**Limitations of Eculizumab**

- Bone marrow failure
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**Bone Marrow Failure**

- Eculizumab prevents circulating cells from breaking down
- Has no effect if the marrow is not producing adequate blood cells
- Aplastic anemia
- Myelodysplastic syndrome

**Pipeline**

- Many drugs are in development to inhibit various complement components by various mechanisms
  - Many are being developed for other diseases but may be useful in PNH
- Increase the half-life of eculizumab or related drugs to reduce the frequency of infusions

**Some Candidates**

<table>
<thead>
<tr>
<th>Target</th>
<th>Name</th>
<th>Company</th>
<th>Class</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Coversin</td>
<td>Volution</td>
<td>Protein from tick saliva</td>
<td>Preclinical Phase I</td>
</tr>
<tr>
<td>C5</td>
<td>ALN-C05</td>
<td>Alnylam</td>
<td>si-RNA</td>
<td>Preclinical</td>
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<tr>
<td>C3</td>
<td>H17</td>
<td>Ellypsis</td>
<td>Monoclonal antibody</td>
<td>Preclinical</td>
</tr>
<tr>
<td>C3/Cb</td>
<td>APL-2</td>
<td>Apliris</td>
<td>Complementin family</td>
<td>Preclinical and phase I</td>
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<tr>
<td>Alt pathway C3 convertase</td>
<td>TT30</td>
<td>Alexion</td>
<td>CFH-based protein</td>
<td>Phase I</td>
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<tr>
<td>Alt pathway C3 convertase</td>
<td>Mini-CFH</td>
<td>Amyndas</td>
<td>CFH-based protein</td>
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<td>MASP-2</td>
<td>OM9721</td>
<td>Omeros</td>
<td>Monoclonal</td>
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<tr>
<td>Factor D</td>
<td>--</td>
<td>Achillion</td>
<td>Oral small molecule</td>
<td>Preclinical</td>
</tr>
<tr>
<td>C1/NH</td>
<td>Cyrinze</td>
<td>Shire</td>
<td>C1 esterase inhibitor</td>
<td>Available for C1/NH-def</td>
</tr>
</tbody>
</table>
**Stem Cell Transplantation**

**Benefits**
- The only curative therapy
- No further infusions
- Less expensive

**Limitations**
- Donor availability
- Transplantation related complications
  - Graft rejection
  - Graft-vs-Host disease
  - Infection
- Susceptibility to infection results in limited ability to be in public for about 1 year

**Stem Cell Transplantation is Curative for PNH**

**Overall Survival**

**URD Transplantation for Aplastic Anemia**

<table>
<thead>
<tr>
<th>Probability (%)</th>
<th>Months Post Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
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<tr>
<td>80</td>
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</tr>
<tr>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>12</td>
</tr>
</tbody>
</table>

- 50 mg/kg at 1 year: 97.4% (95% CI: 82.8% - 99.0%)
- 100 mg/kg at 1 year: 80.5% (95% CI: 64.8% - 89.7%)

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**Eculizumab Does Not Prevent Extravascular Hemolysis**

- Eculizumab prevents the MAC complex from forming, so no intravascular lysis of the cells
- Does not inhibit C3 activation which is normally blocked by DAF (CD55)
- Cells are coated with C3 components which do not induce lysis but are recognized and removed from the circulation by liver and spleen – extravascular hemolysis

**Newer Approaches in PNH**

- Serine protease inhibitor (serpin family)
- Regulates several inflammatory cascades
  - Blood coagulation
  - Complement (C1s, C1r, and MASP)
- Role to mitigate inflammation
- Approved for hereditary angioedema
- Also inhibits the alternative pathway by C1INH blocking the accumulation of C3 degradation products on CD55 deficient erythrocytes

Ritchie and Lambros 2006
Newer Approaches in PNH

- Small molecule ACH-4471
- Potentially orally administered
- Inhibits the alternative pathway (Factor D)
- Might prevent extravascular hemolysis

http://www.achillion.com/ACH-CFDIs

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Higher Dose or More Frequent Administration may be Necessary

Newer Approaches in PNH

- Monoclonal antibody


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Weston-Davies ASH 2014

Newer Approaches in PNH

- Protein derived from tick saliva (Ornithodoros moubata)
- Subcutaneous administration
- Effective in eculizumab resistance
- Works at C5
Newer Approaches in PNH

- RNAi (RNA interference) technology – reduces protein production
- Subcutaneous administration
- Long lasting
- Will not prevent extravascular hemolysis

ALN – CC5 Phase I/II

Hemolysis Control Can be Durable but Less Robust C5 Depression

Conclusions

- PNH is quite treatable:
  - supportive care
  - C5 inhibition via eculizumab or newer agents
  - Stem cell transplantation
- New therapies are being developed
  - Inhibition of C3 and other C components
    - Less extravascular hemolysis
  - Prolong the half-life for less frequent administration
  - Oral dosing