Complement and SLE

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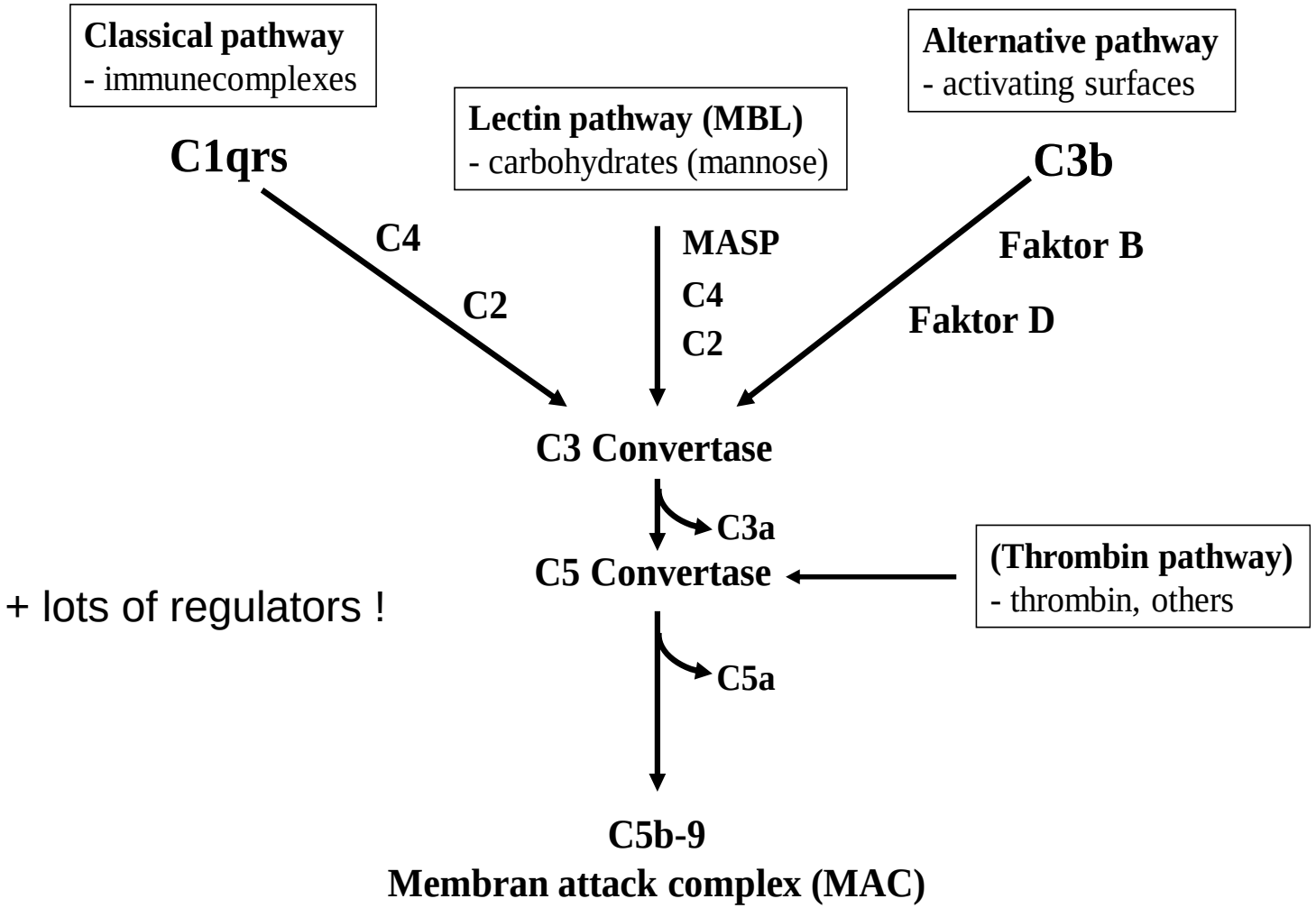
The complement system

