RegenaVision

Scientific Team

A medicinal chemist, cell biologists and a retinal specialist are interested in dry AMD, a leading cause of blindness with no approved treatment

Mark Fields,
MPH, PhD
Assistant Professor
Yale Ophthalmology and Visual Science

Cell biologist with experience in academic and industrial ophthalmic therapeutic development and retinal disorders.

Lucian Del Priore,
MD, PhD
Vitreo-retinal Specialist
Yale Ophthalmology and Visual Science

Vitreo-retinal specialist with first-hand insights into patient populations and current treatments of ocular disorders.

Hui Cai,
MD, PhD
Research Scientist
Yale Ophthalmology and Visual Science

Research Scientist with over 30 years ophthalmic R&D drug discovery experience in the area of retinal degenerative disease.

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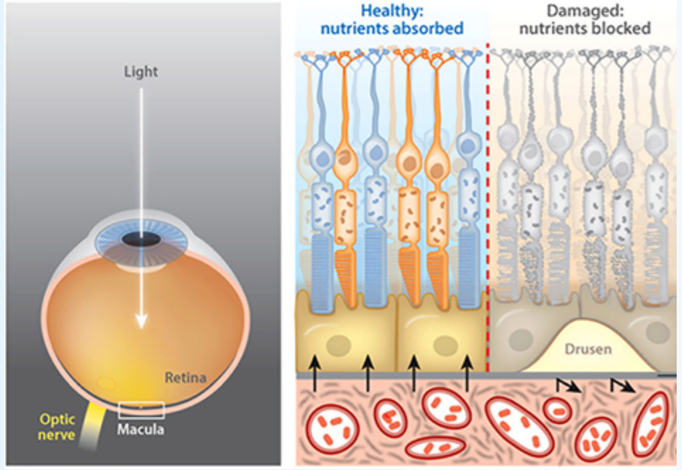
Denton Hoyer,
PhD
Medicinal Chemist
Independent consultant

Expertise in critical assessment of lead matter from HTS campaigns and new target discovery, formulation development for *in vivo* and pharmacokinetic studies.

No approved therapies to prevent the onset or progression of dry AMD

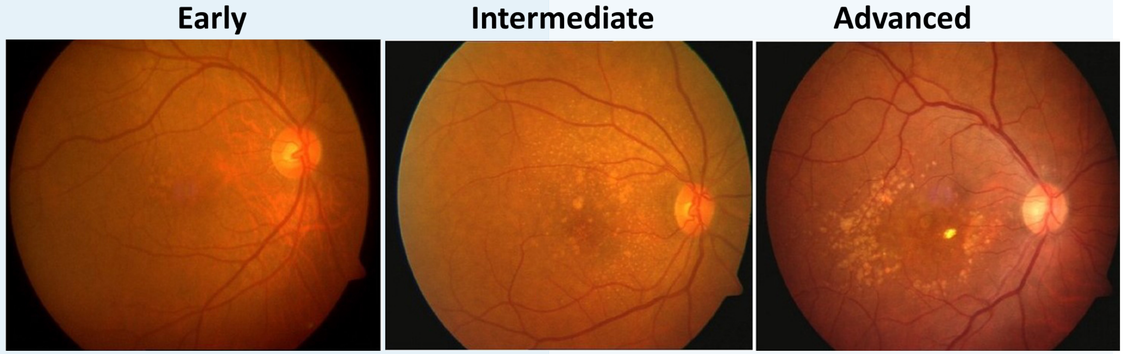
Disease Overview

- AMD is a progressive degenerative disease of the retina
- Major cause of legal blindness
- Patient population - **11 million** (US);**186 million** (WW)
- Advanced AMD characterized by retinal pigment epithelium (RPE) and photoreceptor cell death



Contributors to disease pathology

Stages of dry AMD



- **Oxidative stress** drives disease pathology in AMD
- Mitochondrial dysfunction occurs early in disease
- Development of drusen (lipid deposits under retina)
- Provides some target for preventing disease progression

