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

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

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

Denton Hoyer, PhD
Medicinal Chemist
Independent consultant

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

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

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

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

Disease drivers

- 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

Stages of dry AMD

- Early
- Intermediate
- Advanced
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
- 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.
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

**Identification of lead compounds**
- *Ciclopirox* Repurposed Small Molecule used for **comparison**
- M434 New chemical entity
- M414 New chemical entity

**In vitro validation in AMD models**

**In vivo model validation**

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

Ciclopirox show efficacy in 4 different models that mimic AMD

- **TBHP-induced Oxidative Damage**
  - Non-toxic
  - Protective

- **UV-B Light Damage**
  - Protective

Diseased Bruch’s Membrane

- **Normal ECM**
  - Protective

- **Diseased ECM**
  - Protective

- **ciclopirox + Diseased ECM**
  - Protective

**ATP Production**

- **cell only**
  - Protective

- **MAM only**
  - Protective

- **TBHP only**
  - Protective

- **MAM + TBHP**
  - Protective

Caged ciclopirox successfully delivered to the retina and choroid in rabbit

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

Caged ciclopirox prevents retinal stress after BLD in rat
M414 and M434 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

M414 and M434 restore visual function after BLD in rat

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

Representative OCT images

OCT - optical coherence tomography

*Experiments conducted by third party: Comparative Biosciences, Inc., San Francisco, CA
Testing of key derivatives in vivo

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

Comparative Biosciences
$80,000

Target deconvolution

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

Pelago Biosciences
$120,000

Ocular formulation

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

PharmOptima, LLC
$50,000
NCEs and ciclopirox would offer significant advantages over current competitors in the form of a more convenient ROA and broader patient population.

<table>
<thead>
<tr>
<th>APL-2</th>
<th>Zimura/ARC1905</th>
<th>Elamipretide</th>
<th>M414 and M434</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Apellis Pharmaceuticals</td>
<td>Iveric Bio</td>
<td>Stealth Therapeutics</td>
</tr>
<tr>
<td>Phase</td>
<td>Ph III</td>
<td>Ph III</td>
<td>Ph IIb</td>
</tr>
<tr>
<td>Study population</td>
<td>GA secondary to Dry AMD</td>
<td>GA secondary to Dry AMD</td>
<td>AMD w/ non central GA</td>
</tr>
<tr>
<td>ROA</td>
<td>Intravitreal injection</td>
<td>Intravitreal injection</td>
<td>Subcutaneous Injection</td>
</tr>
<tr>
<td>MOA</td>
<td>Complement Pathway C3 therapy</td>
<td>Complement Pathway C5a therapy</td>
<td>Mitochondrial dysfunction/ROS</td>
</tr>
<tr>
<td>Primary endpoints</td>
<td>• Change in total area of GA Lesion(s) in the study eye (in mm²) as Measured by Fundus Autofluorescence (FAF) (Baseline, 12 months)</td>
<td>• Mean rate of change in GA over 12 months (measured at three time points: Baseline, Month 6, and Month 12)</td>
<td>• Change in low-luminance best-corrected visual acuity</td>
</tr>
<tr>
<td>Data readout from phase 2 trials</td>
<td>• GA growth rate reduction: 29% and 20% compared to sham depending on dosing regiment</td>
<td>• GA mean growth reduction: ~27% compared to sham</td>
<td>• N/A</td>
</tr>
</tbody>
</table>
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 \textit{in vitro} and \textit{in vivo} models of dry AMD

• Looking to raise $250,000 for formulation development and pre-IND studies.