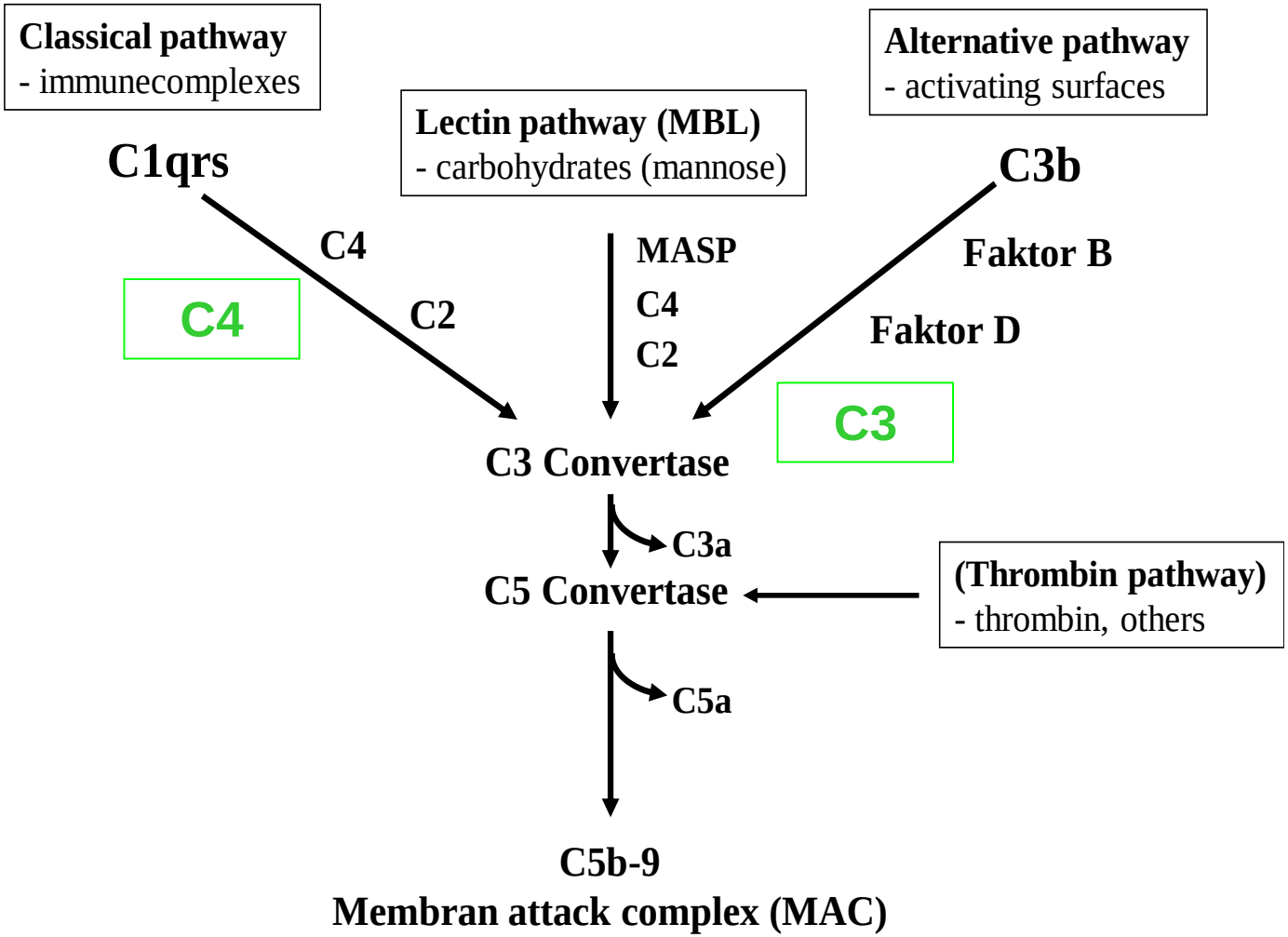


+ lots of regulators !