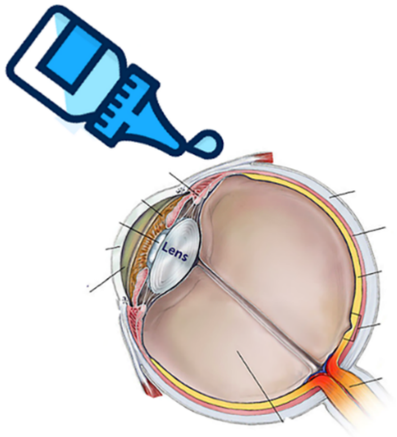
Disease drivers

Our goal is to develop local therapy to prevent progression of dry AMD

Target Product Profile

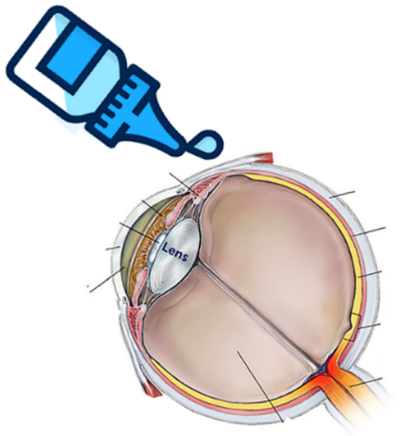
New small molecule eye drops that:

- Prevents progression of:
  - Early to intermediate dry AMD
  - Intermediate to advanced AMD
  - Worsening of advanced AMD



- Will reach the back of the eye

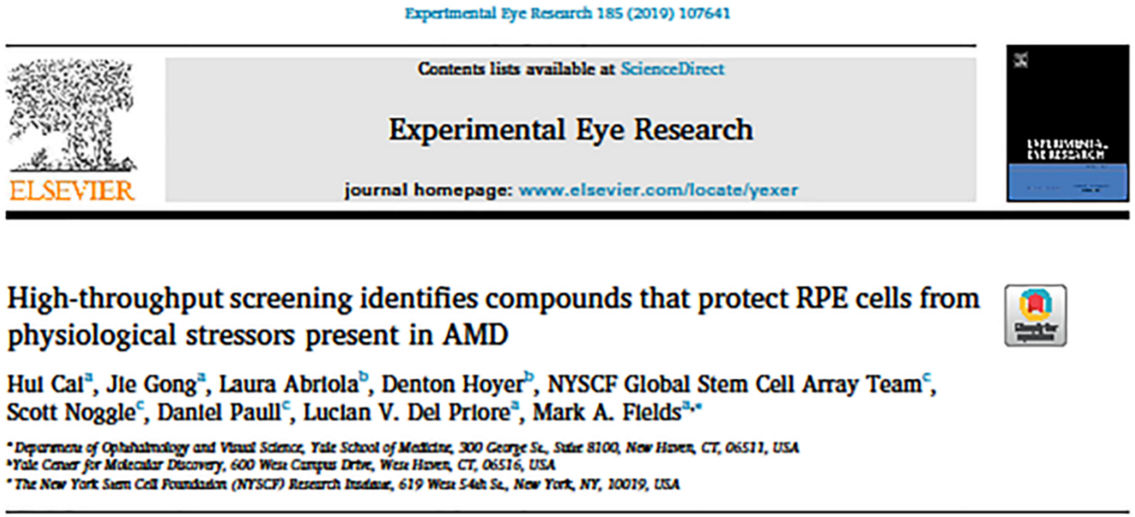
- Has a known safety profile and drug-drug interactions



- Protect RPE from oxidative damage/ and mitochondrial dysfunction

Primary Screening Rationale

- We developed a phenotypic high-throughput screen that mimics the effects of oxidative damage in RPE cells at the Yale Center for Molecular Discovery (Cai et al., 2019).
- ~85,000 compounds screened
- Libraries: Pharmakon 1600, Enzo FDA Approved drugs, SelleckChem Kinase Inhibitor, Enzo Kinase inhibitor library 2016,YCMD Tested in Humans, Analyticon MACROx and NATx, ChemDiv Synthetic, and ChemBridge DiverSet
- 132 “screen actives” over threshold
- Lead were reviewed by 3 expert medicinal chemist and computationally assessed for drug-like properties.
- 3 compounds from the hit series were selected for follow up studies.



