Suprachoroidal CLS-AX (axitinib injectable suspension), as a Potential Long-Acting Therapy for Neovascular Age-Related Macular Degeneration (nAMD)

Peter Kaiser, MD
Professor of Ophthalmology
Chaney Family Endowed Chair for Ophthalmology Research
Cleveland Clinic, Cole Eye Institute

Co-Authors:
Thomas Ciulla, MD, MBA
Viral Kansara, PhD

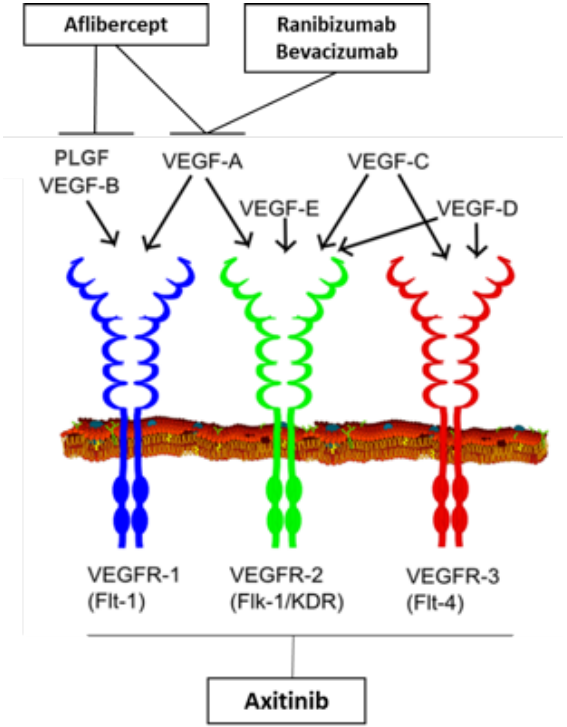
ARVO 2020 Annual Meeting
Baltimore, MD

Financial Disclosures

Consultant for Aerie, Aerpio, Alcon, Allegro, Allergan, Alzheon, Annexon Biosciences, AsclepiX, Bayer, Bausch and Lomb, Biogen Idec, Boerenger Ingelheim, Carl Zeiss Meditec, **Clearside Biomedical**, Eyevensys, Formycon/BioEq GmbH, Galecto Biotech, Galimedix, Glaukos, Innovent, iRenix, jCyte, Kala Pharmaceuticals, Kanghong, Kodiak, NGM Biopharmaceuticals, Inc., Novartis, Ocugenix, Oculis, Omeros, Opthea, Oxurion, PalatinRegeneron, RegenxBio, Retinal Sciences, Roivant, Sandiz, Santen, SciFluor, Spark, Stealth Biotherapeutics, Takeda, Thea, Verana

AMD Vascular Endothelial Growth Factor Treatment Approaches

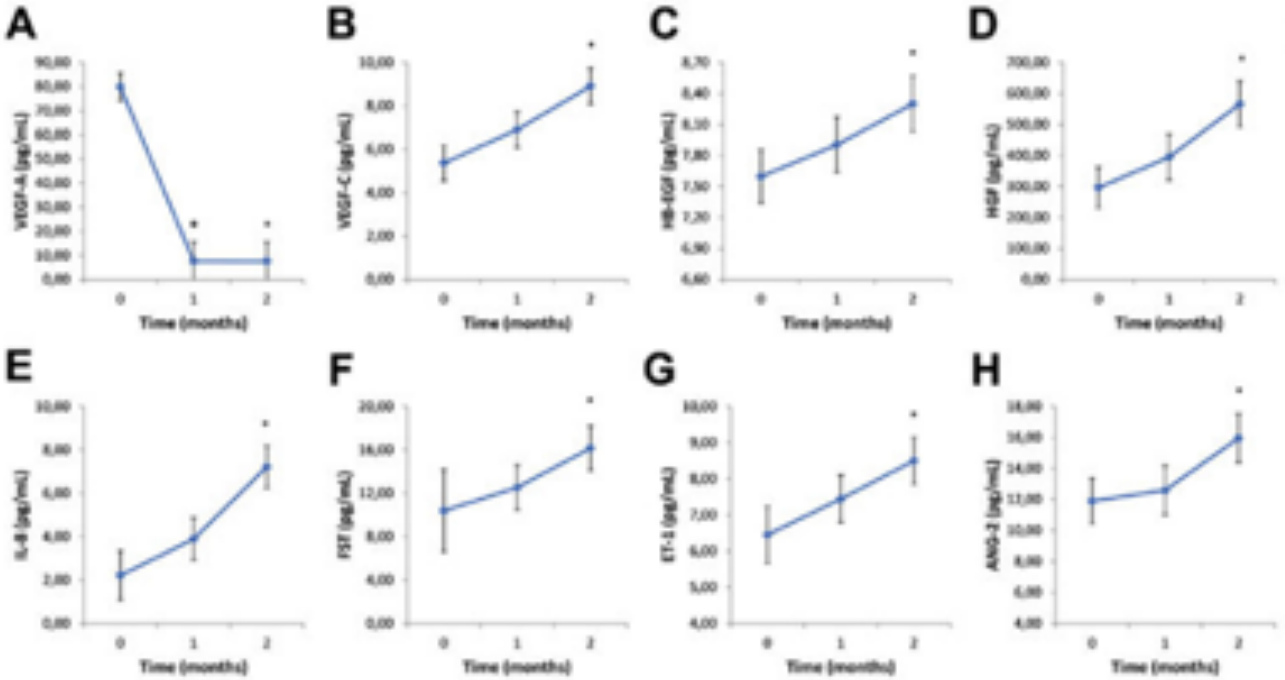
Current AMD Therapies Predominantly Focus on VEGF-A Blockade, not VEGF Receptors