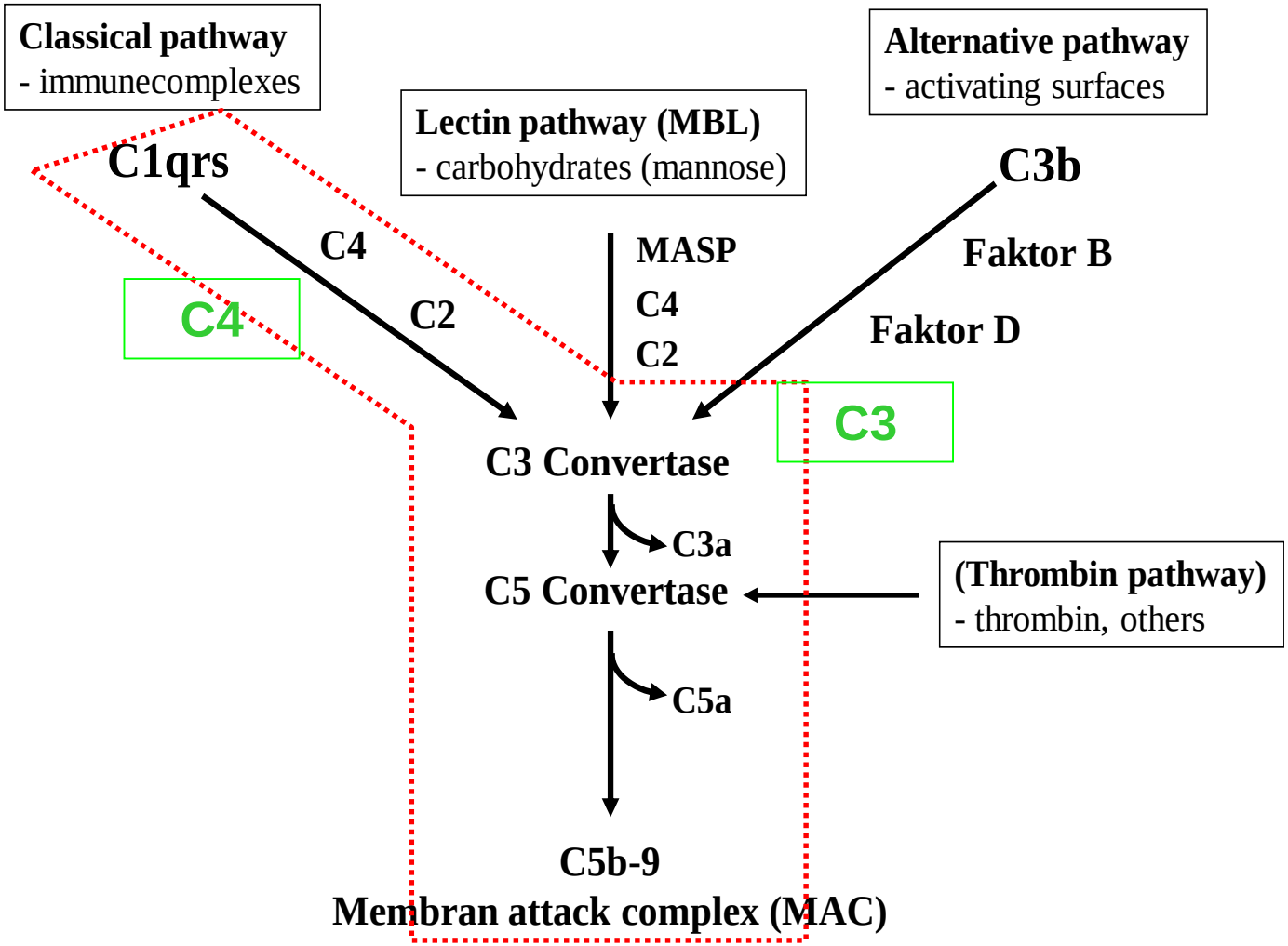
Functions of complement

- Opsonisation
  - Accelerated phagocytosis
  - Inactivation/neutralisation
  - Aggregation
- Lysis of bacteria, cells, viruses
  - Membrane attack complex (MAC)
  - Viruses with envelope
- Chemotaxis
  - C3a, C4a, C5a
- Induction of humoral immune response
  - Antibodies
- Possibly damaging inflammatory reactions
- Not well understood (coagulation etc.)