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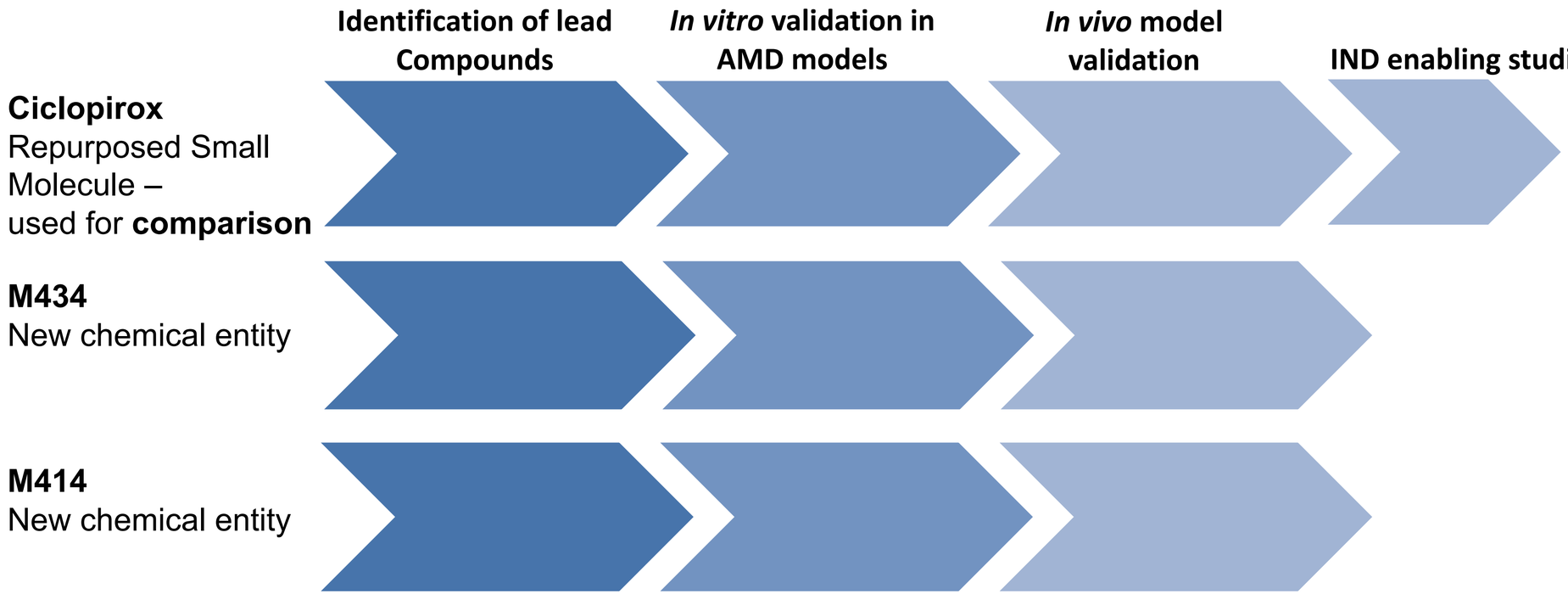
High-throughput screening identifies compounds that protect RPE cells from physiological stressors present in AMD

Hui Cai[a], Jie Gong[a], Laura Abriola[b], Denton Hoyer[b], NYSCF Global Stem Cell Array Team[c], Scott Noggle[c], Daniel Paull[c], Lucian V. Del Priore[a], Mark A. Fields[a,*]

[a] Department of Ophthalmology and Visual Science, Yale School of Medicine, 300 George St., Suite 8100, New Haven, CT, 06511, USA
[b] Yale Center for Molecular Discovery, 600 West Campus Drive, West Haven, CT, 06516, USA
[c] The New York Stem Cell Foundation (NYSCF) Research Institute, 619 West 54th St., New York, NY, 10019, USA

