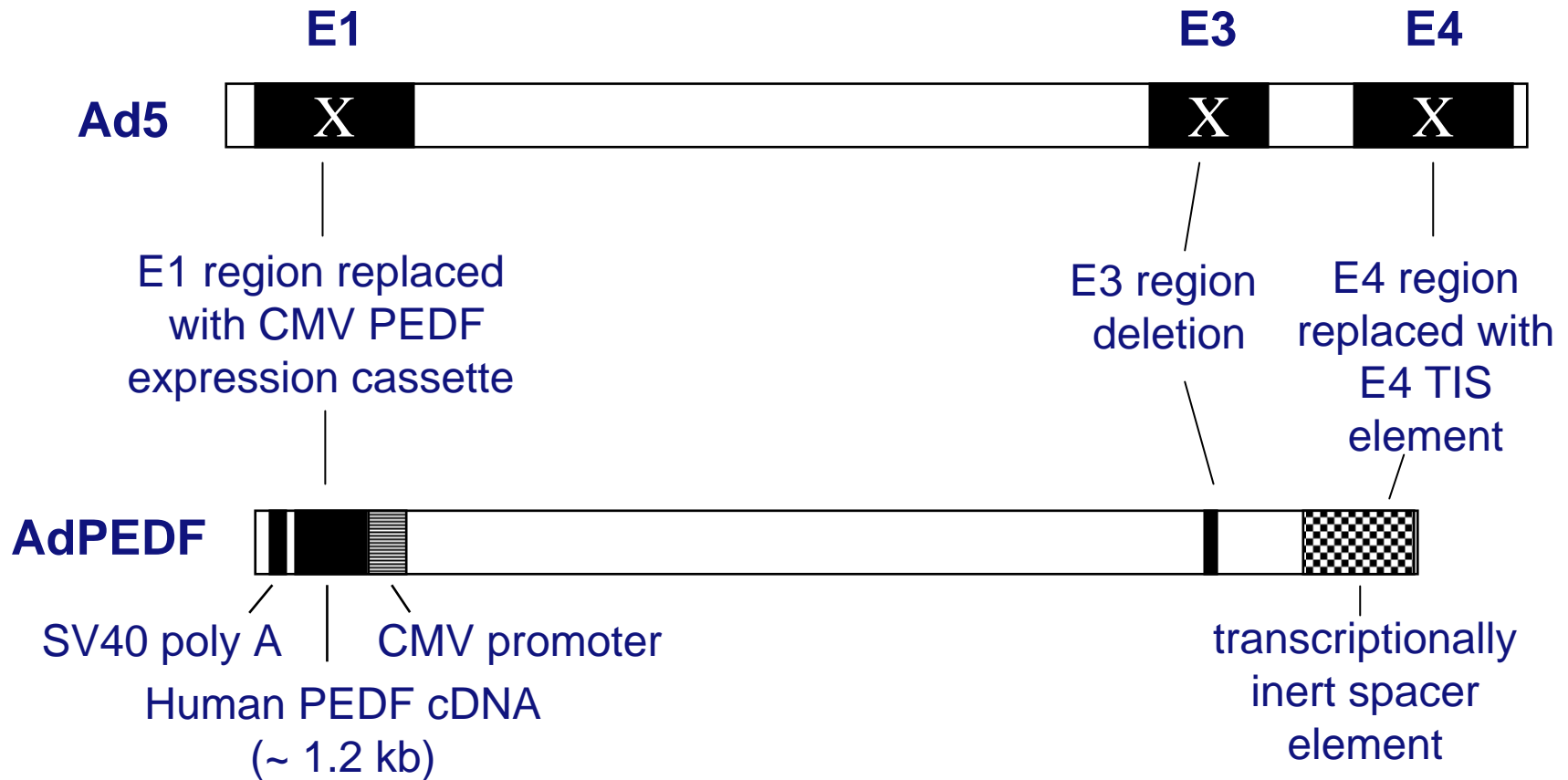


Tombran-Tink J. 2005. Frontiers in Bioscience 10: 2131-49.

Volpert OV et al. 2002. Nat Med. 8(4); 349-357.

Cai J et al. 2006. J Biol Chem. 281(6):3604-13.

Local Therapy Using AdPEDF -- a Second Generation Adenovector Expressing the Human PEDF cDNA