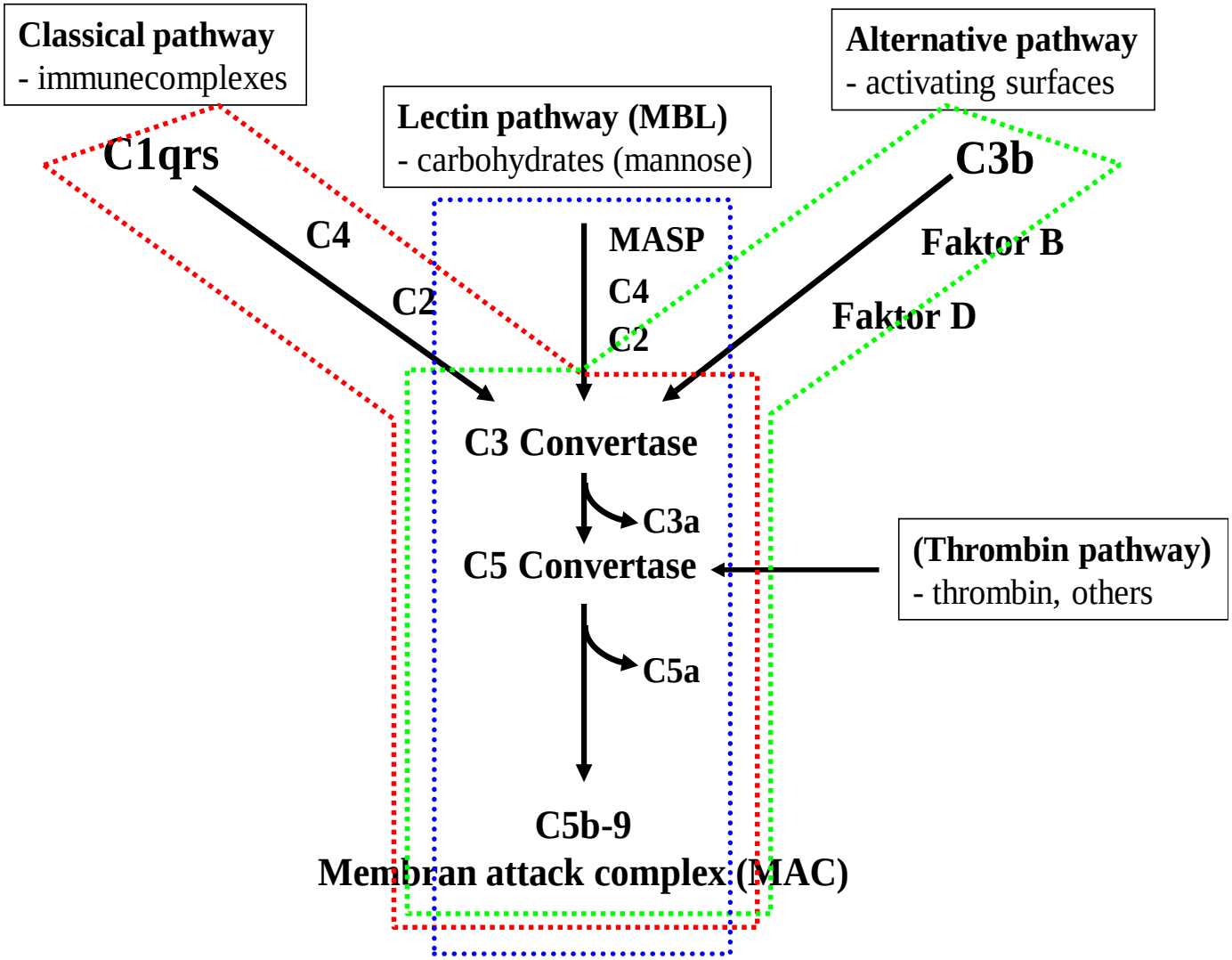
C3 and C4: Single components and their split products