3 Assets in Preclinical Development



In vitro models of AMD

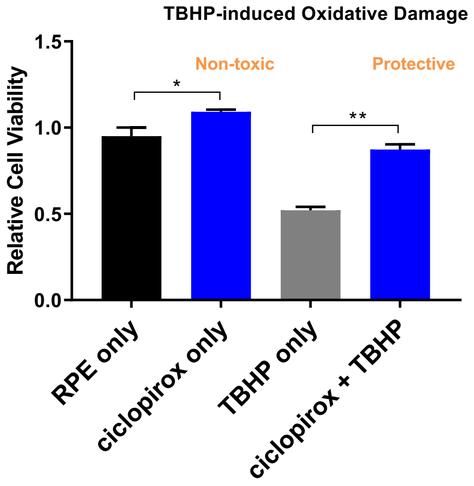
- Oxidative damage
- UV-B light damage
- Aged/Damaged Bruch's membrane
- Oxidative stress-induced mitochondrial dysfunction

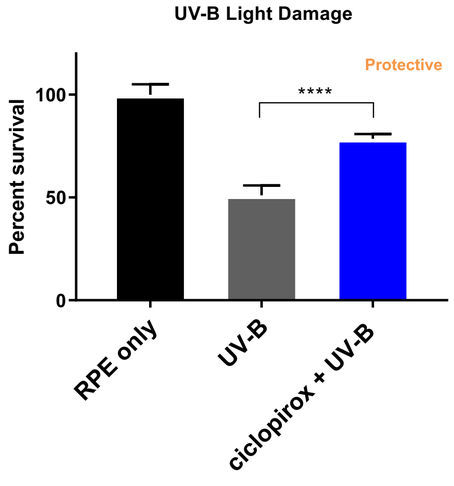
In vivo models of AMD

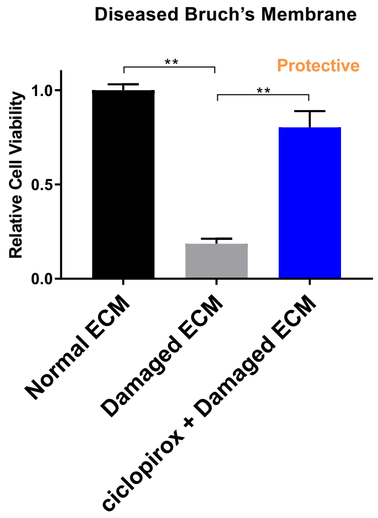
- Blue light damage model of geographic atrophy
  - ❑ Photo-oxidative damage induces apoptosis and retinal atrophy
  - ❑ Disease model MOA also associated with retinitis pigmentosa and retinal detachment

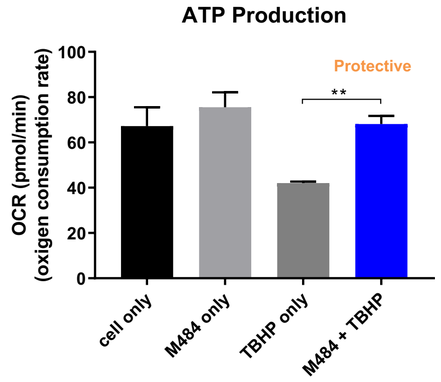
Ciclopirox shows efficacy in both *in vitro* and *in vivo* models of AMD

Ciclopirox show efficacy in 4 different models that mimic AMD

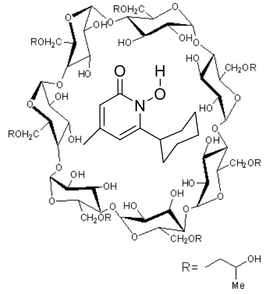


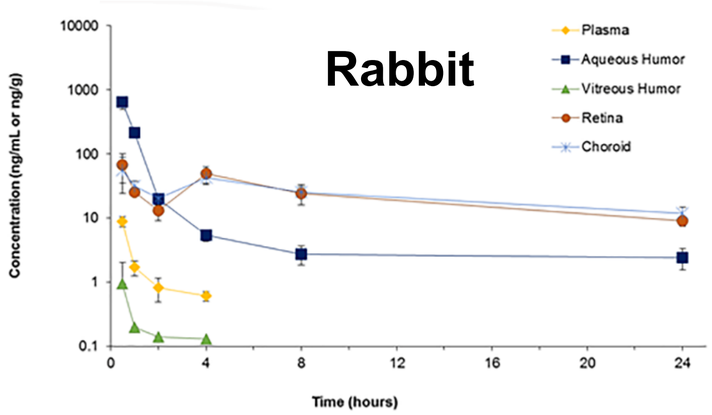






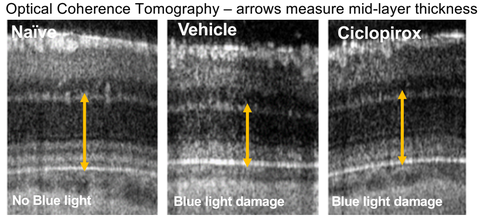
Caged ciclopirox successfully delivered to the retina and choroid in rabbit