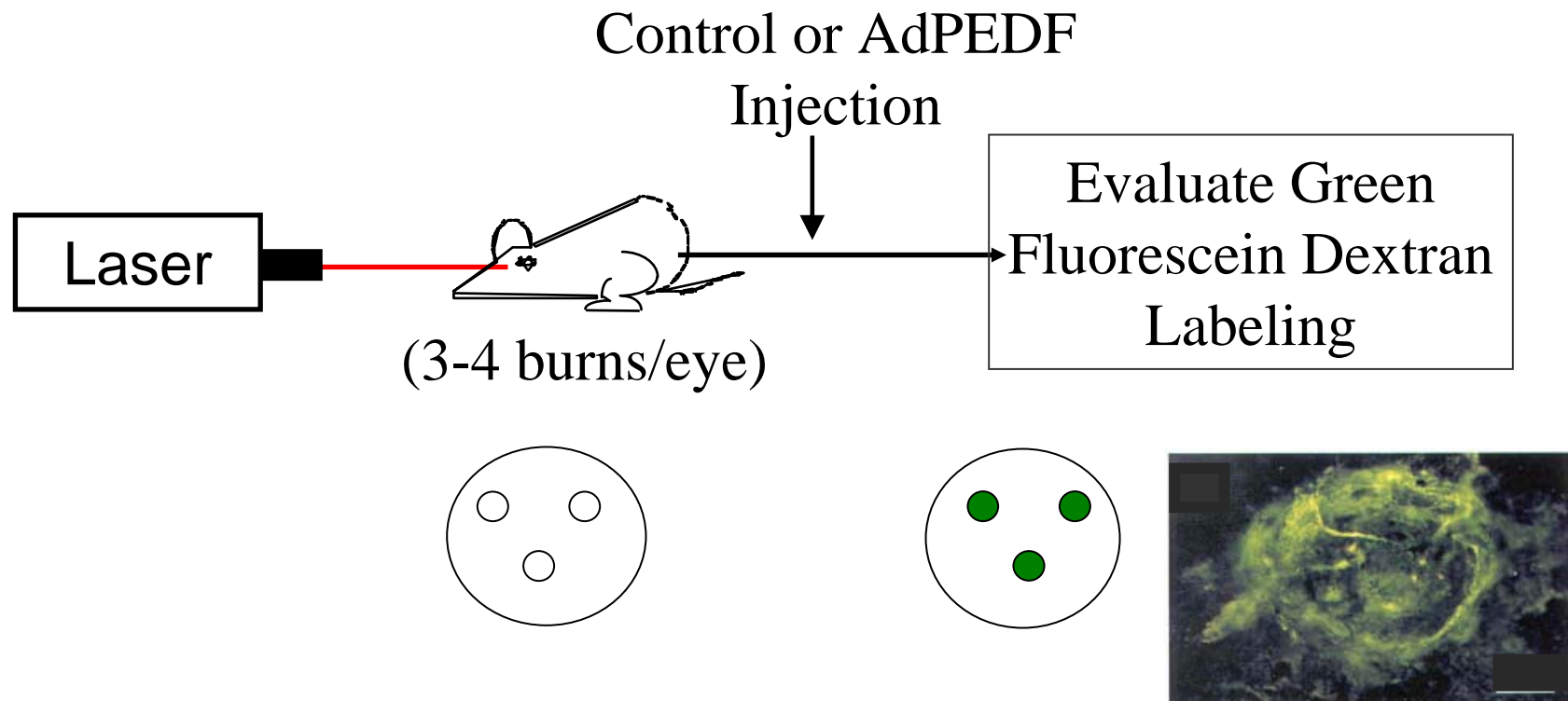


Brough D et al. 1996. J Virol. 70: 6497-500.

AdPEDF Activity in Three In Vivo Experimental Ocular Mouse Models

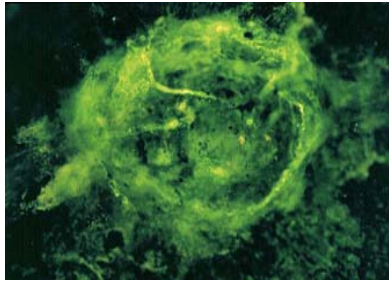
- **Choroidal neovascularization model (Wet AMD)**
- **Retinal neovascularization model (Diabetic Retinopathy)**
- **VEGF transgenic mouse– retinal neovascularization**

Laser-induced Choroidal Neovascularization Model for Wet AMD

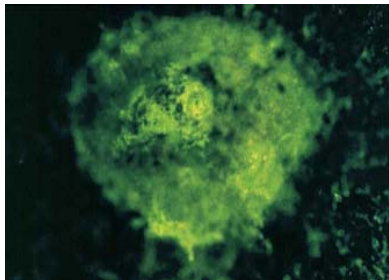


Mori K et al. 2001. *J Cell Physiol.* 188(2):253-63.

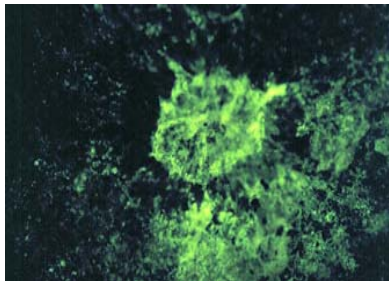
AdPEDF Inhibits Blood Vessel Growth in Laser-Induced CNV Model