CH50: Classical pathway



Complement activity or screening

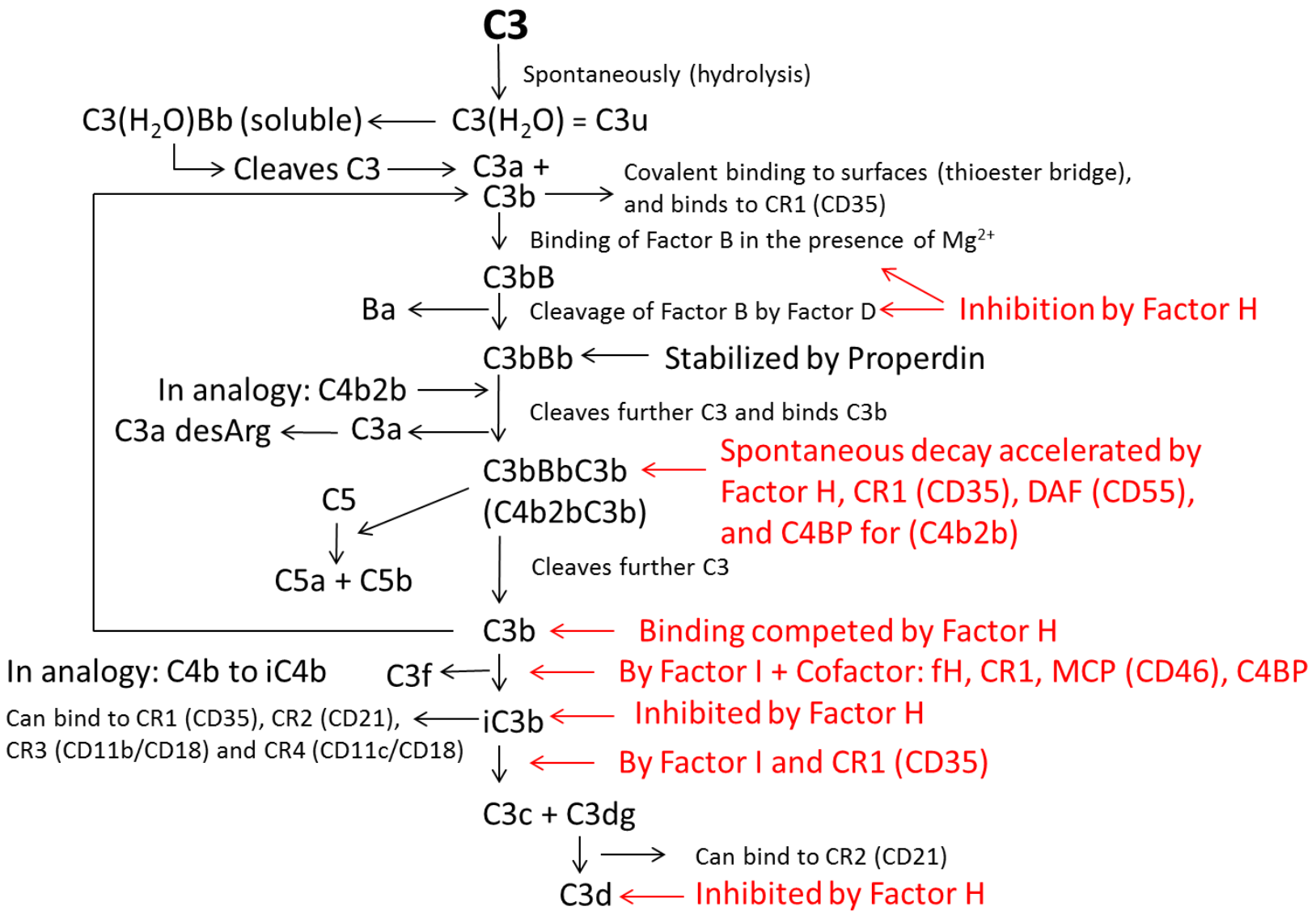


Complement deficiencies and disease

- Classical pathway: *SLE, bacterial infections*
- Lectin pathway: *Bact. infections in childhood, SLE ? Others ?*
- C1 Inhibitor: *Angioedema, SLE ?*
- Alternative Pathway: *Bacterial Infections*
- Terminal Pathway: *Meningococcal infection*

