RegenaVision
Retinal Therapies to Restore Vision
TEAM

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No Approved Therapies to Treat Dry Age-Related Macular Degeneration

Disease Overview

• Thinning of macula at the functional center of retina
• Results in blurred vision and, eventually, blindness
• Affects people over the age of 50
• ~11 Million patients in US
• ~196 Million worldwide
• Advanced AMD or geographic atrophy characterized by *RPE cell death

Disease Drivers

• Oxidative Stress
• Mitochondrial Dysfunction
• Development of Drusen (lipid deposits under retina)
• Therapies targeting mitochondrial dysfunction are the best approach to reduce inflammation and disease progression

*RPE, Retinal Pigment Epithelium
Our Goal is to Develop Eye Drops to Treat Dry AMD

**Target Product Profile**

New small molecule eye drops that:

- Treat early to intermediate dry AMD
- Reach the back of the eye
- Protect *RPE from oxidative damage and mitochondrial dysfunction
- Has a known safety profile and DDIs

Eye drop formulation will provide a convenient, patient compliant, and non-invasive mode of delivery

*RPE, Retinal Pigment Epithelium*
M484: a candidate molecule for dry AMD

- **IP**
  - Lead candidate **M484 and 2 novel chemical entities were identified** via phenotypic high-throughput screen (Cai et al., 2019).
  - Composition is off patent for M484, PCT application WO2019136466A1 with broad utility claims was filed in 2019 for the treatment of ocular diseases.
  - **M484** is FDA-approved as a topical antifungal medication and its composition is off-patent.
  - **M484** validated in RPE-based AMD assays (Cai et al., 2019).

- We have **successfully formulated M484 for ocular delivery**.
M484: Presumed Mechanism of Action

HIF prolyl hydroxylase inhibitor improves mitochondria function

Metabolic Stress

↓

Reactive oxygen species production

↓

HIF-1 stabilization

↓

HIF-1 prolyl hydroxylase inhibition

M484

↑ Mitochondrial Function

↑ Neuroprotection

Ma et al., 2013; Liu et al., 2016; Cai et al. 2019

HIF-1 - Hypoxia-inducible factor 1
HIF-PHD - Hypoxia-Inducible Factor Prolyl Hydroxylase
TBHP - Tert-butyl hydroperoxide

RPE Exposure to Oxidative Stress

ATP Production

HIF-1 stabilization

↑ Mitochondrial Function

↑ Neuroprotection
M484 Successfully Delivered to the Retina and RPE in Rat and Rabbit

Topical ocular delivery of M484 still in retina at 45 nM conc. at 24 h post-treatment

- An efficacious dose delivered to retina at 24 hrs based on \textit{in vitro} EC\textsubscript{50} (>45 nM)
- No abnormal observations noted in the eye at 24 hrs

**Hydroxypropyl-β-cyclodextrin based formulation**
- Well tolerated in eye
- Increases bioavailability
- Excellent water solubility achieving high concentrations within acceptable osmolality

\[ \text{R}=\text{CH}_2\text{CH}(-\text{Me}) \]
M484 in Preclinical Development

Efficacy data in blue light damage model of geographic atrophy in rat (topical delivery of M484) available this month

As determined by:

- Electroretinography (ERG)
- Optical coherence tomography (OCT)
- Histopathology
- Polymerase chain reaction (PCR)

*Fields lab and Comparative Biosciences, Inc.*
**Competitive Landscape**

M484 would offer significant advantages over current competitors in the form of a more convenient ROA and broader patient population.

<table>
<thead>
<tr>
<th></th>
<th>APL-2</th>
<th>Zimura/ARC1905</th>
<th>Elamipretide</th>
<th>M484</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>Ph III</td>
<td>Ph III</td>
<td>Ph IIb</td>
<td>Preclinical</td>
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<tr>
<td><strong>Study population</strong></td>
<td>GA secondary to Dry AMD</td>
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<td>AMD w/ non central GA</td>
<td><strong>Early to intermediate Dry AMD</strong></td>
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<td><strong>ROA</strong></td>
<td>Intravitreal injection</td>
<td>Intravitreal injection</td>
<td>Subcutaneous Injection</td>
<td><strong>Topical</strong></td>
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<td><strong>MOA</strong></td>
<td>Complement Pathway C3 therapy</td>
<td>Complement Pathway C5a therapy</td>
<td>Mitochondrial dysfunction/ROS</td>
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<td><strong>Primary endpoints</strong></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>
<td>Considerations: • Change in low-luminance best-corrected visual acuity • Rate of anatomic progression of geographic atrophy</td>
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<td><strong>Data readout from phase 2 trials</strong></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>
<td>• N/A</td>
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Our proposal: M484 lead optimization

1. Synthesis of key derivatives
   - Optimize for potency and develop novel compositions of matter and strengthen the IP position
   - Med. Chem. – Denton Hoyer, Ph.D.
   - $100K

2. Target identification chemistry
   - Determine where a linker may be added for protein pull-down for target identification experiments in-house.
   - YCMD
   - $100K

3. Ocular toxicology
   - 28 Day GLP Toxicology Study of Lead Compound for IND-enabling studies
   - PharmOptima, LLC
   - $100k

Timeline:
- 2-3 months
- 2-3 months
- 4-6 months
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