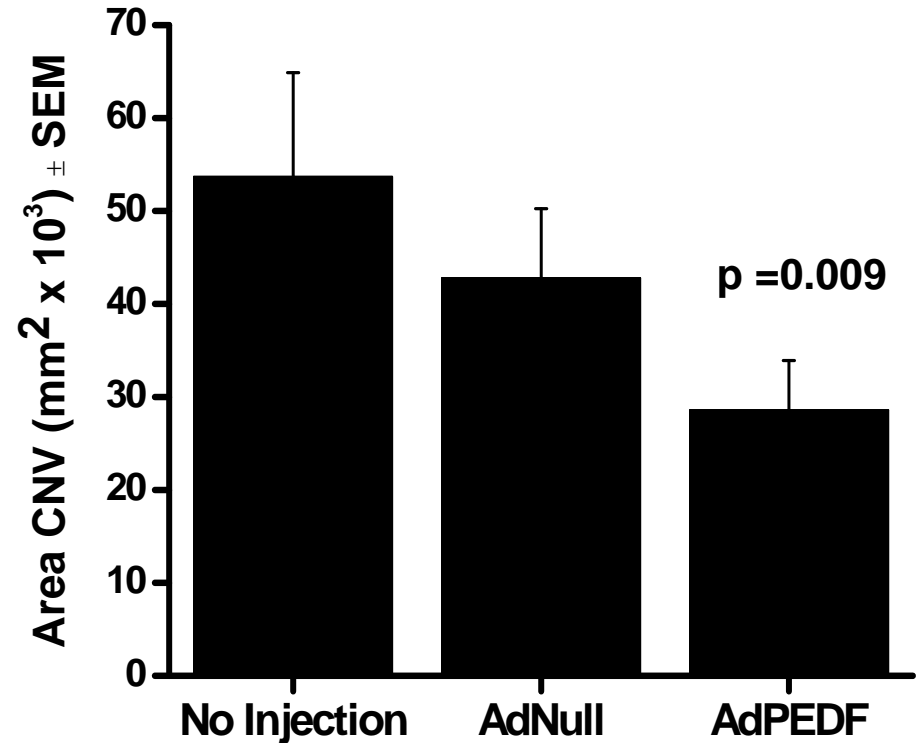
No Injection



AdNull

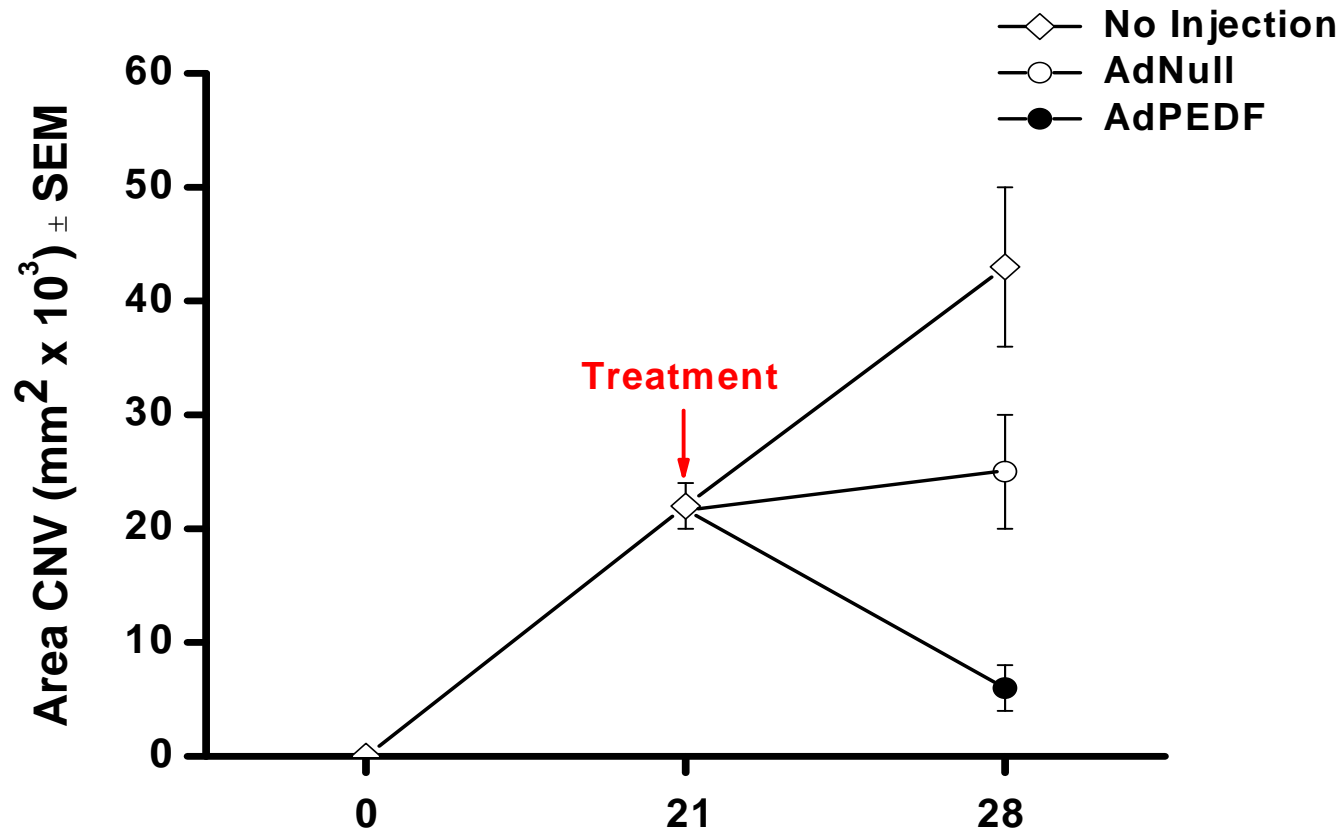


AdPEDF



Mori K et al. 2001. *J Cell Physiol.* 188(2):253-63.

PEDF Causes Selective Regression of Abnormal Vessels



Mori K et al. 2002. IOVS. 43 (7): 2428-34.