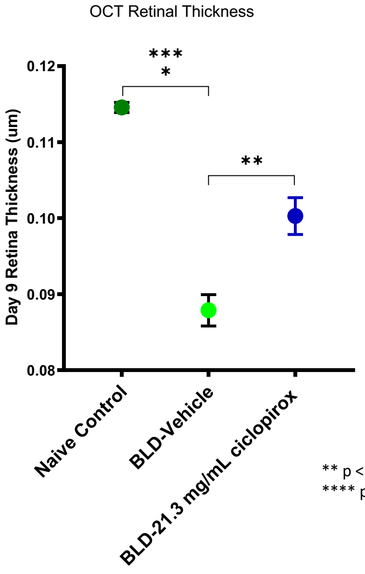


Cage ciclopirox improves retinal thickness after blue light damage (BLD) in rat

Optical Coherence Tomography – arrows measure mid-layer thickness

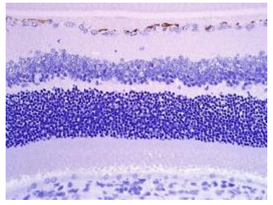


Hematoxylin & Eosin

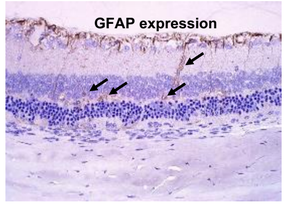


** p < 0.001
**** p < 0.00001

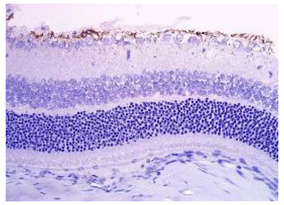
Caged ciclopirox prevents retinal stress after BLD in rat