Sources: 1. Cabral T et al. Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers. Ophthalmol Retina. 2018 January ; 2(1): 31–37. doi:10.1016/j.oret.2017.04.004. | 2. Lieu et al. The Association of Alternate VEGF Ligands with Resistance to Anti-VEGF Therapy in Metastatic Colorectal Cancer. PLoS ONE 8(10): e77117. | 3. Riquelme et al. Topical axitinib is a potent inhibitor of corneal neovascularization. Clinical and Experimental Ophthalmology 2018; 46: 1063–1074 | 4. Yuan et al. Ocular Drug Delivery Nanowafer with Enhanced Therapeutic Efficacy. ACS Nano. 2015 Feb 24;9(2):1749-58. | 5. Giddabasappa et al. Axitinib inhibits retinal and choroidal neovascularization in in-vitro and in-vivo models. Exp Eye Res. 2016, 145: 373-379. | 6. Nakano et al. Short-term treatment with VEGF receptor inhibitors induces retinopathy of prematurity-like abnormal vascular growth in neonatal Rats. Exp Eye Res. 2016. 143: 120-131. | 7. Kang et al. Antiangiogenic Effects of Axitinib, an Inhibitor of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase, on Laser-Induced Choroidal Neovascularization in Mice. Curr Eye Res. 2012. 38: 119-127. | 8. Theile et al. Multikinase Inhibitors as a New Approach in Neovascular Age-Related Macular Degeneration (AMD) Treatment: In Vitro Safety Evaluations of Axitinib, Pazopanib and Sorafenib for Intraocular Use. Klin Monatsbl Augenheilkd

Cleveland Clinic

Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers

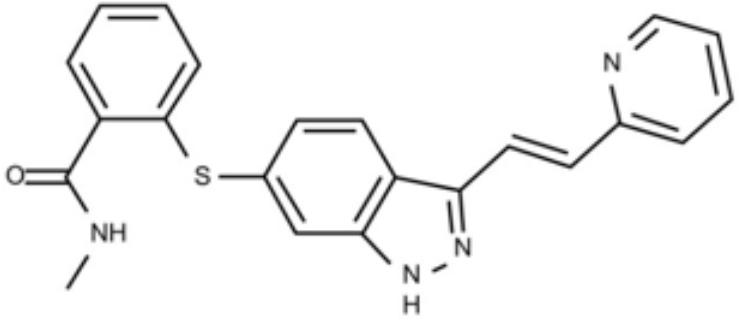


Cabral et al. Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers. Ophthalmol Retina. 2018 January ; 2(1): 31–37

Cleveland Clinic

Axitinib: Introduction

- Axitinib effectively inhibits corneal, retinal and choroidal angiogenesis in multiple preclinical models
- Axitinib has better biocompatibility with ocular cells than other tyrosine kinase inhibitors



Tyrosine Kinase Inhibitors: Potency

Inhibitory concentrations (IC50 in nmol) for targets with multitargeted TKIs.