Dysregulation and/or consumption

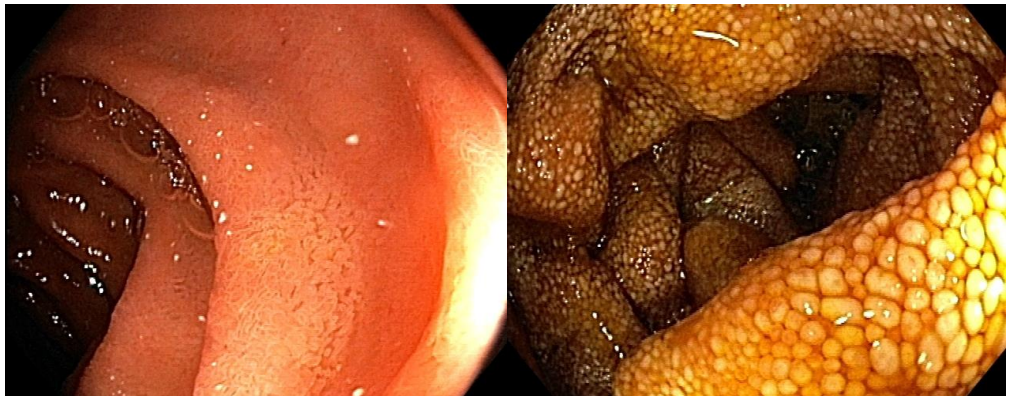
The alternative pathway



Diseases associated with hereditary dysregulation of complement

Loss and gain of function mutations

- Atypical hemolytic uremic syndrome (aHUS)
- Age-related macular degeneration (AMD)
- C3 glomerulopathy
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Others: Intestinal lymphangiectasia ?



Bogdanović R et al.,Nephron 1997

Kalman S et al., J Nephrol 2007

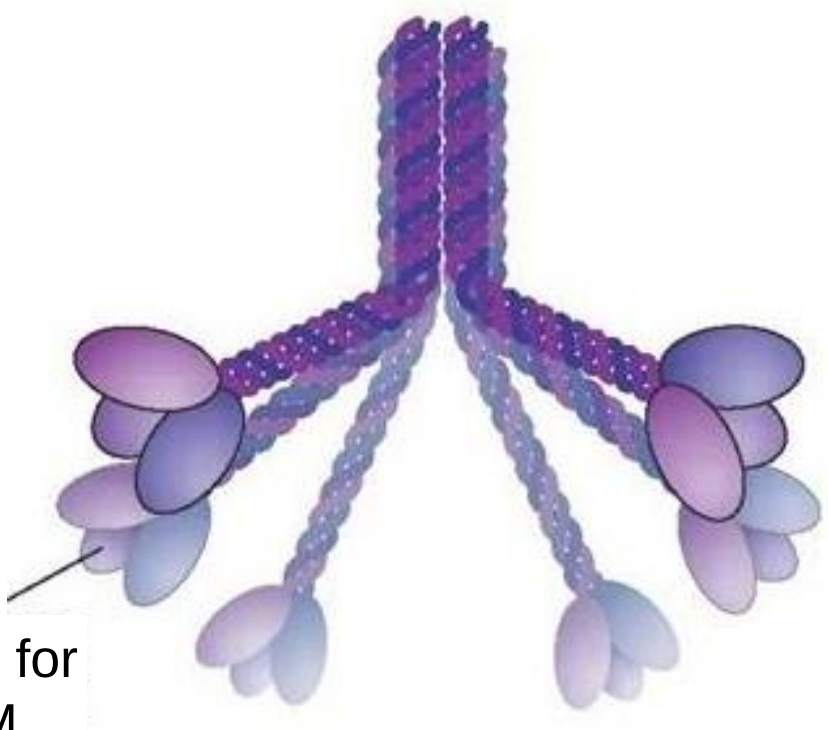
Ozen A et al., N Engl J Med 2017

Huber X et al., Medicine 2017

Diseases with signs of complement activation (selected)

- Infections ! incl. meningitis and Acute Post-Streptococcal Glomerulonephritis (APSGN)
- Cryoglubulinemia
- Autoimmune hemolysis (cold agglutinin disease etc.)
- Neuromyelitis optica (NMO)
- Some paraproteinemias
- Systemic lupus erythematosus (SLE)
- …