Phase I AdPEDF Clinical Trial Design in Wet AMD (Part 1)

- **Objective:**
 - Determine safety of a single intravitreal dose of AdPEDF
- **Patient Population:**
 - Severe neovascular AMD
 - Best Corrected Visual Acuity 20/200 or worse in study eye
 - Active leaking, subfoveal, CNV lesion
 - Patients must have exhausted current available therapies (not current candidate or refused PDT)
- **Design:**
 - Open label, dose-escalation study
 - 8 dose levels; 28 patients
 - 1×10^6 - $1 \times 10^{9.5}$ pu in $\frac{1}{2}$ log increments
 - Multicenter study (6 sites)

Phase I AdPEDF Clinical Trial Design in Wet AMD (Part 2)

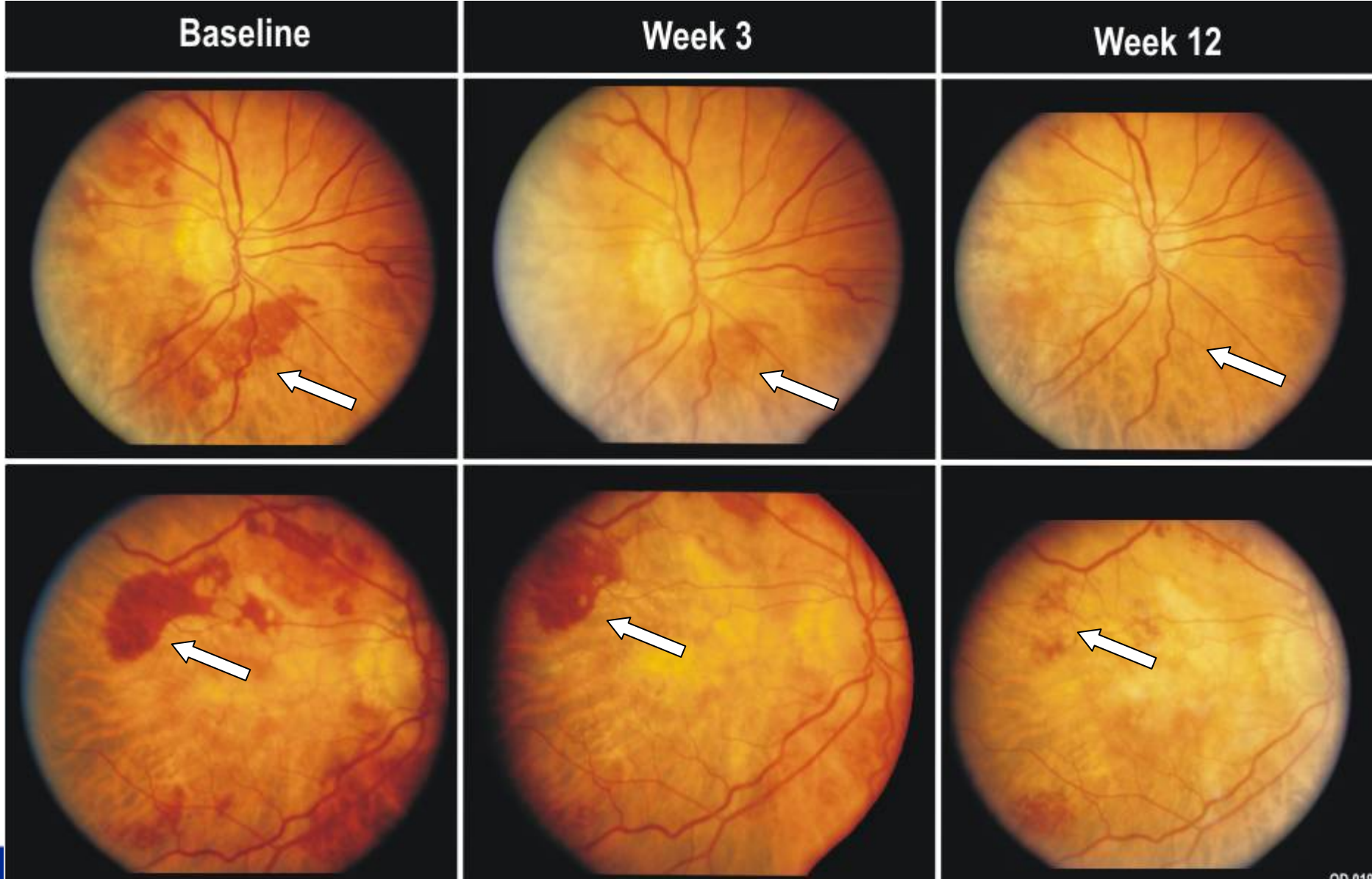
- **Objective:**
 - Determine safety of a single intravitreal dose of AdPEDF in a population with better vision
- **Patient Population:**
 - BCVA 20/40 to 20/320
 - Active leaking, subfoveal, CNV lesion
 - Patients must have exhausted current available therapies (not current candidate or refused PDT)
- **Design:**
 - Open label, single injection
 - Two dose levels; 22 patients
 - $1 \times 10^{8.5}$ (n=10) or $1 \times 10^{9.5}$ (n=12)
 - Multicenter study (9 sites)

