THE FUTURE OF COMPLEMENT TREATMENT

Antonio M. Risitano, M.D., Ph.D.
Federico II University of Naples
Anti-complement treatment for PNH...

...is there any room for improvement?

... and if yes, how we can do it?
Splenectomy for C3-mediated extravascular hemolysis

Risitano et al, Blood 2008

Transfusions (PRBC/month)

3-4

2

No transfusion

Eculizumab  Splenectomy

Hb g/dL, Bil mg/dL, PNH RBC %, C3+ RBC %, ARC x100/uL, LDH IU/L
The list of candidate complement inhibitors (n=29)

<table>
<thead>
<tr>
<th>Target</th>
<th>Name</th>
<th>Company</th>
<th>Class of molecule</th>
<th>Status of development</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>C5</td>
<td>LFG316</td>
<td>Novartis/Morphosis</td>
<td>Monoclonal antibody</td>
<td>Clinical (Phase II, AMD)</td>
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<td>C5</td>
<td>Mabdominab</td>
<td>Adimune</td>
<td>Monoclonal antibody (minibody)</td>
<td>Preclinical (non-PNH)</td>
<td>38,39</td>
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<td>C5</td>
<td>Coveratin (OmCl)</td>
<td>Volution Immunopharmaceuticals</td>
<td>Small animal protein (recombinant)</td>
<td>Preclinical (PNH); clinical (Phase I, healthy volunteers)</td>
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<td>C5 (αC5)</td>
<td>Aurin Tricarboxylic Acid (ATA)</td>
<td>n.a.</td>
<td>Chemical</td>
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<td>C5</td>
<td>ARC1005</td>
<td>Novo Nordisk</td>
<td>Aptamers</td>
<td>Preclinical (non-PNH); clinical (Phase I, AMD)</td>
<td>50,51</td>
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<td>C5</td>
<td>SOMAmers</td>
<td>Somalogic</td>
<td>Aptamers (SELEX)</td>
<td>Preclinical (non-PNH)</td>
<td>50,52</td>
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<td>C5</td>
<td>SGO1002</td>
<td>Swedish Orphan Biovitrum (Affibody)</td>
<td>Affibody (fused with albumin-binding domain)</td>
<td>Preclinical (PNH); clinical (Phase I, healthy volunteers)</td>
<td>50,54,35</td>
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<td>C5</td>
<td>RA101348</td>
<td>RaphaPharma</td>
<td>Small molecules (unnatural peptide)</td>
<td>Preclinical (unknown)</td>
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<td>C5</td>
<td>Anti-C5 siRNA</td>
<td>Alnylam</td>
<td>Si-RNA</td>
<td>Preclinical (non-PNH and PNH)</td>
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<td>C3 (C3b/3b)</td>
<td>H17</td>
<td>EchaSys Therapeutics</td>
<td>Monoclonal antibody</td>
<td>Preclinical (PNH and non-PNH)</td>
<td>63,64</td>
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<td>C3/C5b</td>
<td>4-1MWJ/POT-4</td>
<td>Poesiins</td>
<td>Complement family</td>
<td>Preclinical (non-PNH); clinical (Phase I and AMD)</td>
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<td>C3/C5b</td>
<td>4-1MWJ/APL-1, API-2</td>
<td>Apellis</td>
<td>Complement family</td>
<td>Preclinical (PNH and non-PNH); clinical (PNH and non-PNH, planned)</td>
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<td>C3/C5b</td>
<td>Cp40/AMY-101, PEG-Cp40</td>
<td>Amyndas</td>
<td>Complement family</td>
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<td>AP C3 convertase</td>
<td>TT30 (CR2/CR1)</td>
<td>Alexion</td>
<td>Fc-based protein</td>
<td>Preclinical (PNH and non-PNH); clinical (Phase I, AMD)</td>
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<td>Mini-FH</td>
<td>Amyndas</td>
<td>Fc-based protein</td>
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<td>Fc-based protein</td>
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<td>AP C3 convertase</td>
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<td>Fc-based protein</td>
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<td>AP and C3/C5 convertase</td>
<td>oCR1 (CDX-1135)</td>
<td>Cellnex</td>
<td>CR1-based protein</td>
<td>Preclinical (non-PNH); clinical (Phase I, DB1)</td>
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<td>Miroceci (APT010)</td>
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<td>CR1-based protein</td>
<td>Preclinical (non-PNH), clinical (Phase I, kidney transplantation)</td>
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<td>AP and C5/C5 convertase</td>
<td>TT32 (CR2/CR1)</td>
<td>Alexion Pharmaceuticals</td>
<td>CR1-based protein</td>
<td>Preclinical (non-PNH)</td>
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<td>FB</td>
<td>TA106</td>
<td>Alexion Pharmaceuticals</td>
<td>Monoclonal antibody</td>
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<td>FD</td>
<td>FCH4514S</td>
<td>Generebec/Roche</td>
<td>Monoclonal antibody</td>
<td>Preclinical (non-PNH); clinical (Phase II, AMD)</td>
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<tr>
<td>FB</td>
<td>Anti-Hb siRNA</td>
<td>Alnylam</td>
<td>Si-RNA</td>
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<td>FB and FD</td>
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<td>FB and FD</td>
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<td>Properin</td>
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<td>NovelMed</td>
<td>Monoclonal antibody (and mAb derivatives)</td>
<td>Preclinical (unknown)</td>
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<td>C1r/C1s</td>
<td>Cyamine®</td>
<td>ViroPharma/Haemostasis</td>
<td>Human purified protein (C1r-INH)</td>
<td>Clinical (approved for Hereditary Angio-Edema)</td>
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<td>C1s</td>
<td>TNT003</td>
<td>True North Therapeutics</td>
<td>Monoclonal antibody</td>
<td>Preclinical (Ab-mediated hemolytic anemia)</td>
<td>113</td>
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<td>MASP-3</td>
<td>n.a.</td>
<td>Omeros</td>
<td>n.a.</td>
<td>Preclinical (PNH and non-PNH)</td>
<td>114</td>
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From:
Risitano (2014)
“Future strategies of complement inhibition in paroxysmal nocturnal hemoglobinuria”.