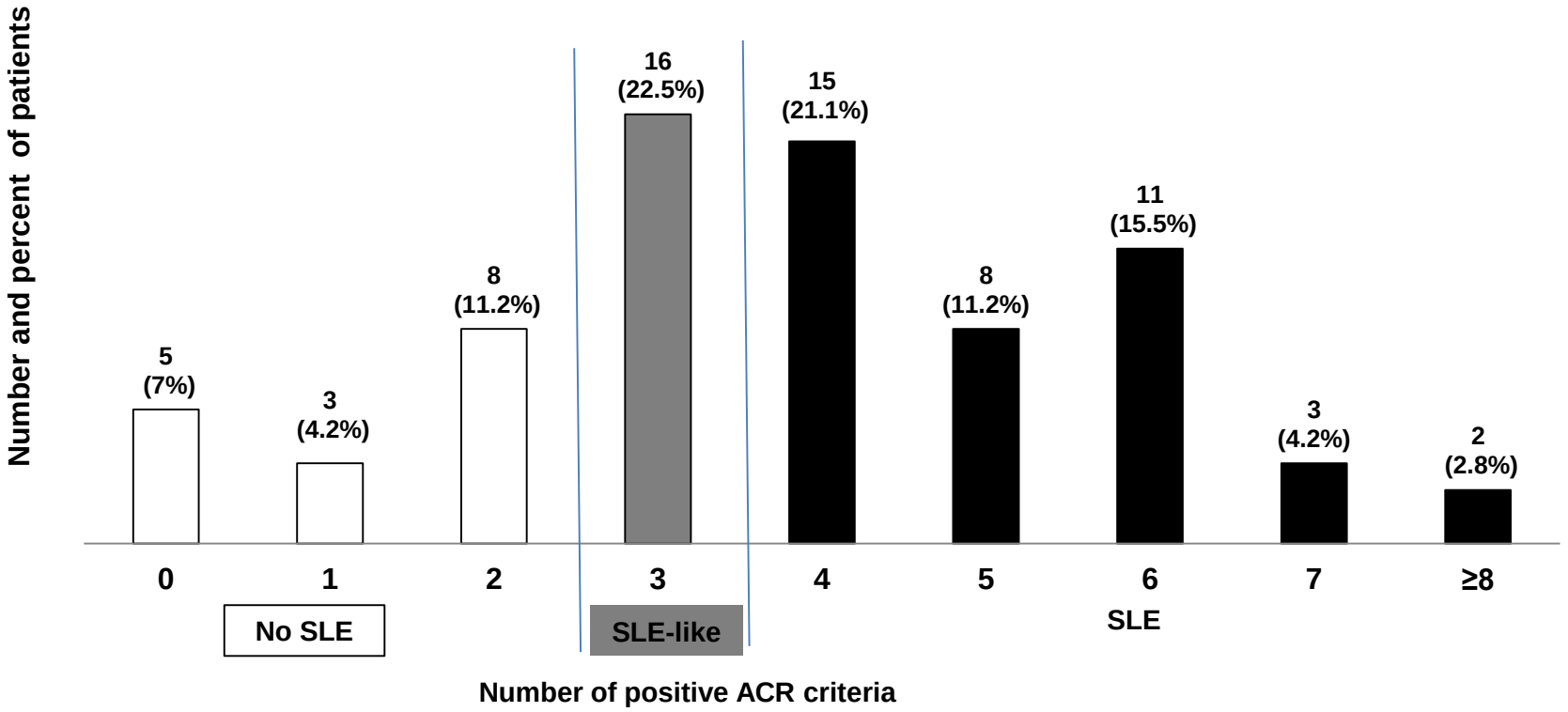
Complement C1q



Binding site for
IgG and IgM

Important for fight against bacterial infections (pro-inflammatory), …
… but also against autoimmunity (anti-inflammatory)

C1q deficiency and SLE



SLE patients with C1q deficiency have significantly more frequent discoid rash and oral ulcers than conventional SLE patients

