PNH: What is on the Horizon?

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Limitations of Eculizumab

- Bone marrow failure
- C3-mediated extravascular hemolysis
  - Complement receptor 1 mutations enhance this problem
- Residual intravascular hemolysis
  - May require higher dose or shorter intervals
- Intrinsic resistance to eculizumab due to altered C5 found n 3.5% of Japanese patients and rarely others
- Frequency of administration/logistics

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

Target	Name	Company	Class	Status
C5	Coversin	Volution	Protein from tick saliva	Preclinical Phase I
C5	ALN-CC5	Alnylam	si-RNA	Preclinical
C3	H17	EluSys	Monoclonal antibody	Preclinical
C3/Cb	APL-2	Apellis	Compstatin family	Preclinical and phase I
Alt pathway C3 convertase	TT30	Alexion	CFH-based protein	Phase I
Alt pathway C3 convertase	Mini-CFH	Amyndas	CFH-based protein	Preclinical
MASP-2	OMS721	Omeros	Monoclonal	Preclinical
Factor D	--	Achillion	Oral small molecule	Preclinical
C1INH	Cyrinze	Shire	C1 esterase inhibitor	Available for C1INH def

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Bone Marrow Failure

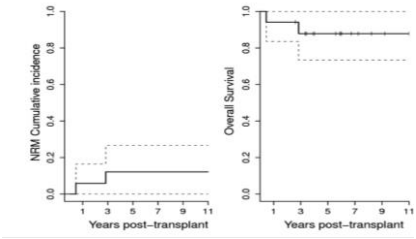
- Eculizumab prevents circulating cells from breaking down
- Has no effect if the marrow is not producing adequate blood cells
- Aplastic anemia
- Myelodysplastic syndrome

Stem Cell Transplantation

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

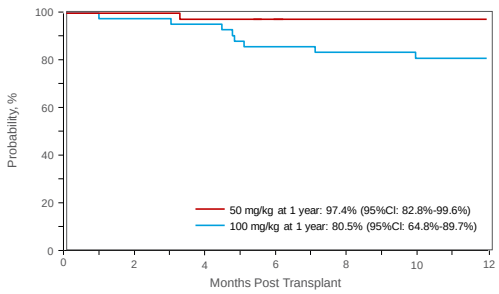
Limitations
- Donor availability
- Transplantation related complications
  - Graft rejection
  - Graft-vs-Host disease
  - Infection
- Susceptibility to infection results in limited ability to be in public for about 1 year

Stem Cell Transplantation is Curative for PNH



Pantin, et al. BBMT 2014;20:1435-9

Overall Survival URD Transplantation for Aplastic Anemia



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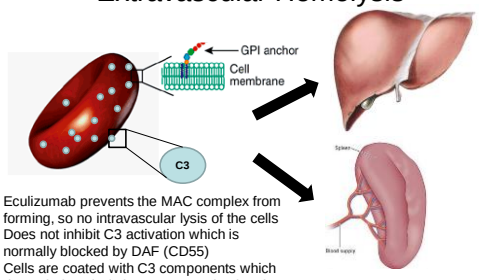
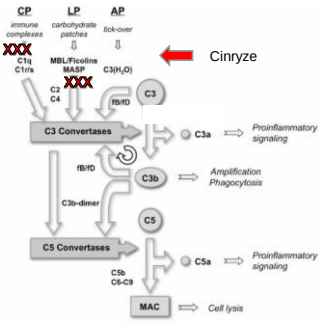
Eculizumab Does Not Prevent Extravascular Hemolysis



- 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 MASPs)
- 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

DeZern, et al. Exp Hematol. 2014; 42: 857–861
Ricklin and Lambris 2008

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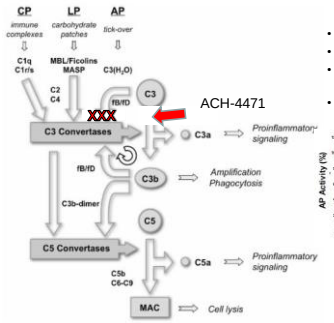
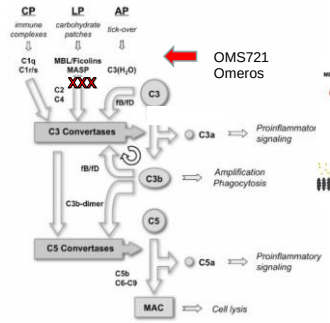


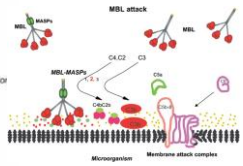
- Small molecule ACH-4471
- Potentially orally administered
- Inhibits the alternative pathway (Factor D)
- Might prevent extravascular hemolysis

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

Newer Approaches in PNH



- Monoclonal antibody



Garred, F Larsen, J Seyfarth· R Fujita,H O *Genes and Immunity* 2006; **7**:85–94.

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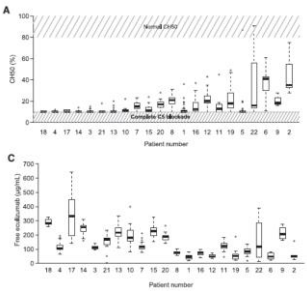
Higher Dose or More Frequent Administration may be Necessary



Peffault de la Tour, Blood 2015

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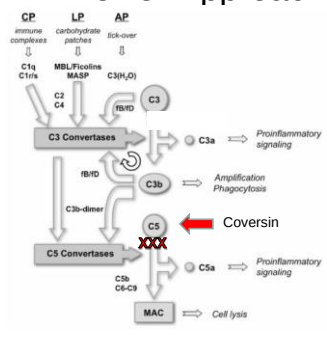
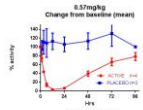
Newer Approaches in PNH



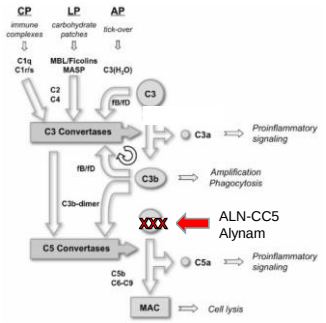
- Protein derived from tick saliva (*Ornithodoros mubata*)

- Subcutaneous administration
- Effective in eculizumab resistance
- Works at C5



Weston-Davies ASH 2014

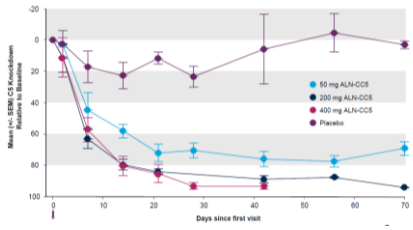
Newer Approaches in PNH



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

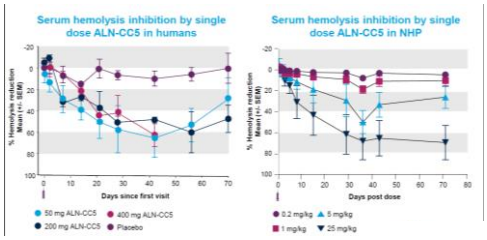
Ricklin and Lambris 2008

ALN – CC5 Phase I/II



http://www.alnylam.com/capella/roundtables/rnai-roundtable-aln-cc5-for-the-treatment-of-complement-mediated-diseases/

Hemolysis Control Can be Durable but Less Robust C5 Depression



New data to be presented at the American Society of Hematology

http://www.alnylam.com/capella/roundtables/rnai-roundtable-aln-cc5-for-the-treatment-of-complement-mediated-diseases/

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