Combined Phase I Results: AdPEDF is Well-tolerated in Both Populations*

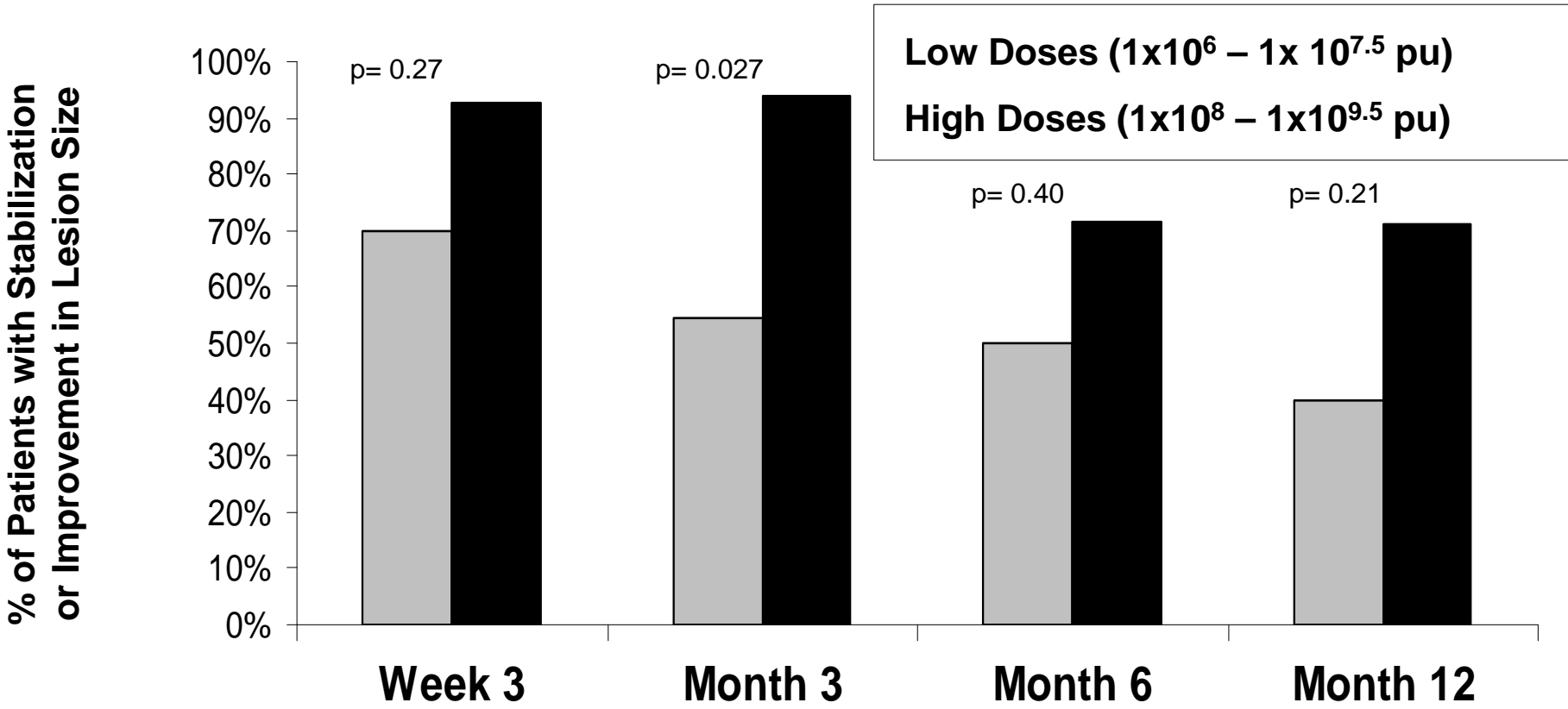
- Safe at all dose levels (including top dose of $10^{9.5}$ pu)
 - No dose-limiting toxicities
 - No infection or endophthalmitis
 - No retinal or vitreous detachment
 - No cataracts or glaucoma
 - No MTD
- Occasional trace- mild, transient anterior chamber flare and cells that is dose-dependent
- Transient IOP elevations that were managed medically without surgical intervention
- Negative cultures for adenoviral vectors in sputum and urine from patients

*Data set– April 12, 2007

Part 1:Pt 019 Fundus Photographs (1x10^{9.0} pu)



