Complement: the next frontier in immunology?
Cedric Francois, MD, PhD
Corfu, May 2017
Similarities between starfish and humans?

COMPLEMENT
The Complement System
The Complement System

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

Eculizumab

C3b

C5b

MAC

Inflammation

Cell destruction

Cell removal
Complement central to innate immunity

Innate
“Shock and Awe”

Adaptive
“Self vs Non-Self”
## Rise of Adaptive Immunity

<table>
<thead>
<tr>
<th>Palaeozoicum</th>
<th>Mesozoicum</th>
<th>Cenozoicum</th>
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<tbody>
<tr>
<td>Cmb</td>
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<td>Sil</td>
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<tr>
<td>Dev</td>
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<td>Per</td>
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<tr>
<td>Tri</td>
<td>Jur</td>
<td>Cre</td>
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<tr>
<td>Tert</td>
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</table>

### RAG genes

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

### Biological Functions

- Inflammation
- Cell destruction
- Cell removal

**VERTEBRATA**

![Cell Image](image)
Roles of Complement
Approved Complement Inhibitors

Activation Pathways
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C5
- C5a: Inflammation
- C5b MAC: Cell destruction

Approved Complement Inhibitors
- Cinryze (C1 inhibitor)
- Berinert (C1 Esterase Inhibitor)
- Ruconest (factor D inhibitor)
- Soliris (Eculizumab)
Complement Immunotherapy? in Refractory Myasthenia Gravis

>3 point change clinically meaningful
Complement Immunotherapy? in Neuromyelitis Optica

- Transverse myelitis
- Optic neuritis
- Optic neuritis and transverse myelitis
- Other
- Temporary discontinuation of eculizumab
- Eculizumab resumed
- Died

Before screening → Screening → First infusion → Treatment → After treatment

Before screening: -2 years to -1 year
Screening: 0
First infusion: 2 weeks
Treatment: 12 months, 15 months, 24 months
Temporary courses of complement inhibition to correct auto-immunity in diseases like PNH and AMD
Lead candidates target C3 central in the complement cascade

Activation Pathways

- Classical pathway: Activated by antibody-antigen complex
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Broad inhibition of complement cascade

- C3a: Inflammation
- C3b: Cell removal
- C5a: Inflammation
- C5b: MAC, Cell destruction

APL-2 inhibits C3, resulting in broad inhibition of the complement cascade.
APL-2 is a potent and selective C3 inhibitor

- APL-2
  - Long-acting version of APL-1
  - Subcutaneous for PNH
  - Intravitreal for GA

Peptides of the APL-1 / APL-2 family bind to a pocket of C3 and inhibit activation*

Complement in Paroxysmal Nocturnal Hemoglobinuria
Meaningful unmet need in PNH

DISEASE
- ~4,700 patients in the US
- Severe anemia and thrombotic risk
- ~35% 5-year mortality if left untreated (main cause: thrombosis)

STANDARD OF CARE
- Soliris® only approved therapy
  - ~$583,000 / year / adult patient

UNMET NEED SOLIRIS
- Average Hb ~10 g/dL
- Continued Transfusion dependency 35% - 40%

(Dr. Hillmen is an advisor to Apellis)
Intravascular vs extravascular hemolysis

Soliris does not block extravascular hemolysis

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

- **C3**
  - Leads to:
    - C3a → Inflammation
    - C3b → C5
  - In extravascular space, C3b on RBC

- **C5**
  - Leads to:
    - C5a → Inflammation
    - C5b → MAC
  - In extravascular space, C5b on immune cells

- **C5b MAC**
  - Exerts effects on intravascular space

**Notes**

- Soliris does not block extravascular hemolysis.
- C3b on RBC in extravascular space.
- C5b MAC in intravascular space.

**Abbreviations**

- C3b: Complement component 3b
- C5b: Complement component 5b
- MAC: Membrane Attack Complex
- RBC: Red Blood Cell
Can APL-2 block extravascular hemolysis?