Drug	VEGFR1	VEGFR2	VEGFR3	PDGFRα	PDGFRβ	c-Kit	RET	RAF	FLT3
Axitinib[9]	0.1	0.2	0.1–0.3	5	1.6	1.7	>1000	NA	>1000
Pazopanib[24]	10	30	47	71	84	74	>1000	NA	>1000
Sunitinib[25]	10	10	10	5–10	10	13	100–200	NA	1–10
Sorafenib[26]	NA	90	20	50–60	50–60	68	100–150	5–10	46

Gross-Goupil et al. (2013). Axitinib: a review of its safety and efficacy in the treatment of adults with advanced renal cell carcinoma. *Clinical Medicine Insights. Oncology*, *7*, 269–277. doi:10.4137/CMO.S10594

Topical Axitinib More Effectively Inhibited Experimental Murine Corneal Neovascularization than Sunitinib and Sorafenib (at same dose)

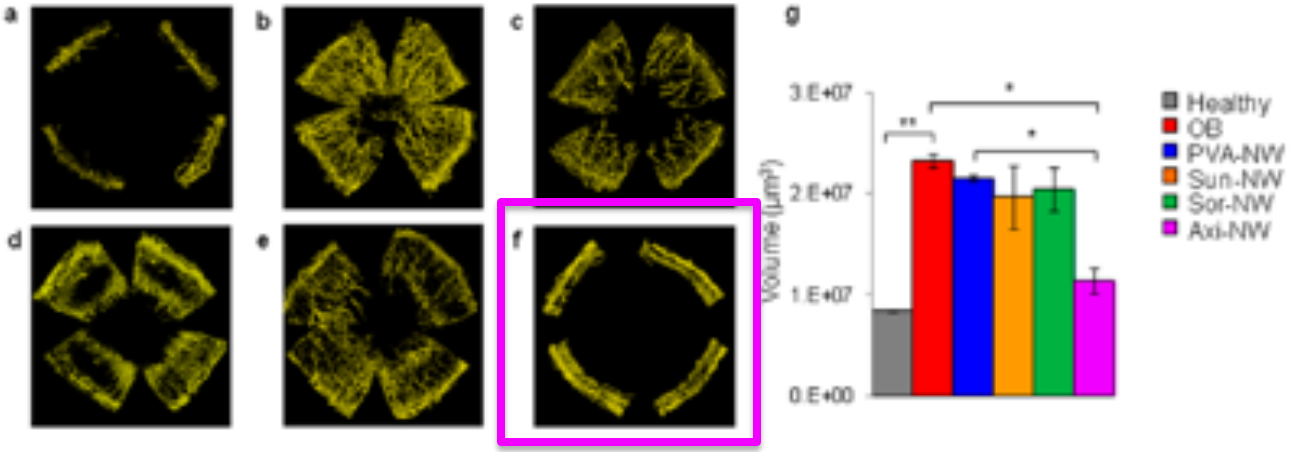
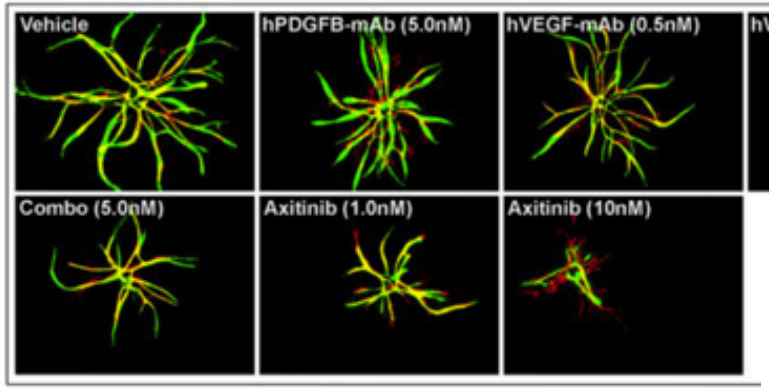