Part 1: Stabilization or Improvement in Study Eye - Lesion Size

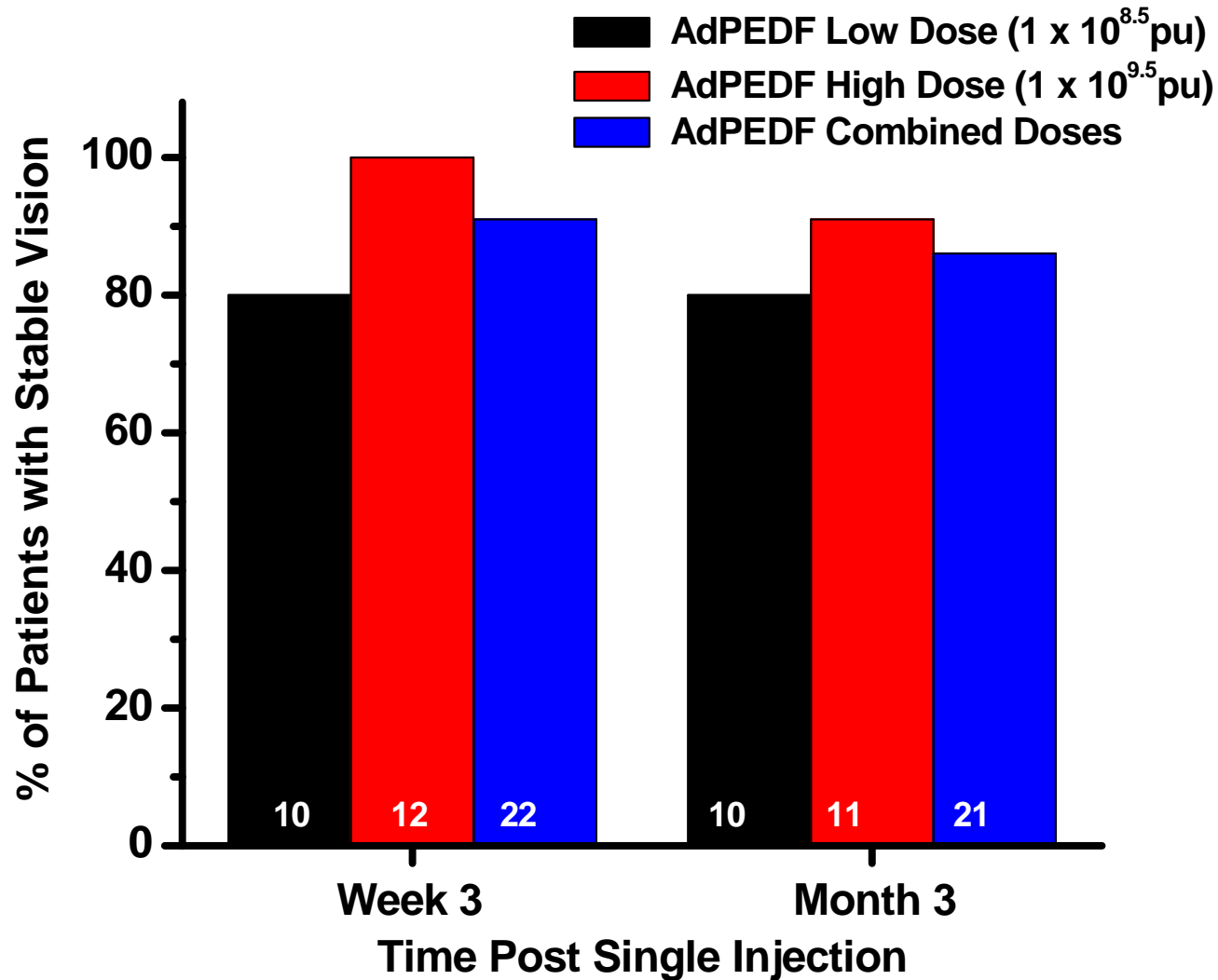


Low doses	n=	10	11	10	10
High Doses	n=	14	16	14	14

* Stabilization defined as no change in category on the following scale:

Lesion Size: (MPS ≤ 1 ≤ 2 ≤ 3 ≤ 4 ≤ 5 ≤ 6 ≤ 9 ≤ 12 ≤ 16 >16 cd cg
DA)

Part 2: Visual Acuity Changes Following Single Injection with AdPEDF



*Stable vision defined as < 15 letter loss

Clinical Summary

- AdPEDF is well-tolerated up to $1 \times 10^{9.5}$ pu in patients with moderate and severe wet AMD
- Data support continued advancement