In “Paroxysmal Nocturnal Hemoglobinuria: From Bench to Bedside”,
Ed. Nishimura, Kinoshita, Kanakura
Novel complement inhibitors

1. Terminal effector complement inhibitors

2. Broad C3-inhibitors
   • Monoclonal antibodies
   • Small molecules

3. Alternative pathway inhibitors
   • Regulator of complement activation (RCA)-based inhibitors
   • Small inhibitors

4. Classical pathway inhibitors

5. Mannose/lectin pathway inhibitors
Targeted Complement Inhibition

**Classical Pathway Activation**
*Antibody/Antigen Complexes*

**Lectin Pathway Activation**
*(MBL)*

**Weak Anaphylatoxin**

**Immune Complexes and Microbial Opsonization**

**Alternative Pathway Activation**
*Microbiological membranes*
*Bacterial LPS*
*Immune Complexes Mammalian Cell Membranes*

**C3 inhibitors?**

**Potential Anaphylatoxin Chemotaxis Cell Activation**

**Cell Activation Lysis**

**C1q → Activated C1 → C3 Convertase → C4b2a → C4b2a3b → C5 Convertase → C5b → C5b-9**

**C3, C3H₂O → C3b, C3bBb → C3bBb3b → C3 Convertase → C5 Convertase → C5a → C5b → C5b-9**

**C3a**

**C4+C2 → C4b2a → C4b2a3b → C5 Convertase → C5b → C5b-9**
Anti-C3 mAb as candidate agents for PNH

**Preclinical data**

A novel approach to preventing the hemolysis of paroxysmal nocturnal hemoglobinuria: both complement-mediated cytolysis and C3 deposition are blocked by a monoclonal antibody specific for the alternative pathway of complement.

