Therapeutic Complement Intervention
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- Complement-mediated diseases
- Therapeutic intervention
The complement system is involved in the pathogenesis of multiple diseases
PID - ESID registry
(http://www.esid.org/)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>2010</th>
<th>2011</th>
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</thead>
<tbody>
<tr>
<td>Predominantly antibody disorders</td>
<td>55.75% (n=8,087)</td>
<td>55.60% (n=7,238)</td>
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<td>Predominantly T-Cell deficiencies</td>
<td>7.68% (n=1,114)</td>
<td>7.62% (n=992)</td>
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<td>Phagocytic disorders</td>
<td>8.25% (n=1,197)</td>
<td>10.22% (n=1,330)</td>
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<td>Complement deficiencies</td>
<td>4.46% (n=647)</td>
<td>4.73% (n=616)</td>
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<tr>
<td>Other well defined PIDs</td>
<td>15.66% (n=2,271)</td>
<td>16.83% (n=2,191)</td>
</tr>
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<td>Autoimmune &amp; autoinfl. syndrome</td>
<td>1.84% (n=267)</td>
<td>1.88% (n=245)</td>
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<tr>
<td>Defects in innate immunity</td>
<td>0.84% (n=122)</td>
<td>0.00% (n=0)</td>
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<tr>
<td>Unclassified PIDs</td>
<td>1.79% (n=259)</td>
<td>1.72% (n=224)</td>
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</table>

Total number of patients: 100.00% (n=14,506) 100.00% (n=13,017)
Exogenous Danger
- Microbes

Endogenous Danger
- Apoptotic cells
- Altered Self

Danger Sensing

Soluble Immune Sensors

MBL/ Ficolins
C1q
Properdin

Danger Transmission
Activation of complement receptors

TLR
C2
C3
C4

C3
C5b
C5b-9
MAC

C3a
C3aR
CR1
C3dg
CR2
C4
CR3

C5a
C5aR
CR4
CD46
C5L2
CR1g
Activation and Recruitment of inflammatory cells

Lysis

Regulation of adaptive immune response

Phagocytosis

Opsonisation

Biological Functions

DC

RES

IC
Therapeutic Complement Inhibition
-soluble inhibitors-

Classical Pathway

- C1
- C3
- C5
- C5b-9

Alternative Pathway

- C3b
- C5a

Coagulation-/Kininesystems

- C1-Inhibitor

Compstatin

- APT070
- srCR1

Serinproteinase-Inhibitors

Inhibition

anti-C5

Eculizumab

C5aR-Antagonist

C1-Inhibitor
**C1 Inhibitor - multi system inhibition**

**Classical Pathway**

1. C1
2. C1-Inhibitor
3. C4
4. C2
5. C3
6. C5
7. C5b-9

**Lectin Pathway**

1. MBL
2. MASP1
3. C4
4. C2
5. C3
6. C5
7. C5b-9

**Alternative Pathway**

1. Inhibition
2. Coagulation-/Kininesystems
3. Animal models (rat, rabbit, dog, cat, pig)
   - trauma, burn*, sepsis*
   - pancreatitis
   - capillary leak*
   - ischemia-reperfusion injury
   - transplantation*/
   - xenotransplantation

* Clinical application
rsCR1(TP10) - C3/C5 convertase inhibition

Classical Pathway

Alternative Pathway

C1 → C4 → C2 → P B D → C3b

rsCR1/TP10
rsCR1-sLe*/TP20

C3 → C5 → C5b-9

Inhibition

animal models (mouse, rat, guinea pig, rabbit, pig, primate)
- sepsis
- pancreatitis, arthritis, encephalitis
- ischemia-reperfusion injury, stroke*
- lung injury, nephritis
- transplantation/xenotransplantation
- cardiopulmonary bypass*

*clinical trial

cell adhesion (selectin-mediated)
Liver I/R injury (rat)

LC-adhesion in sinusoids (/mm² liver surface)

LC-adhesion in venules (/mm² endothelium)

LC-rolling in venules (% of all moving leukocytes)