Potential Benefit APL-2
- Reduced anemia and transfusion dependency

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

C3

C3b on RBC

C5

C5b MAC

Inflammation

C3a

C5a

Inflammation
APL-2 improves Hb and normalizes reticulocytes

Hemoglobin

Transfusions

Normal

Reticulocyte Count

Normal

Five of six subjects receiving 900mg / week or 1,200mg / 2 weeks
Phase 3 Superiority APL-2 vs Soliris

2017  2018  2019

Enrollment

Expected Hb

n=TBD

6-month efficacy

APL-2

APL-2 Twice per Week

n=TBD

Expected Hb

n=TBD

Expected Hb
Complement in Age-related Macular Degeneration
Meaningful unmet need in age-related macular degeneration

**DISEASE**

- **Intermediate AMD**: drusen but no serious vision loss
- **Wet AMD**: blood leakage in retina
- **GA**: slow progressive retinal death → starts in periphery / blind when central
- ~15M patients with AMD, ~1M with GA in US*

**STANDARD OF CARE**

- **Wet AMD**: anti-VEGF (Lucentis, Avastin, Eylea)
- **iAMD and GA**: supportive care

**UNMET NEED**

- **Intermediate AMD**: no approved therapies
- **GA**: no approved therapies

* http://www.asrs.org/patients/retinal-diseases/2/agerelated-macular-degeneration
GA Market Opportunity

Note: Assumes EU-5 and ROW launches 2 and 3 years after U.S., respectively. ~60% U.S. sales to total global used as a proxy in each year. A review of the landscape suggested that while Lucentis and Eylea were analogs, Eylea was a stronger analog. A blended average of U.S. to global sales was weighted toward Eylea, and used to inform the EU-5 and ROW scale-ups.

Source: L.E.K. analysis
Phase 2 GA – Filly design

Safety, Tolerability and Evidence of Activity N=246

Randomized 2:1:2:1

APL-2 15 mg
Monthly
(AM) N=86

Sham
Monthly
(SM) N=41

APL-2 15 mg
Every Other Month
(AEOM) N=79

Sham
Every Other Month
(SEOM) N=40

Randomization

Treatment Period

Follow up

AM=2

AEOM=2

SM=1

SEOM=1

D0 M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12 M15 M18

D0 M2 M4 M6 M8 M10 M12

D0 M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 M12 M15 M18

D0 M2 M4 M6 M8 M10 M12

D0 M2 M4 M6 M8 M10 M12
Phase 2 GA – Filly design

Safety, Tolerability and Evidence of Activity
N=246 subjects randomized 2:2:1:1

- APL-2 15 mg Monthly  
  N=86

- APL-2 15 mg EOM  
  N=79

- Sham Monthly  
  N=41

- Sham EOM  
  N=40

- APL-2 Monthly  
  N=84*

- APL-2 EOM  
  N=78*

- Sham Pooled  
  N=81*
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).
### Wet AMD conversions in **FILLY**

<table>
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<th>EOM (n=79)</th>
<th>EM (n=86)</th>
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<tr>
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<td>%</td>
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**Contralateral Wet AMD**

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<tr>
<td>%</td>
<td>0%</td>
<td>2%</td>
<td>17%</td>
<td>4%</td>
<td>29%</td>
<td>8%</td>
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- DSMB allowed study to continue based on stable VA
- Updated Investigator Brochure and Informed Consent
- Last patient last treatment: July 2017
Advancement of Disease PRE-2005

- HEALTHY → GA
- WET AMD → BLIND
Advancement of Disease 2005 - 2017

- Healthy
- ~20% require only few injections

- Wet AMD
- ~80% require chronic anti-VEGF

- GA
- ~98% develop GA after 7 years of anti-VEGF

- Blind

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Flow Superimposed on Structure

En face flow and intensity image

En face intensity image

CNV

ZEISS AngioPlex

ZEISS AngioPlex
Advancement of Disease POST-2017?

- Healthy
- C3 Inh.
- GA
- WET AMD
- BLIND

~20% require only few injections
~80% require chronic anti-VEGF
~98% after 7 years chronic anti-VEGF
Therapeutic Potential

Complement Immunotherapy

- AMD
- Dry Eye
- Uveitis

- PNH
- aHUS
- AIH

- C3G
- IgA Nephropathy
- Lupus Nephritis
- Transplantation

- COPD
- Fibrosis

- rMG
- NMO
- MS
- Guillain Barre
- Alzheimer’s
Fun Facts about Complement

- C3 is required to mount a Th1 response

- Local organ synthesis of C3 is required to reject organs

- There is a fully functional complement system INSIDE intracellular vesicles that plays a key autocrine and regulatory role in immune cell biology

- Modulating complement in synaptic pruning and microglial regulation might have disease modifying potential in neurodegenerative diseases

- Complement regulation in immuno-oncology virtually unexploited
Complement in Reproduction
Thank you Dad
Thank you Mom