Margaret A. Lindorfer,1 Andrew W. Pawluczkowycz,1 Elizabeth M. Peek,1 Kimberly Hickman,2 Ronald P. Taylor,1 and Charles J. Parker2

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**3E7 and its chimeric deimmunized derivative H17 are anti-C3 mAb which inhibit the C3 convertase**

- Inhibit hemolysis of PNH RBCs in vitro
- Prevent C3 accumulation on surviving PNH RBCs in vitro
- Specific for CAP C3 convertase (CCP is preserved)

*Lindorfer et al, Blood 2010*
Concerns about the therapeutical use of anti-C3 mAb

- Huge plasma concentration of C3 (~1 mg/mL)
- No room for anti-C3 mAb (native protein)
- mAb targeting activated C3 (C3b? Neo-epitopes?)
- 3E7 and H17, specific for circulating C3b and C3b of the alternative C3 convertase (C3bBb)

Concerns specific to PNH:

- Full Ab (IgG1): extravascular hemolysis via Fc-receptors
- Engineered derivatives lacking the Fc portion

A Humanized Antibody That Regulates the Alternative Pathway Convertase: Potential for Therapy of Renal Disease Associated with Nephritic Factors

Danielle Paixão-Cavalcante,*† Eva Torreira,† Margaret A. Lindorfer,* Santiago Rodríguez de Cordoba,† B. Paul Morgan,* Ronald P. Taylor,*† Oscar Llorca,† and Claire L. Harris*


A Fab-based derivative of H17, which retains H17 specificity (Ron Taylor, and EluSys Therapeutics)
COMPSTATIN
A Peptide Drug to Block Complement at the C3 Level

1:1 (molar) binding

1996
4V9H
3,000 nM

2006
4(1MeW)
10 nM
AMD [Phase II]
POT-4 [Potentia/Alcon]

2012
Cp40
0.5 nM
AMD, PNH, Sepsis, Hemodialysis, ...

Qu et al., 2012, Immunobiology
COMPSTATIN AND C3 ACTIVATION

Mechanism of action

(A) C3 binding to convertase

(B) Blockage of cleavage site

(C) Conformational change

(D) Blockage of interaction

COMPSTATIN ANALOGS
Improving potency and pharmacokinetic properties

POT-4 (K_D 10.3 nM)
Cp20 (K_D 2.4 nM)
#3 = Cp30 (K_D 1.6 nM)
#14 = Cp40 (AMY-101) (K_D 0.5 nM)

Selecting modifications at the N-terminus
Novel analogs exhibit a better affinity, higher potency and increased solubility
Supercompstatin?

Qu et al., 2012, Immunobiology
COMPSTATIN ANALOGS
PEGylation as optimization of PK profile

Cp40 was PEGylated at either its N- or the C-terminus

Novel analogs designed to increase the half-life for clinical use

Risitano et al, Blood 2014
FUNCTIONAL PROPERTIES OF PEGYLATED Cp40
C3b-binding and complement inhibition

**Binding to surface-bound C3b**

- Lower on-rate on surface-attached C3b: restricted accessibility of compstatin binding site?
- Similar inhibitory activity (especially with the N-term PEGylation)

**Inhibition of complement**

Risitano et al, Blood 2014
Cp30 and Cp40 prevent hemolysis of PNH erythrocytes

PNH erythrocytes incubated in acidified NHS (EASA)

Both Cp30 and Cp40 completely abolish hemolysis of PNH erythrocytes in the "Extended Acidified Serum Assay"

Risitano et al, Blood 2014
Effect of compstatin analogs on hemolysis of PNH RBCs

*Dose-dependent inhibition*

PNH RBC hemolysis and Cp40 (AMY-101)

Risitano et al, Blood 2014
Effect of compstatin analogs on C3-opsonization
Prevention of C3 fragment deposition on PNH erythrocytes

- Unmanipulated erythrocytes
- Erythrocytes in acidified serum + Cp40 10 uM
- Erythrocytes in acidified serum + PEG-Cp40 10 uM

✓ Compstatin analogs Cp40 and PEG-Cp40 completely prevent C3 fragment deposition on PNH RBCs incubated in aNHS

Risitano et al, Blood 2014
PK of PEGylated Cp40 in monkeys

**PEGylation prolongs half-life of Cp40 in vivo**

Single bolus injection (PEG-Cp40)
i.v., 200 mg/animal (~2 mg of active peptide/kg)

- Largely improved half-life (5-6 dd) possibly allowing weekly dosage regimen
- Possible C3 accumulation: interference with normal clearance by PEG-Cp40?