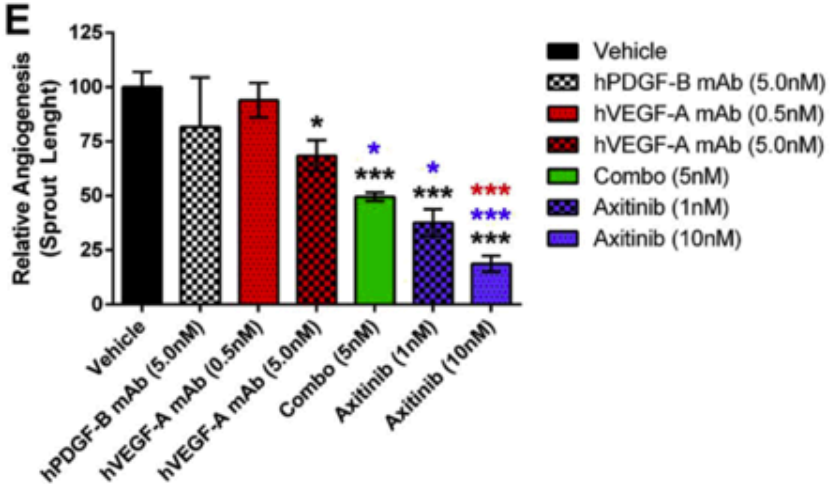
Figure 5. Selection of tyrosine kinase receptor inhibitor drugs. Screening of tyrosine kinase inhibitor drugs loaded nanowafers for their relative therapeutic efficacy in inhibiting corneal neovascularization after 10 days of treatment. Representative 3D reconstructed corneal images of fluorescence confocal microscopy: (a) healthy cornea (control); (b) untreated ocular burn (control); (c) blank PVA-NW; (d) Sora-NW; (e) Suni-NW; (f) Axi-NW. (g) Quantification of corneal neovascularization volume. $n = 3$ animals, $^{*}P < 0.05$ *vs* OB control and $P < 0.05$ *vs* PVA-NW, $^{**}P < 0.01$. All error bars represent standard deviation from the mean.

Yuan et al. Ocular Drug Delivery Nanowafer with Enhanced Therapeutic Efficacy. ACS Nano. 2015 Feb 24;9(2):1749-58.

Cleveland Clinic

Axitinib inhibits angiogenic sprouts more potently than anti-VEGF-A, anti-PDGF-B and combination





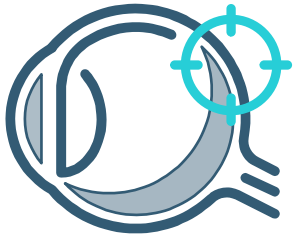
Giddabasappa A, Lalwani K, Norberg R, et al. Axitinib inhibits retinal and choroidal neovascularization in in vitro and in vivo models. *Exp Eye Res*. 2016;145:373–379. doi:10.1016/j.exer.2016.02.010

Cleveland Clinic

Suprachoroidal Injection Procedure

Cleveland Clinic

Core Advantages of Treating Via the Suprachoroidal Space



TARGETED

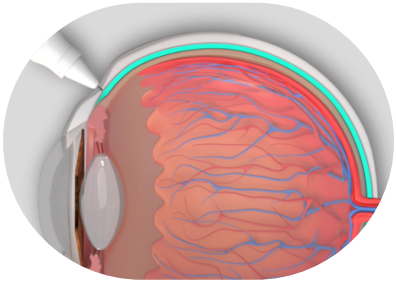
The back of the eye is the location of many irreversible and debilitating visual impairments[1]

for efficacy

COMPARTMENTALIZED

Drug is compartmentalized in the suprachoroidal space, which helps keep it away from non-diseased tissues[2]

for safety



BIOAVAILABLE

Fluid spreads circumferentially and posteriorly when injected within the suprachoroidal space, bathing the choroid and adjacent areas with drug[3]

for durability

Sources: PK = pharmacokinetic | 1. Rai UDJ, Young SA, Thrimawithana TR, et al. The suprachoroidal pathway: a new drug delivery route to the back of the eye. Drug Discov Today. 2015;20(4):491-495. 2. Chiang B, Jung JH, Prausnitz MR. The suprachoroidal space as a route of administration to the posterior segment of the eye. Adv Drug Deliv Rev.

