Financial Disclosures

- Shareholder (>5%) of Apellis Pharmaceuticals
- Shareholder (>5%) of Revon Systems, LLC
Complement C3 Inhibition in AMD

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Complement Inhibitors under development in Geographic Atrophy

**Activation Pathways**

- **Classical pathway**
  - Activated by antibody-antigen complex

- **Lectin pathway**
  - Activated by lectin and mannose complex

- **Alternative pathway**
  - Spontaneous C3 convertase activation

**C3**

- **C3a**
  - Inflammation

- **C3b**
  - Cell removal

- **C5**

  - **C5a**
    - Inflammation

  - **C5b MAC**
    - Cell destruction

**Lampalizumab**
Complement Inhibitors under development in Geographic Atrophy

Activation Pathways

- Classical pathway: Activated by antibody-antigen complex
- Lectin pathway: Activated by lectin and mannose complex
- Alternative pathway: Spontaneous C3 convertase activation

- C3
  - C3a: Inflammation
  - C3b: Cell removal
- C5
  - C5a: Inflammation
  - C5b: MAC

Cell destruction

Lampalizumab

Eculizumab, Zimura, LFG-316
Complement Inhibitors under development in Geographic Atrophy

Activation Pathways
- Classical pathway: Activated by antibody-antigen complex
- Lectin pathway: Activated by lectin and mannose complex
- Alternative pathway: Spontaneous C3 convertase activation

C3 → C3a, C3b → Cell Removal → C5 → C5a, C5b → MAC → Cell Destruction

Inflammation → C3a, C5a → POT-4 APL-2, Lampalizumab → Eculizumab, Zimura LFG-316
Inhibiting complement might reduce progression of GA

**LAMPALIZUMAB**
- Selectively inhibits alternative pathway
- Reduced GA progression by 44% in CFI+ patients
- No apparent effect in CFI- patients
- Monthly injections

**OPPORTUNITY**
- Efficacy in CFI- patients
- Further reduction of progression in CFI+ patients
- Reduced frequency of injections

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Emerging data indicates that neo-auto-antigens drive persistent, steroid-unresponsive and targeted inflammation and tissue damage via complement activation.
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Role of Complement in AMD?

Tissue specific Dendritic Cells

Th17 Polarization

Break Self-Tolerance

Fluid Phase Activation

Phagocyte Activation (e.g. M1/ M2)
  Oxidation of proteins / phospholipids
  Adduct formation

Low affinity Polyclonal Antibodies

B Cells

T Cells

Th17 Signaling

Oxidative Damage, Allergens Infections?

Alternative (MDA → CFH₄₀₂)

IMMUNE

Cell Death

LYSIS

Classical

Complement Activation

C₅, fD

fD

IMMUNE

C₅, fD

fD

Classical
Emerging data indicates that neo-auto-antigens drive persistent, steroid-unresponsive and targeted inflammation and tissue damage via complement activation.

**MAC or Complement Immunotherapy in GA?**

- Tissue specific Dendritic Cells
- Break Self-Tolerance
- Fluid Phase Activation
  - Phagocyte Activation (e.g. M1/ M2)
    - Oxidation of proteins / phospholipids
    - Adduct formation
- Th17 Polarization
- Oxidative Damage, Allergens Infections?
- Infections?
- Complement Activation
  - Classical
  - Alternative (MDA à CFH₄₀)
- Cell Death
- Low affinity Polyclonal Antibodies
- MAC or Complement Immunotherapy in GA?
Emerging data indicates that neo-auto-antigens drive persistent, steroid-unresponsive and targeted inflammation and tissue damage via complement activation.

Which antigens?

Role of Complement in AMD?
Which antigens?

CEP has been associated with AMD but its role never elucidated

1. Mice and non-human primates immunized against CEP develop GA

![Diagram of CEP and HOHA formation](image)


2. Antibodies are found in patients with AMD and correlate with disease severity

![Graphs showing CEP adduct levels in AMD and controls](image)

T-cell autoreactivity against CEP

Cell-based assay to identify at risk patients on the point of convergence to advanced AMD and to evaluate the efficacy of drugs in patients, which will be demonstrated by immunoconversion of T-cell auto-reactivity. Cellular technology Limited (CTL), OH.
A randomized sham-controlled prospective Phase II clinical trial to assess the safety, tolerability and evidence of activity of APL-2 as a treatment for Geographic Atrophy

(Enrollment complete Summer 2016 – readout Summer 2017)
APL-2

APL-2 is a potent C3 inhibitor that combines good solubility with a long intravitreal half-life. It is a PEGylated conjugate of APL-1 (aka POT-4).

**APL-2**

- Freely soluble in water
- No MTD identified in monkeys
- Dose limited only by viscosity
- ↑Activity than POT-4
- Inhibits all 3 complement pathways
- Can be formulated in solution to be stable for months at room temperature

**PK in cyno after single IVT injection**

- Intravitreal $T_{1/2}$ (cyno) $\sim$ 3.2 days
- Serum $T_{1/2}$ (cyno) $\sim$ 10.4 days

![Graph showing PK in cyno after single IVT injection](image)
APL-2 systemically inhibits C3 in humans

Rabbit Red Blood Cell Alternative Pathway Hemolysis
(1:8 Plasma Dilution)
Filly – APL-2 Phase II Geographic Atrophy

Safety, Tolerability and Evidence of Activity N=240

Randomized 2:1:2:1

- APL-2 15 mg Monthly (AM) N=80
- Sham Monthly (SM) N=40
- APL-2 15 mg Every Other Month (AEOM) N=80
- Sham Every Other Month (SEOM) N=40

Randomization

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Follow up

- M15 M18
- M15 M18
- M15 M18
- M15 M18
Filly – APL-2 Phase II Geographic Atrophy

Key Inclusion Criteria

- **Study eye only (!)**

- ETDRS BCVA of 20/320 or better

- Total GA of 1 to 7 disk areas by FAF

- If GA is multifocal, at least one focal lesion must be ≥ 0.5 DA

- Presence of hyperautofluorescence in the junctional zone of GA
Primary Efficacy Endpoint
- The primary endpoint is the change in square root geographic atrophy (GA) lesion size from baseline at month 12 as measured by FAF.

Primary Safety Endpoint
- Number and severity of local and systemic treatment emergent adverse events (TEAE).
Recruitment acceleration

- Large, cloud-based database of patients signed up by their physicians

- Easy to use, free system (web and app) tracks disease relevant data

- Triad of outcome-based medicine
  - Confirmed Diagnosis
  - Standard Stratification
  - Standard Physician- and Patient-reported Outcomes
Recruitment acceleration

- Free software to stratify and follow patients
- Compensate physicians for very little work
- Give access to research to patients who are otherwise not exposed
- Patients become visible to research coordinators and can be invited in trial if prescreen matches
Conclusion: Evolution of Standard of Care in AMD

- **WET**
  - Standard: Anti-VEGF
  - Need: Improved Vision, Fewer Injections, No GA

- **GA**
  - Standard: Supportive
  - Need: First Approved Rx (anti-complement?), Fewer Injections, All Patients

- **INTERMEDIATE**
  - Standard: Supportive
  - Need: First Approved Rx, ID at-risk patients, Acceptable Product (oral?), Regulatory Path
Thank you Phil, Carmen and Harry!!!