Risitano et al, Blood 2014
Non-PEGylated Cp40 in monkeys
An alternative strategy for clinical utilization

✓ High bioavailability after s.c. injection, but short half-life (12-15h)

✓ Repetitive s.c. injections every 12 hours (1 mg/kg) resulted in sustained pharmacological levels

✓ Twice daily s.c. administration of Cp40 (1 mg/kg) seems the optimal schedule for initial clinical investigation in humans

✓ pro: C3 activity can be regained rapidly in case of adverse event)

Risitano et al, Blood 2014
Committee for Orphan Medicinal Products (COMP) meeting report on the review of applications for orphan designation
July 2014

Orphan medicinal product designation

Positive opinions

2. Opinions adopted at the first COMP discussion:

Other compstatin analogs (Apellis Pharmaceuticals)

- APL-1 and APL-2: PEGylated derivatives of the first-generation compstatin (POT-4)
- *In vitro*, efficacy comparable to that of novel derivatives
  - Complete inhibition of lysis
  - Complete prevention of C3 deposition
- Clinical translation plans on their way
TARGETING THE COMPLEMENT INHIBITION

Combining a targeting protein (CR2) with a complement regulator (fH)

SCR 1-4 of CR2 (targeting module) fused to SCR 1-5 of fH (complement inhibitor module)
Equimolar concentrations of soluble fH result in a partial inhibition of hemolysis.

The blocking anti-CR2 mAb 1048 reverts the effect of TT30 to that of fH.

Proof for a membrane-bound effect of TT30

Effect of soluble fH and blocking experiments by the anti-CR2 mAb 1048

PNH patients not on eculizumab

% lysis of PNH RBCs

- aNHS
- aNHS+TT30 1μM
- aNHS+FH 1μM
- aNHS+TT30 1μM+mAb 1048 3μM

Mean
RBCs from untreated PNH patients

**TT30 inhibits C3 fragment deposition on RBCs incubated in aNHS**

- 1 h
  - Anti CD59 APC
  - Anti-C3b/iC3b FITC
  - Anti-C3d FITC
  - Anti-C3d PE
  - Anti-C3b/iC3b FITC

- 24 h
  - Anti CD59 APC
  - Anti-C3b/iC3b FITC
  - Anti-C3d FITC
  - Anti-C3d PE
  - Anti-C3b/iC3b FITC

✓ TT30 completely prevents C3 fragment deposition on PNH RBCs
TT30 binding to RBCs

TT30 binds to C3fragment+ PNH RBCs

✔ RBCs from a PNH patient on eculizumab, unmanipulated (control)
TT30 binding to RBCs

**TT30 binds to C3fragment+ PNH RBCs**

RBCs from a PNH patient on eculizumab, incubated 1h in aNHS

- **TT30 3 μM**
  - TT30 3 μM
  - A702 C3d PE
  - fH FITC
  - CR2 FITC

- **TT30 1 μM + anti-CR2 mAb 1048 3 μM**
  - TT30 binds to C3d+ PNH RBCs, and the amount of TT30 correlates with that of C3d
  - The anti-CR2 mAb 1048 inhibits TT30 binding to membrane-bound C3d
TT30 effect in normal-like conditions
Prediction of unique pharmacokinetics

Dose-response curve at different hematocrits, to better mimic physiological conditions

TT30 retains its inhibitory effect even in physiological-like hematocrits
The recombinant human complement receptor 2/factor H fusion protein TT30 protects paroxysmal nocturnal hemoglobinuria erythrocytes from both complement-mediated hemolysis and C3 fragment opsonization

Antonio M. Risitano, Rosario Notaro, Caterina Pascariello, Michela Sica, Luigi del Vecchio, Christopher J. Horvath, Masha Fridkis-Hareli, Carmine Selleri, Margaret A. Lindorfer, Ronald P. Taylor, Lucio Luzzatto, and V Michael Holers