Cleveland Clinic

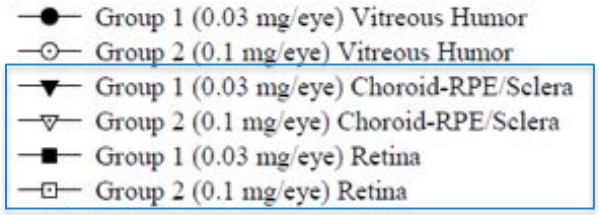
Suprachoroidal Axitinib: Ocular Distribution & Pharmacokinetics

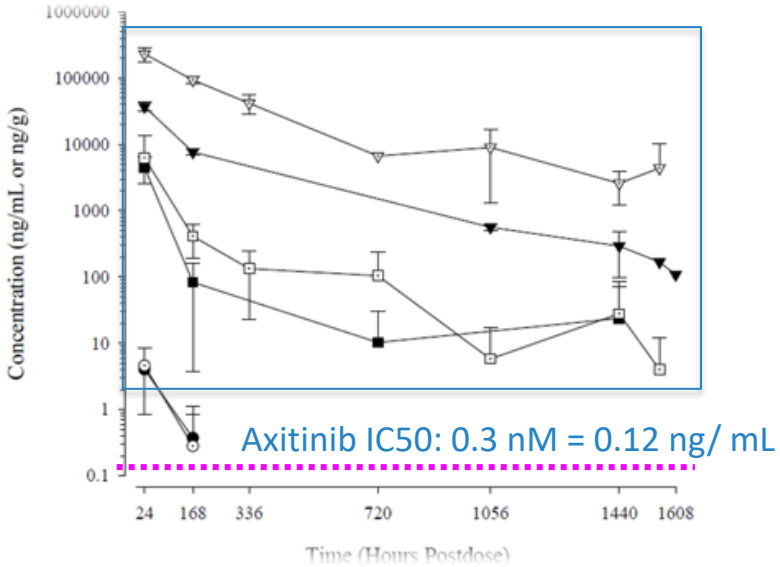
METHOD:

- Dutch-belted pigmented rabbits
- Single bilateral suprachoroidal injection axitinib
  - Group 1: 0.03 mg / eye
  - Group 2: 0.1 mg / eye

RESULTS

Mean concentration of suprachoroidally injected axitinib in ocular tissues for male Dutch Belted rabbits





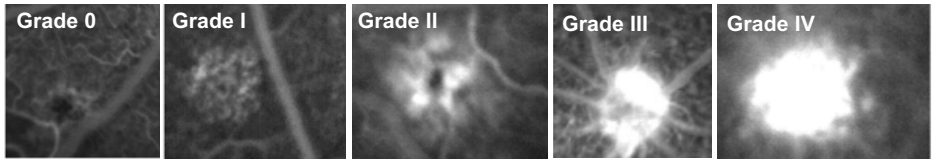
Cleveland Clinic

Suprachoroidal Axitinib: Efficacy in Brown Norway Rats

METHOD

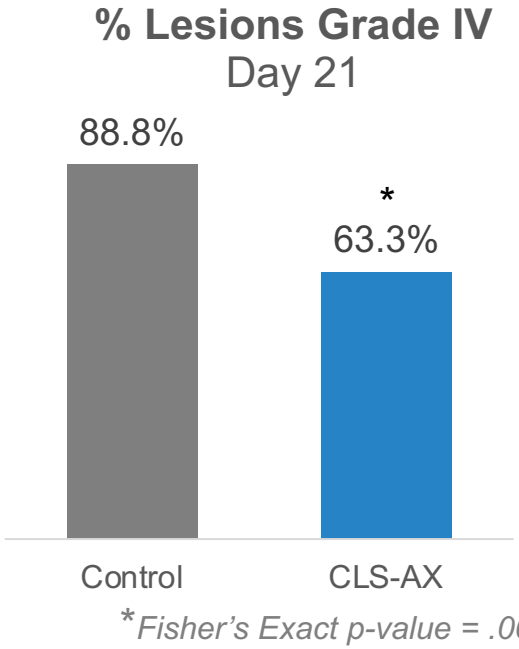
- Laser CNV: 4 lesions per eye
- N=20 eyes (n=10 specimens, bilateral SC injections)
- Two (2) doses, days 1 & 8, 0.4 mg/eye/dose

FLUOROSCEIN ANGIOGRAPHY GRADING SCALE



RESULTS

- At Day 21: CLS-AX lesion reduction in severe (Grade IV) lesions versus control – see graph



Cleveland Clinic

Suprachoroidal Axitinib: Efficacy in Weanling Pigs

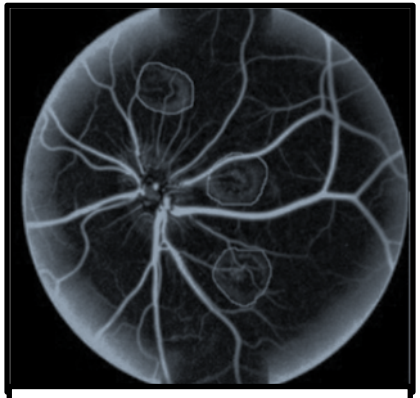
METHOD

- Laser CNV created 6 lesions per eye
- N=8 Weanling Pigs
  - OD: 4mg/ 0.1 mL **Suprachoroidal CLS-AX**
  - OS: 0.1 mL Saline
- Single dose followed by imaging at weeks 1 and 2