No BLD
Naïve



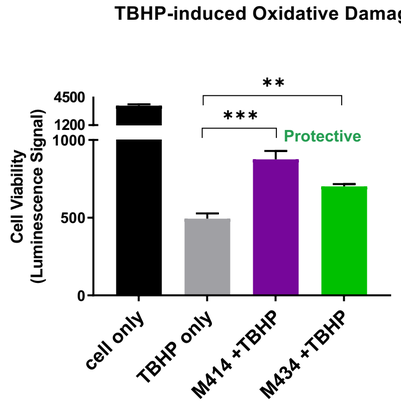
BLD
Vehicle alone

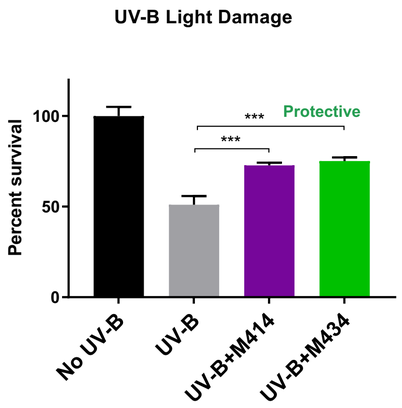


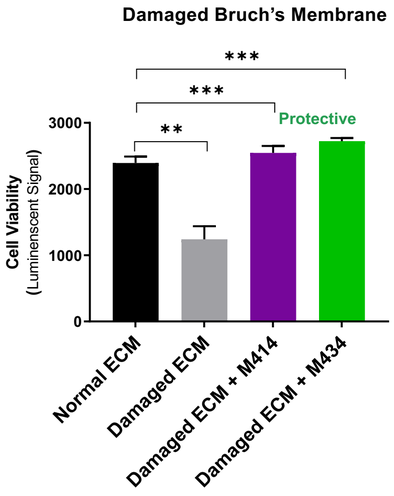
BLD
Ciclopirox

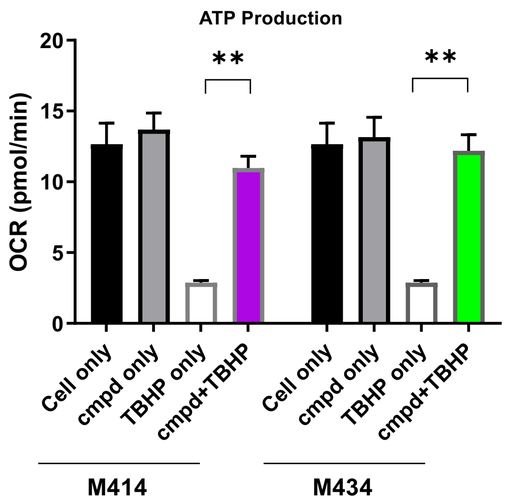
NCEs show efficacy in both *in vitro* and *in vivo* models of AMD

M414 and M434 show efficacy in 4 different models that mimic AMD

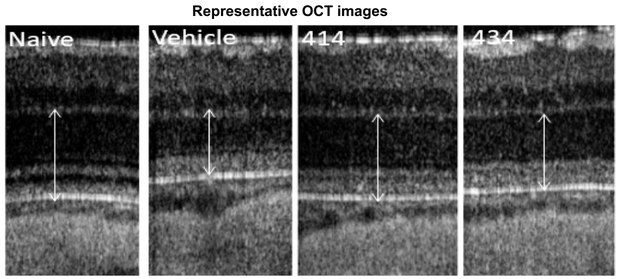




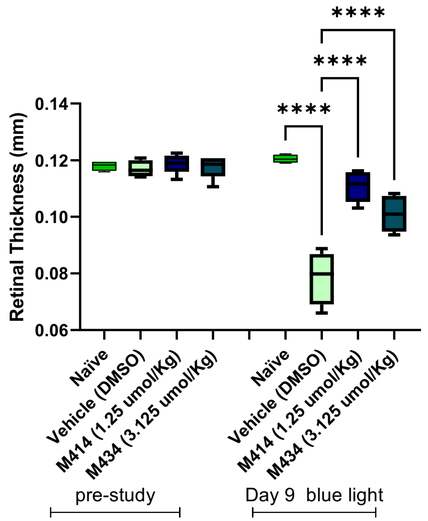




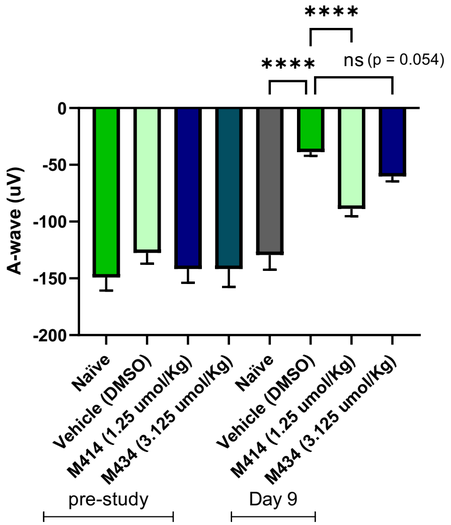
M414 and M434 improve retinal thickness after blue light damage (BLD) in rat



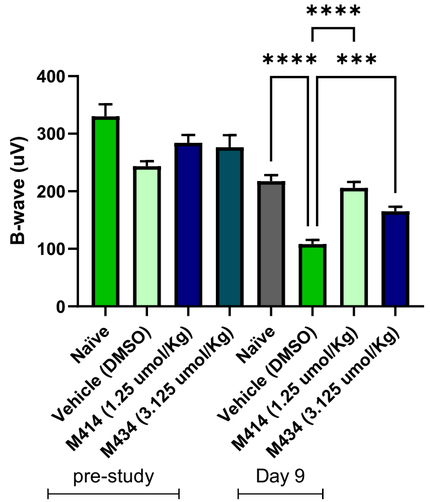
OCT - optical coherence tomography
*Experiments conducted by third party: Comparative Biosciences, Inc., San Francisco, CA