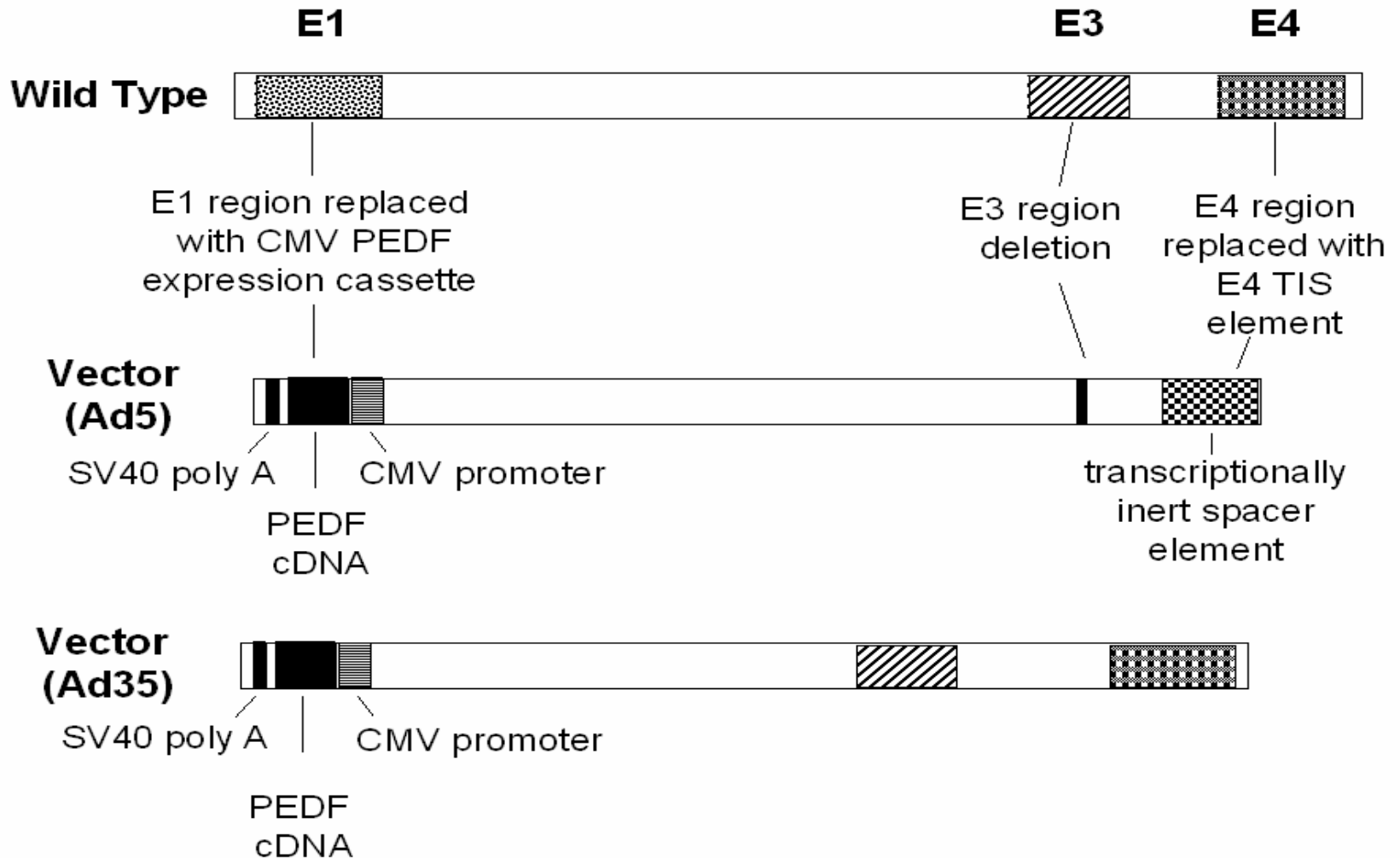
Research Discoveries

Next Generation PEDF Therapeutics

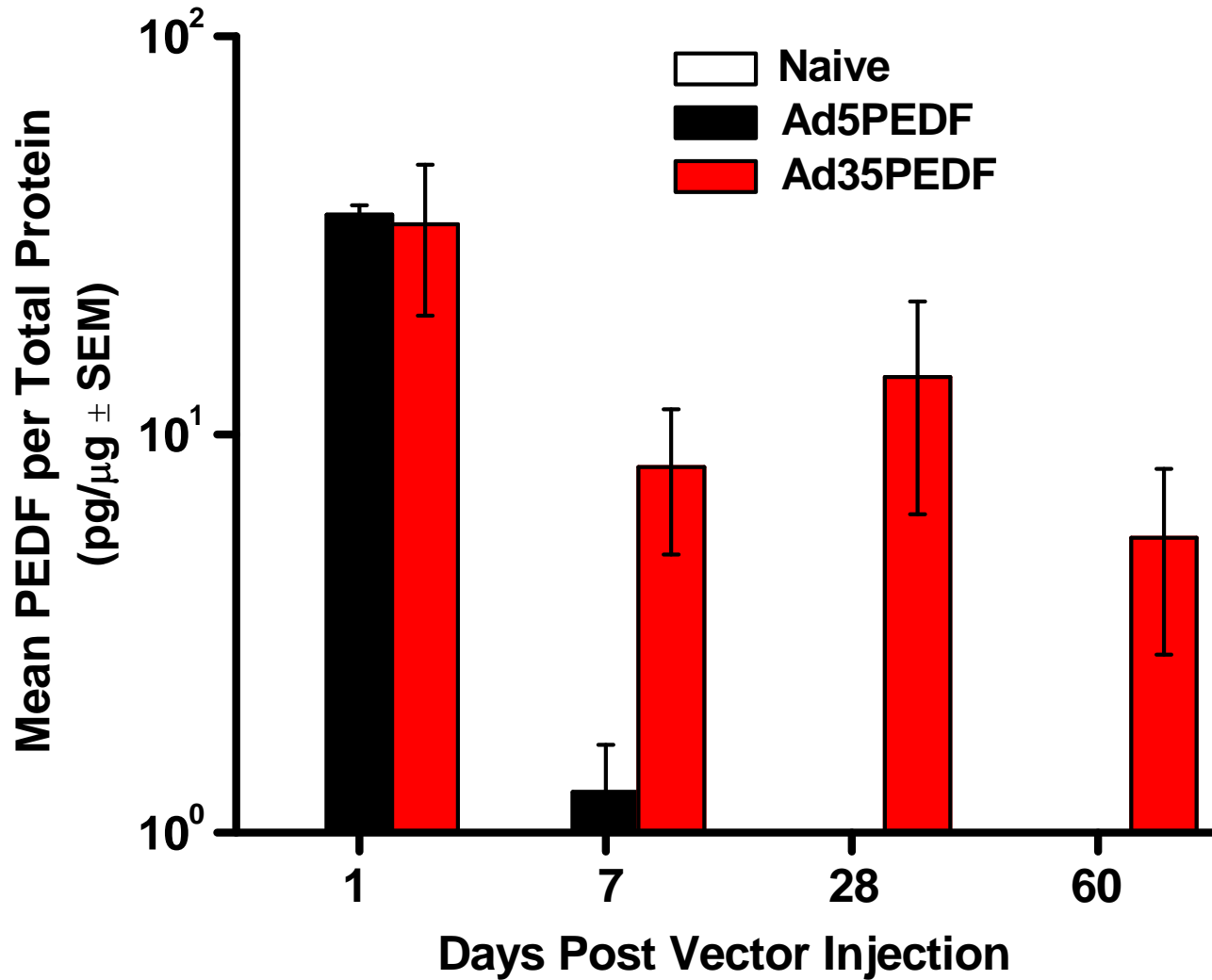
Current Medical Need for Treatment for Wet AMD--
To decrease frequent repeat intraocular
injections

- Induction of PEDF expression with small molecule
- Prolonged PEDF expression with an alternate adenovector backbone