Blood 2012
MINI-FACTOR H (Mini-FH)
Engineering the FH protein to maximize its complement regulation

Factor H (fH)

Complement regulatory domain

C3-targeting domain

Mini-FH

SCR 1-4 (complement inhibitor module) fused to SCR 19-20 (targeting enhancer module)
MINI-FACTOR H (Mini-FH)
An Engineered Multi-Targeted Complement Inhibitor

- mini-FH has been rationally designed to combine the complement regulatory (CCP1-4) and surface-targeting domains (CCP19-20) of factor H
- It maintains binding affinity to C3b and both decay acceleration and cofactor activity
- mini-FH can target to markers of self-cells (e.g., glycosaminoglycans), ongoing amplification (opsonins C3b/iC3b/C3dg) and oxidative damage (e.g. malondialdehyde)
Targeting of mini-FH to C3-activation products
SPR assay with “physiologically” immobilised C3-fragments

- Mini-FH binds to C3b as efficiently as FH
- Mini-FH binds better to iC3b and C3dg than FH

Schmidt et al, JI 2013
mini-FH retains complement regulatory activity

Cofactor activity (*fluid phase*)

Decay accelerating activity (*SPR assay*)

- FH
- C3α
- C3β
- C3α⁺-68
- mini-FH
- C3α⁺-46
- C3α⁺-43

mini-FH retains both, cofactor activity and decay accelerating activity

Schmidt et al, JI 2013
Mini-FH prevent hemolysis of PNH erythrocytes

PNH erythrocytes incubated in acidified NHS (EASA)

Hemolysis of PNH erythrocytes

✓ Mini-FH, but not equimolar concentrations of full FH or distinct SCRs of FH, completely abolish hemolysis of PNH erythrocytes in the EASA (Schmidt et al, JI 2013)
Effect of Mini-FH on hemolysis of PNH erythrocytes

*Dose-dependent inhibition*

PNH RBC hemolysis and Mini-fH

Schmidt et al, JI 2013
Effect of Mini-FH on C3-opsonization of PNH erythrocytes
Prevention of C3 fragment deposition

Unmanipulated erythrocytes

Erythrocytes in acidified serum

Erythrocytes in acidified serum + mini-FH 0.1 uM

✓ Mini-FH completely prevents C3 fragment deposition on PNH RBCs incubated in aNHS

Schmidt et al, JI 2013
CR1 polymorphisms affect complement regulation on PNH RBCs

Effect on C3 deposition in vitro

Kinetics of C3 deposition on PNH RBCs exposed to complement activation

- RBCs from PNH patients carrying the CR1 phenotype associated with lower surface CR1 expression exhibit a much faster C3 deposition after exposure to complement activation in vitro
- Dose effect (heterozygous subjects have slight faster C3 deposition)
- Complement regulation in vivo may be affected by genetic factors independent from PIG-A mutation (e.g., CR1 and possibly FH, C3, etc.)
CR1-based complement inhibition

Soluble CR1 (CDX-1135, Celldex Therapeutics)

- In vitro, full complement inhibition along all complement activating pathways (alternative, classical and mannose/lectine)
- Effect on both late (C5 convertase) and early (C3 convertase) of complement activation
- PK/PD: since CDX-1135 affects only activated complement and it is not consumed, it may recycle in the inhibitory process
- Acceptable tolerance (and pharmacological complement inhibition) demonstrated in >500 patients in different clinical trials
- In phase I for kidney disorders (Dense Deposit Disease); promising experimental and clinical data *(Richard Smith, University of Iowa)*

TT32 (Alexion Pharmaceuticals)

- A CR2-CR1 fusion protein in preclinical development
- Twin molecule of TT30, with anti-complement activity targeting both the alternative and the classical pathways (as well as mannose/lectine one)
Mirococept (APT070)

A membrane localized complement inhibitor based on recombinant fragment of soluble CR1 (SCR1-3) fused with membrane-localizing motif (myristoyl and hexa-lysine positively charged linker)