Lehmann et al, 1998
Complement inhibition by eculizumab

- Humanized monoclonal antibody against complement protein C5 that blocks terminal complement activation

\[ \text{Human IgG2 heavy chain constant region 1 and hinge} \]
\[ \rightarrow \text{Does not bind to Fc receptor} \]
\[ \text{Human IgG4 heavy chain constant regions 2 and 3} \]
\[ \rightarrow \text{Does not activate the complement cascade} \]

\[ ^1 \text{Thomas TC, et al. Mol Immunol. 1996;33:1389.} \]
Improvement of hemolysis during eculizumab treatment

Transition of TRIUMPH placebo patients to eculizumab in the extension trial

Hemolytic Uremic Syndrome (HUS)

Clinical Triade:
- Thrombocytopenia
- Microangiopathic hemolytic anemia
- Impaired renal function

Pathogenesis:
- Endothelial cell injury

Typical (D+) HUS
- Shiga-Toxin *E. coli* O157:H7
  - children + adults, Diarrhea

Atypical (D-) HUS:
- sporadic and familiar
- adults + children
  - vWF CP deficiency
    -(ADAMTS13)

Gasser et al, Schweiz Med Wochenschr 1955
Multiple Genetic Defects cause aHUS

- **Factor H (Frequency ~15%)**

- **MCP Mutations**
  Richards et al. 2003, Noris et al. 2003

- **Factor I Mutations**
  Dragon Durey et al. 2005

- **Factor B Mutations**
  Rodriguez de Cordoba et al. 2006

- **C3 Mutations**
  Dragon Durey et al. 2008

- **CFHR1/CFHR3 Deficiency**
  Zipfel et al. 2007

- **Autoantibodies to Factor H**
Case of a 37 year old woman

37-year old woman with relapsing atypical HUS

− Heterozygous missense mutation in CFH gene (exon 10, codon 475), homozygous deletion comprising exon 2 within the CFHR1 gene

− First HUS manifestation with 25 years (begin of dialysis)

− 1. HUS-relapse 5 weeks following first renal transplantation (30 years)
  • Loss of transplant function despite 18 plasma exchanges

− 2. HUS-relapse 6 weeks after second transplantation (37 years)
  • 4 days after initiation of low-dose Tacrolimus (2.3 ng/ml) (3 episodes of acute rejection)

− Administration of 600 mg Eculizumab

Renal biopsy

Elastic Masson’s trichrome stain:
- Intracapillary fragmentocytes

Hematoxylin/eosin stain:
- Hyaline microthrombi occluding glomerular capillaries

Positive immunostaining for C4d:
- Glomerular capillaries
- Preglomerular arterioles

Time course following complement blockade

C analysis

aHUS
Effect of dialysis and anti-C5 antibody (Eculizumab) treatment

Mai-Juli 2011: 3845 diseased, 855 HUS Patients, 53 died (RKI, Berlin)
Cases of a 3 three- year old children with STEC-HUS (Paris, Monteal, Heidelberg)

- Bloody diarrhea, thrombocytopenia, on hemodialysis
- Stx-2 producing *E. coli* (O157/O157H7/O157H7) serotype
- Progressive CNS involvement (2 patients):
  - High lactate dehydrogenase, low platelets, high plasma creatinine
  - Low C3, high C3d, no mutations in fH, fI, MCP, C3, no auto-anti-fH

  - Administration of 2x600 mg/week Eculizumab,
  - 1 patient 600mg-300-300-600 mg eculizumab/week

MPGN associated with complement dysregulation

- C3 nephritis factor
- Genetic Factor H deficiency (mouse, pig, dog, man)
- Autoantibody to factor H
- C3 mutation (fH binding site)

∑ Complement (AP C3 convertase) dysregulation as priming factor for MPGN upon injurious insult
Case of a 16 year girl with MPGN I

- fever and pancytopenia
- C3 undetect., SC5b-9 high, C3 Nef pos. ; Deficiency of Factor H-related protein 1 (CFHR1)
- Proteinuria, normal, lactate dehydrogenase and haptoglobin
- Renal biopsy showed mesangial interposition, wire loops,
- subendothelial and mesangial deposits; staining was positive for all immunoglobulins