RESULTS

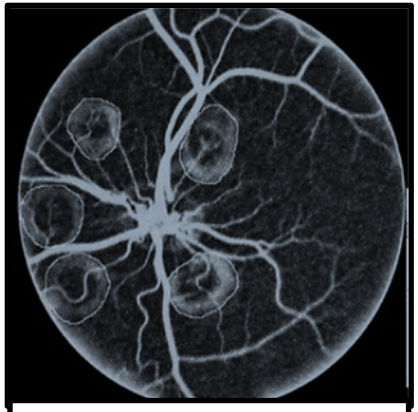
- SC CLS-AX significantly reduced fluorescein leakage
  - 10.5% @ week 1 (p=0.009)
  - 16.0% @ week 2 (p=0.0015)
- SC CLS-AX significantly reduced growth of new blood vessels
  - 18% reduction vs. saline treatment (p=0.03)

CLS-AX treated eye



Significantly reduced vascular leakage
(marked region represents original lesion area)

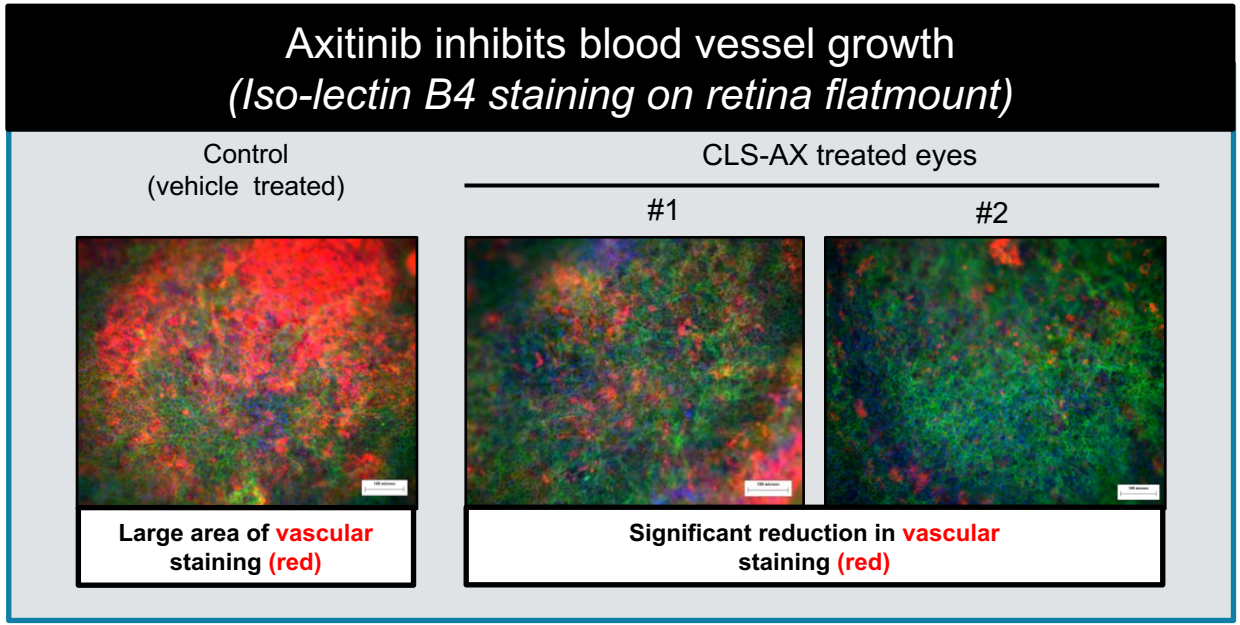
BSS treated eye



Increased vascular leakage
(marked region represents lesion area)

Cleveland Clinic

Suprachoroidal Axitinib: Iso-lectin B4 staining shows reduction in vascular staining in pigs