- Decay acceleration and FI cofactor activity retained
- Membrane-bound (RBC) complement regulatory activity confirmed in vitro and in vivo

In clinical development in kidney transplantation
- Phase III placebo-controlled trial using a protective layer of mirococept for coating the inner surface of donor kidneys, to prevent post-ischemic complement-mediated damage *(Steven Sacks, Richard Smith)*
Other inhibitors of the complement alternative pathway

*Updated to summer 2014, public information only*

**Inhibitors of Factor B**
- Antibody-based inhibitors: TA106 (Alexion Pharmaceuticals), a Fab binding to native FB, preventing its cleavage by FD
- Small inhibitors under development by several Companies (e.g., Novartis: PCT Int. Appl., WO 2013192345)

**Inhibitors of Factor D**
- Antibody-based inhibitors: FCFD4514S (Genentech/Roche), an anti-FD Fab under clinical development as topic therapy in ophthalmologic indication (Phase II, NCT01602120)
- Small inhibitors under development by several Companies (e.g., Novartis: PCT Int. Appl., WO 2012093101)

**Inhibitors of Properdin**
- Antibody-based inhibitors: humanized mAb and antigen-binding Ab portion under development at Novelmed Therapeutics (US Patent #US20140186348)
Other terminal complement inhibitors

Other anti-C5 mAb

✓ LFG316 (Morphosys®; Novartis): fully human anti-C5 mAb under clinical development for ophthalmologic diseases (Phase II, initially local now systemic; NCT01624636)

✓ Mubodina® (Adienne Pharma & Biotech): anti-C5 “minibody”, consisting of Ab fragment including the antigen-specific VL and VH domains of its parental anti-C5 mAb (Orphan status for kidney diseases by both FDA and EMA)

Ready-to-go option for PNH patients with inherited resistance to eculizumab?

Anti-C5 strategies not exploiting mAbs

✓ Coversin

✓ Last generation molecules

Strategies not targeting C5

✓ CD59-based:
  ✓ a soluble, modified recombinant human CD59 (Hill et al, Blood 2006)

✓ TT33 (Alexion): a CR2/CD59 engineered fusion protein

✓ Very terminal targets: C6, C7, C8 or C9?
Coversin (also known as OmCl)

- Isolated from the tick of Ornithodoros moubata
- Small (16 kDa) protein of the lipocalin family with anti-complement activity
- Binds to human C5 and prevents its cleavage by C5 convertases
- Under clinical development by Volution Immuno-Pharmaceuticals: amenable PK/PD in a phase I study in healthy volunteers (sustained pharmacological levels after s.c. injections)

- Status of art in PNH (Wynne H Weston-Davies, 7th International Conference on Complement Therapeutics, Olympia, 2014)
  - Potential effect in preventing hemolysis *(and C3 fragment decoration?)* of PNH erythrocytes, **but:**
    - How a C5 inhibitor may interfere with C3 activation?
    - Immunogenicity (evolutionary distant protein)?
  - A clinical translation plan for PNH has been announced
Last generation technologies to produce complement inhibitors

1. **siRNAs** (Alnylam)
   - *C5* (preclinical; ASH 2013)
   - *Factor B*

2. **Aptamers**: large (oligonucleic or peptide) compounds which selectively bind to specific molecules, eventually impairing their function
   - *Anti-C5 ARC 1905* (Ophtotech Corp; Phase I for AMD)
   - *SOMAmers* (SomaLogic)
     - *C5*
     - *C3*
     - *Factor B and Factor D*

3. **Affibodies** (SOBI): small antibody mimetic proteins displaying high affinity binding to a wide range of protein targets, fused to an albumin-binding domain
   - *Anti-C5 SOBI002* (preclinical development + Phase I)

4. **Cyclomimetics** (Rapharma): small, cyclic, peptide-like polymers, identified from massive libraries for drug screening
   - *Anti-C5 RA101348* (preclinical development)
Inhibitors of the complement classical pathway