- Administration of 900 mg Eculizumab (initiation), 1200mg/2 weeks maintainance

Case: MPGN I

Case of a 17 year patient with MPGN II

- DDD since age of 10 years
- Renal biopsy: mesangial proliferation, subendothelial and mesangial deposits
- Relapsing proteinuria, microhematuria
- Age of 17 years: Focal sclerosis of 40% glomeruli
- C3 low, C3 Nef pos
- No mutations fH, fI

  - Administration of 900 mg Eculizumab/week (4x), 1200mg (1x), 1200 /2 weeks, ramiprilm losartan (maintanance)
  - After 18 months interruption (6 months )- recurrence of severe symptoms
MPGN II
Change in the Patient's Urinary Protein:Creatinine Ratio, the Glomerular Deposition of C3 and C5b-9, and the Thickness of Glomerular Capillary Walls before Treatment and after 6 and 18 Months of Treatment.

Targeted complement inhibition

• Control e.g. CAP amplification
  - Leave other pathways intact
• Local control of C activation
  - Avoid need to block large amounts of complement proteins in the circulation
  - Maximal effects in local inflamed tissue with minimal effects on systemic complement function
• Low risk of infection
  - Regulation of amplification of activation only (CAP)
  - Local effect rather than systemic
Therapeutic Complement Inhibition
Application to Clinic

- **anti-C5**
  Eculizumab: PNH, aHUS, AMD (dry) phase II, TPLrejection (pase I), clinical phase (RA, SLE), cold agglutinin disease
  Pexelizumab: clinical phase 3 (acute myoc. infarction, cardiop.bypass)

- **anti CFD (FCD4514S)**
  AMD (phase Ib/II)

- **C1 inhibitor**
  (Berinert, Serping-1 etc) HAE, transplantation, endotoxemia
  Rhucin/rC1Inh: sepsis, capillary leak syndrome, burn myocardial ischemia/reperf. Injury
  clinical phase 3 (HAE)

- **rhMBL**
  MBL-deficiency (in high dose chemoth., stem cell/liver transplantation (phase 1b)

- **C3 inhibitor**
  sCR1/TP10: cardiopulmonary bypass (clinical phase 2 (completed 2007)
  Compstatin (POT-4): wet AMD (phase I completed)

- **C5aR antagonist**
  PMX-53: RA, psoriasis- clinical phase 2 (completed)
## Therapeutic Complement Inhibition
### Preclinical development

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<tr>
<th>Inhibitors</th>
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<tr>
<td>sCR1-sLe(^x)/TP20</td>
<td>preclinical (stroke, heart attack)</td>
</tr>
<tr>
<td>Microcept/APT070</td>
<td>preclinical (various infl. diseases)</td>
</tr>
<tr>
<td>rec. CFH (Taligen)</td>
<td>AMD</td>
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<table>
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<tr>
<th>Antibodies</th>
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<tbody>
<tr>
<td>anti-fD/TNX-234 (Tanox)</td>
<td>preclinical (wet AMD)</td>
</tr>
<tr>
<td>anti-C5a/TNX-558 (Tanox)</td>
<td>preclinical (various infl. diseases)</td>
</tr>
<tr>
<td>anti-C5aR/Neutrazumab (G2 Therapeutics)</td>
<td>preclinical (RA, stroke)</td>
</tr>
<tr>
<td>anti-fB/TA106 (Taligen)</td>
<td>preclinical (various infl. diseases)</td>
</tr>
<tr>
<td>anti-properdin (Novelmed Therapeutics)</td>
<td>preclinical (various infl. diseases)</td>
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Conclusions

◆ Severe local complement activation provides the rationale for specific complement intervention (vaccination against *Neisseria meningitidis* required)

◆ early treatment appears to be associated with better outcome

◆ Complement activation and therapeutic inhibition needs to be monitored (e.g. CH50; SC5b-9) to reflect treatment efficacy

◆ **Questions**
  - Indications and optimal dosage and treatment duration?
  - E.g. Preemptive complement blockade in renal transplantation?
  - Life long treatment required?
  - *Treatment drives diagnostics (?)*