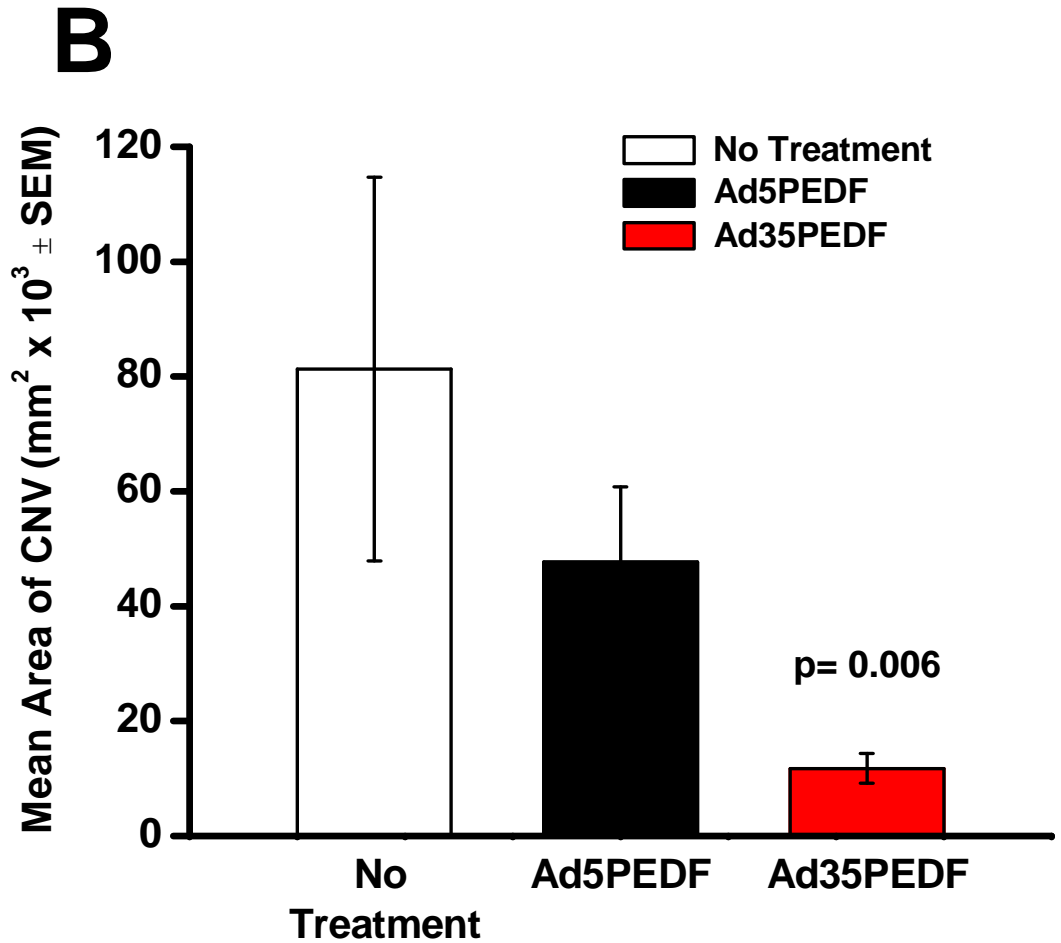
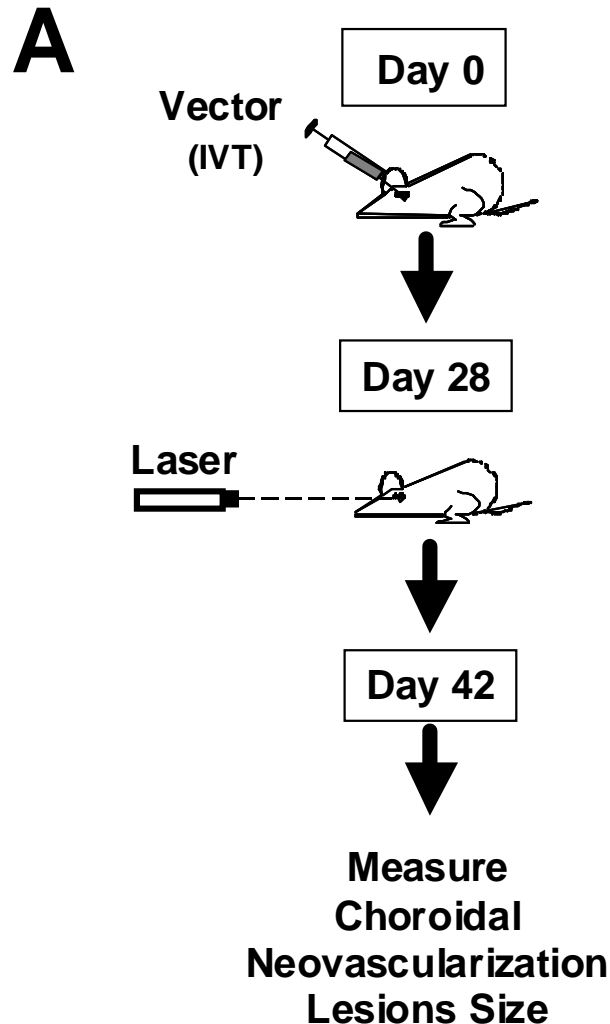
Alternate Serotypes: Ad5PEDF and Ad35PEDF



PEDF Protein Levels from Ad35PEDF



Ad35PEDF Inhibits CNV Lesion Growth 28 Days Post-Ocular Injection



Summary

- Adenovectors are a compelling platform for the treatment of ocular diseases
- AdPEDF has been in two Phase I trials with clinical endpoints achieved
- Advancement to Phase II testing is warranted
- Improvements in platform that bypass frequent repeat intraocular administrations

Acknowledgements

- **Peter Campochiaro (Johns Hopkins University)**
- **Keisuke Mori (Saitama Medical School, Japan)**
- **Melissa Hamilton**
- **Miguel Carrion**
- **Duncan McVey**
- **Douglas Brough**
- **Jason Gall**
- **C. Richter King**
- **PEDF Study Group**
- **Clinical Research Group**

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