Macrophage modulation in blinding eye disease
first focusing on dry Age Related Macular Degeneration
A leading cause of irreversible blindness

The Problem:

Multigenic with environmental overlay

Clinical trial design is difficult:

Complex disease:

No approved therapeutics for dry AMD

Late enrollment
Endpoint: rate of GA expansion

area of tissue loss

Multigenic with environmental overlay

Genetics: complement
Epidemiology: tissue stress
Histopathology: immune cells

… disease of the Innate Immune System
The Innate Immune System:

**Complement & Macrophages**

- a catalytic cascade

- effector arm of the IIS
The Innate Immune System:

...and we suggest macrophages are responsible for GA

Geographic Atrophy tissue is missing...

Drusen regression a predictor of late AMD...

Macrophages & MCP-1 are present in eyes with GA

Senlaab et al
EMBO Mol Med
(2013) 5: 1775-1793
The Innate Immune System:

Complement & Macrophages are in continuous dialogue...

Complement in blood: catalytic cascade

...to rapidly activate, amplify and destroy pathogens
The Innate Immune System:

Complement & Macrophages are in continuous dialogue...

Complement also “decorates self”

...to distinguish self from non-self & abnormal self
Complement & Macrophages are in continuous dialogue...

“macrophages listen”

...and respond by changing their behaviour
Macrophage "polarization" is plastic

- **Inflammatory**
  - Phagocytic
- **Non-Inflammatory**
  - House-keepers
- **Angiogenic**
  - Phagocytic

A Sica & A Mantovani, Macrophage plasticity and polarization:

Transcriptome
Tracery’s approach:

Directly address macrophage plasticity...

Our Disease Hypothesis: responsible for GA

Tracery’s approach:

Directly address macrophage plasticity...

Our Disease Hypothesis: responsible for GA

Our therapeutic Approach: reduce the M1 transcriptome by altering mRNA expression

...converting M1 macrophages back to neutral

Tracery’s Lead:

**TMi-018**

a 1st-in-class transcriptional regulator of inflammation-induced macrophage plasticity

Robust international estate; issued & pending for additional indications, formulations, etc...

MCP-1 (ccl2) is a master switch
TMi-018 reduces its targets at the mRNA and protein level

**Dose-dependently reduces target**
MCP-1, -3 mRNA

**Down-regulates downstream transcription factors**

**Reduces target proteins**

**Down-regulates the inflammasome**
We reduce pro-inflammatory gene expression:

**TMi-018 reduces its targets at the mRNA and protein level**

**Dose-dependently reduces target MCP-1, -3 mRNA**

**Down-regulates downstream transcription factors**

**Reduces target proteins**

**Down-regulates the inflammasome**

**Reduces macrophage infiltration & protects against RPE loss**

...and preserves retinal function
We protect against GA-like tissue loss:

Dose-dependently reduces GA-like patch formation

Dose-dependently reduces GA-like patch expansion

... by making macrophages behave
We protect against GA-like tissue loss:

Dose-dependently reduces
GA-like patch formation

Dose-dependently reduces
GA-like patch expansion

NO upregulation of angiogenic genes

... without inducing wet
Our team:

...is well-versed in drug development

**Founder, CEO**
Shelley Boyd  
MD, FRCSC

**Exec VP, BD & Strategy**
Paul Howes  
MBA, CPA

**CFO**
Ken Howling

**Dir Operations**
Natalie Pankova  
PhD

**Regulatory consultant**
Gary Novack  
PhD

**Partner**
Naheed Kurji  
MBA

Ophthalmologist (retina specialist);  
Clinician-Scientist, U of Toronto, JLABS;  
Former, Global Head, Ocular Angiogenesis Research Program, Novartis (Switzerland)

Former Executive Chair, Thrombogenics US; CEO Inotek Pharma; President Baush & Lomb (Americas), President Merck Frosst; over 30 years experience in Ophtha BD & Strategy, in large pharma, med device, and venture-backed biotech.

Over 25 years experience in pharma financial & corporate affairs, including 11 years with Valeant Pharma, and CFO of Highland Therapeutics

8+ years of TMI technology expertise, team & program management; former Pre-Clinical Team Lead, TMI; growing expertise in blockchain technology

Clinical Pharmacology, 25+ years ophthalmic drug development & regulatory affairs. Brought >40 ophthalmic compounds through

President & CEO, Cyclica Inc, commercialization of artificial intelligence, in silico identification of novel drug targets
Our clinical development plan:

Next steps:

We’re preparing for clinical trial

**CMC:** API production underway  
Intra-vitReal formulation established

**Regulatory:** Completing IND enabling studies  
Preparing IND documentation
Precision Drug Development for Blinding Eye Disease
Macrophage modulation for blinding eye disease
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