M414 and M434 restore visual function after BLD in rat



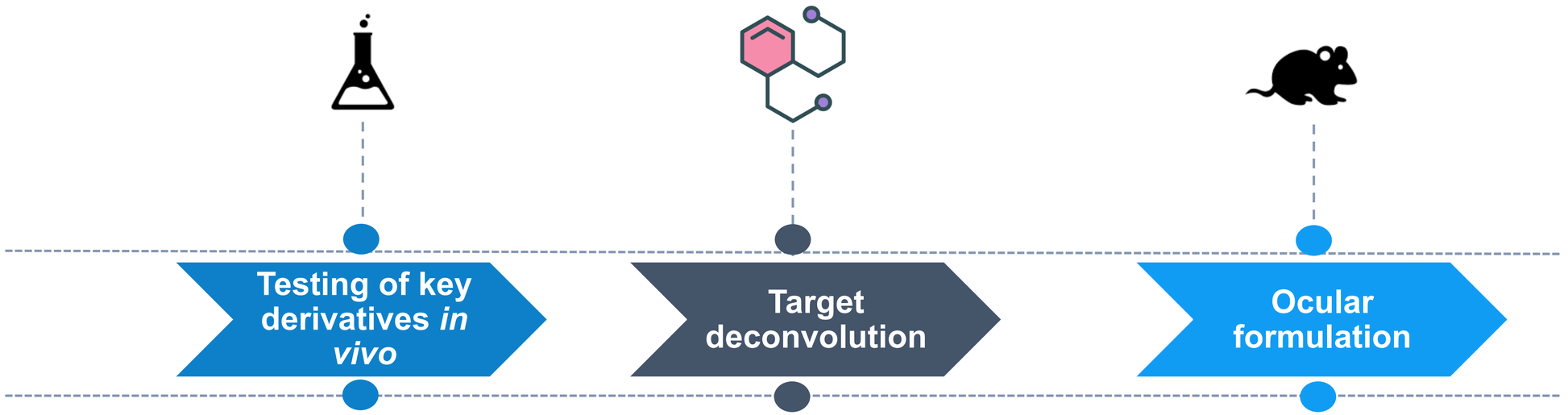
A-wave ERG



B-wave ERG

subcutaneous

Blavatnik award will help progress Regenavision to obtain the following data



Test efficacy of optimized analogs of NCEs in blue light damage model of geographic atrophy.

Comparative Biosciences
$80,000

Cellular thermal shift assay (CETSA) to determine target engagement.

Pelago Biosciences
$120,000

Formulation development for **topical** for early/intermediate AMD and **intravitreal (IVT)** delivery for late AMD.

PharmOptima, LLC
$50,000

Competitive Landscape

NCEs and ciclopirox would offer significant advantages over current competitors in the form of a more convenient ROA and broader patient population

	APL-2	Zimura/ARC1905	Elamipretide	M414 and M434
Manufacturer	**Apellis Pharmaceuticals**	**Iveric Bio**	**Stealth Therapeutics**	**RegenaVision**
Phase	Ph III	Ph III	Ph IIb	Preclinical
Study population	GA secondary to Dry AMD	GA secondary to Dry AMD	AMD w/ non central GA	**Early to intermediate Dry AMD**
ROA	Intravitreal injection	Intravitreal injection	Subcutaneous Injection	**Topical**
MOA	Complement Pathway C3 therapy	Complement Pathway C5a therapy	Mitochondrial dysfunction/ROS	Mitochondrial dysfunction/ROS
Primary endpoints	• Change in total area of GA Lesion(s) in the study eye (in mm2) as Measured by Fundus Autofluorescence (FAF) (Baseline, 12 months)	• Mean rate of change in GA over 12 months (measured at three time points: Baseline, Month 6, and Month 12)	• Change in low-luminance best-corrected visual acuity	Considerations: • Change in low-luminance best-corrected visual acuity • Rate of anatomic progression of geographic atrophy
Data readout from phase 2 trials	• GA growth rate reduction: 29% and 20% compared to sham depending on dosing regiment	• GA mean growth reduction: ~27% compared to sham	• N/A	• N/A

Executive Summary

- Established unique screening process for dry AMD
- Discovered and optimized 3 compounds (1 repo, 2 NCEs)
- Validated in CRO setting using dry AMD models
- Statistically significant improvement in *in vitro* and *in vivo* models of dry AMD
- Looking to raise $250,000 for formulation development and pre-IND studies.