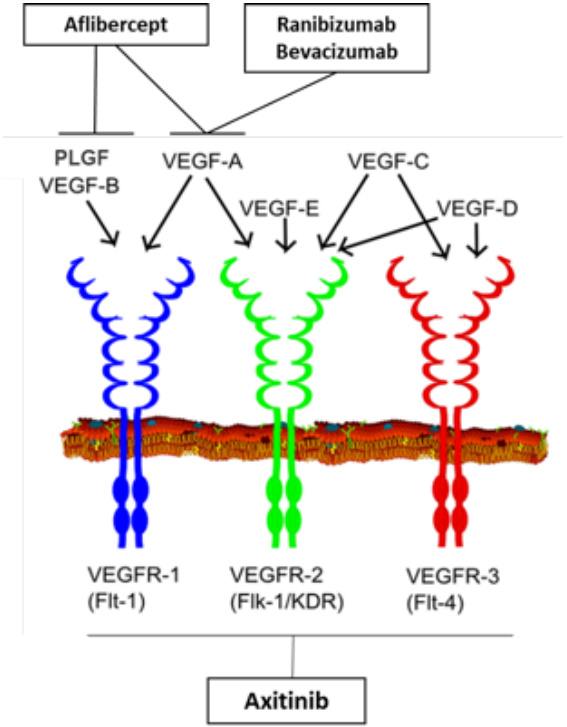


Cleveland Clinic

AMD Vascular Endothelial Growth Factor Treatment Approaches

Current AMD Therapies Predominantly Focus on VEGF-A Blockade, not VEGF Receptors

- Anti-VEGF-A increases VEGF-C [1] & VEGF-D[2]
- Broad VEGF blockade may improve outcomes
- A Phase 2 study yielded better AMD outcomes with anti-VEGF-A,C,D vs anti-VEGF-A



Suprachoroidal Axitinib May Improve Outcomes with Its Broad VEGF Blockade

- Inhibits VEGFR-1, VEGFR-2, VEGFR-3
- Inhibited corneal, retinal, and choroidal angiogenesis in animal models[3-7]
- More effective than other TKIs for experimental corneal neovascularization in animal models
- Better ocular cell biocompatibility than other TKIs[8]

Sources: 1. Cabral T et al. Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers. Ophthalmol Retina. 2018 January ; 2(1): 31–37. doi:10.1016/j.oret.2017.04.004. | 2. Lieu et al. The Association of Alternate VEGF Ligands with Resistance to Anti-VEGF Therapy in Metastatic Colorectal Cancer. PLoS ONE 8(10): e77117. | 3. Riquelme et al. Topical axitinib is a potent inhibitor of corneal neovascularization. Clinical and Experimental Ophthalmology 2018; 46: 1063–1074 | 4. Yuan et al. Ocular Drug Delivery Nanowafer with Enhanced Therapeutic Efficacy. ACS Nano. 2015 Feb 24;9(2):1749-58. | 5. Giddabasappa et al. Axitinib inhibits retinal and choroidal neovascularization in in-vitro and in-vivo models. Exp Eye Res. 2016, 145: 373-379. | 6. Nakano et al. Short-term treatment with VEGF receptor inhibitors induces retinopathy of prematurity-like abnormal vascular growth in neonatal Rats. Exp Eye Res. 2016. 143: 120-131. | 7. Kang et al. Antiangiogenic Effects of Axitinib, an Inhibitor of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase, on Laser-Induced Choroidal Neovascularization in Mice. Curr Eye Res. 2012. 38: 119-127. | 8. Theile et al. Multikinase Inhibitors as a New Approach in Neovascular Age-Related Macular Degeneration (AMD) Treatment: In Vitro Safety Evaluations of Axitinib, Pazopanib and Sorafenib for Intraocular Use. Klin Monatsbl Augenheilkd

Cleveland Clinic

Suprachoroidal Axitinib in Animal Models

Across all animal models

- Suprachoroidal axitinib was well tolerated in all species
- No overt signs of toxicity
- Sustained, high exposure observed in ocular tissues through 10 weeks
  - Highest levels in the sclera/choroid/RPE > retina > vitreous
- No quantifiable axitinib detected in plasma or aqueous humor

Conclusion

Suprachoroidal CLS-AX has potential as a bi-annual therapy for nAMD

- Intrinsic **high potency**, pan-VEGF inhibition through receptor blockade
- **Prolonged duration** observed in PK studies
- **Pharmacodynamic effect** demonstrated in multiple animal models
- **Targeted** therapy for affected tissue layers via suprachoroidal injection