**TNT003 (Truenorth Therapeutics)**

- Anti-C1s mouse mAb
- It prevents early Ab mediated complement activation (i.e., in CAD)
- In CAD, this early complement inhibition results:
  - In prevention of intravascular hemolysis
  - In prevention of C3 opsonization
  - In prevention of C3-mediated phagocytosis
C1-esterase inhibitor /Cynrize/

✓ C1 esterase inhibitor (C1-INH) is an endogenous serine protease inhibitor (SERPIN) with a broad inhibitory activity in the complement
✓ C1-INH inhibits the CP (and MP) activation by binding to C1r and C1s and preventing their catalytic effect on C4 and C2
✓ Constitutional deficiency or dysfunction of endogenous C1-INH results in hereditary angio-edema (HAE), a life-threatening condition
✓ Cinryze® (ViroPharma/Baxter) is a nanofiltered human plasma-derived C1-INH which is used as substitutive therapy in patients with HAE
✓ Cinryze has been tested in vitro in PNH (De Zern et al, Exp Hematol 2014):
  ✓ potential effect in preventing hemolysis and C3 fragment decoration of PNH erythrocytes, but:
  ✓ is C1-INH also an AP inhibitor, or is the CP involved in PNH pathophysiology?
✓ Extremely high therapeutic dosages hamper any clinical translation for PNH
Inhibitors of the mannose/lectin pathway

Any role of the CMP in PNH pathophysiology?

- Distinct protein involved, called mannan-binding lectin-associated serine protease (MASPs)

MASP-2

- Likely involved in classical pathway activation (C4bC3b)
- Selective inhibitors available (Omeros; OMS 721, in Phase I)
- Minor role in PNH (unpublished data)

MASP-3

- Likely involved in alternative pathway activation (BbC3b)
- Selective inhibitors available (Omeros)
- Preliminary data in vitro in PNH suggest possible biological efficacy (Scwaeble WJ, 7th International Conference on Complement Therapeutics, Olympia, 2014)
Looking for the Best C-Inhibitor in PNH

Pros and cons

Autoimmune disorders (immune complexes)
Infections (C3 opsonization)

CAP-mediated C3 activation (continuous)
CCP-mediated C3 activation (infections?)
C3-mediated EVH
Hemolytic crises due to breakthrough or infections

Anti-C5 mAb  RCA-based  C3 inhibitors  Anti-C3 mAb

Broadness of complement inhibition
The spectrum of complement inhibitors

- Mini-FH, CR2/FH, Cr1g/FH
- sCR1 and Mirococept H17
- TT32 (CR2/CR1)
- TA106; other anti-FB
- FCFD4514S; other anti-FD
- Anti- Properdin

MASP2 inhibitors
MASP-3 inhibitors

Alternative Pathway Activation
Spontaneous C3 hydrolysis ("tickover")

Lectin Pathway Activation
Mannose-binding lectin and ficolins

Classical Pathway Activation
Antibody/Antigen Complexes

4(1MeW)/POT-4/APL-1
Cp40
Cynryze
TNT003

LFG316
Mubodina
Coversin
ATA
ARC1005

SOMAmers
SOBI002
RA101348
Anti-C5 siRNA
Novel complement inhibitors: pros and cons in PNH

1. Terminal effector complement inhibitors
   - Same excellent safety profile of eculizumab, possibly improved compliance (e.g., no i.v. injections)
   - Likely no benefit over eculizumab in terms of efficacy

2. Broad C3-inhibitors
   - Improved efficacy, due to effect on both intravascular and extravascular hemolysis; possibly no i.v. formulations
   - Safety concerns: infectious risk (higher than with C5 inhibitors?)

3. Alternative pathway inhibitors
   - Improved efficacy as with broad C3 inhibitors, since complement activation in PNH mostly occurs via the CAP; no i.v. formulations?
   - Hemolytic paroxysms due to classical pathway?
   - Safety concerns: infectious risk (likely less than broad C3 inhibitors)

4. Classical pathway inhibitors
   - Likely useless for PNH, since the CCP play a minor role in complement activation in PNH

5. Mannose/lectin pathway inhibitors
   - Unpredictable, since the role of CMP in PNH has not been proven useless for PNH