Stegert M et al., Mol Immunol 2015

SLE: Low C1q (hypocomplementemia) versus C1q deficiency

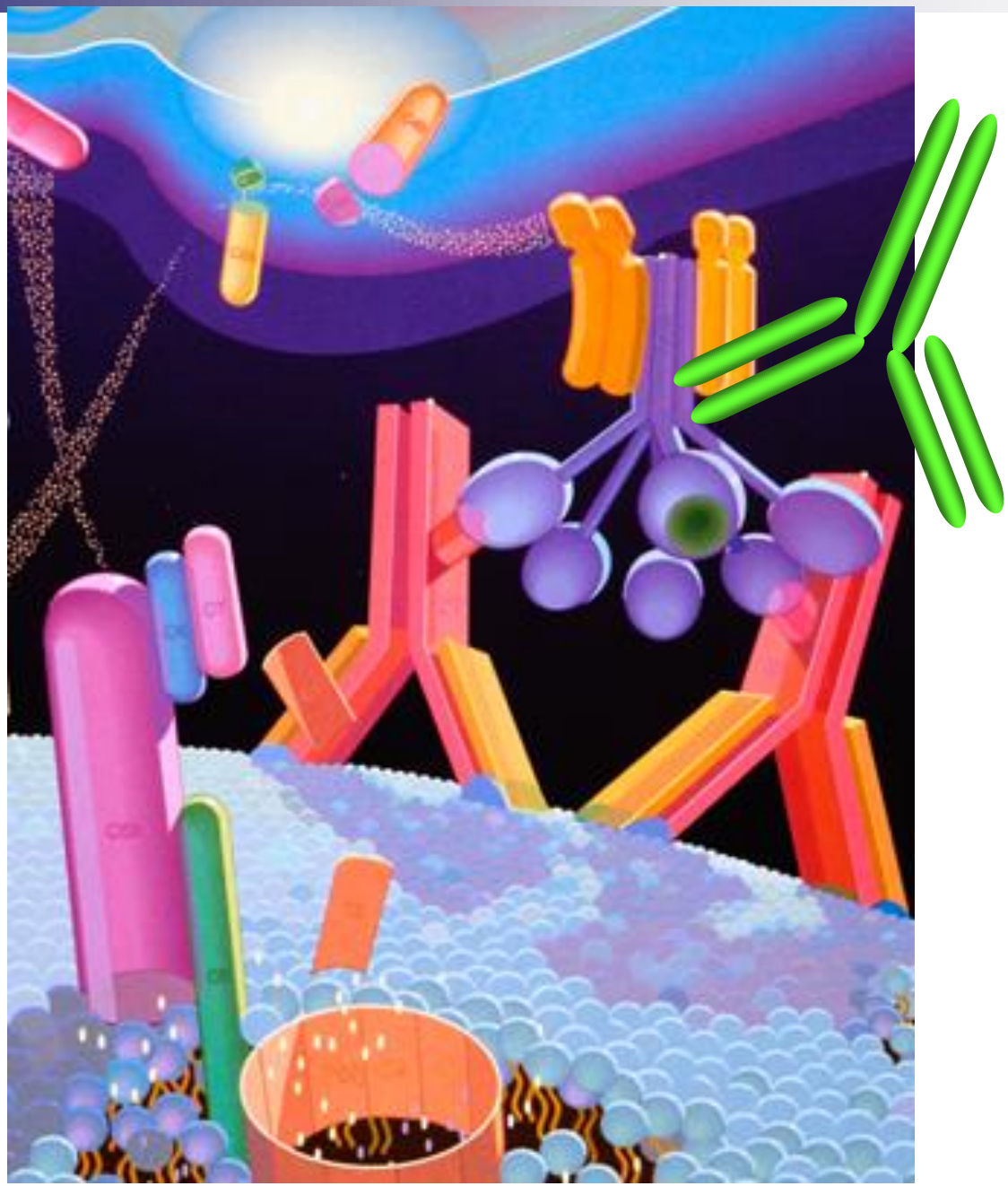
- Cryoglobulins
- Some MGUS/paraproteins
- Coombs positive hemolytic anemia/cold agglutinins
- IgG RF/IgG anti-rat IgG (unpublished)
- Anti-phospholipid antibodies
- (NETs ?)
- Anti-C1q antibodies

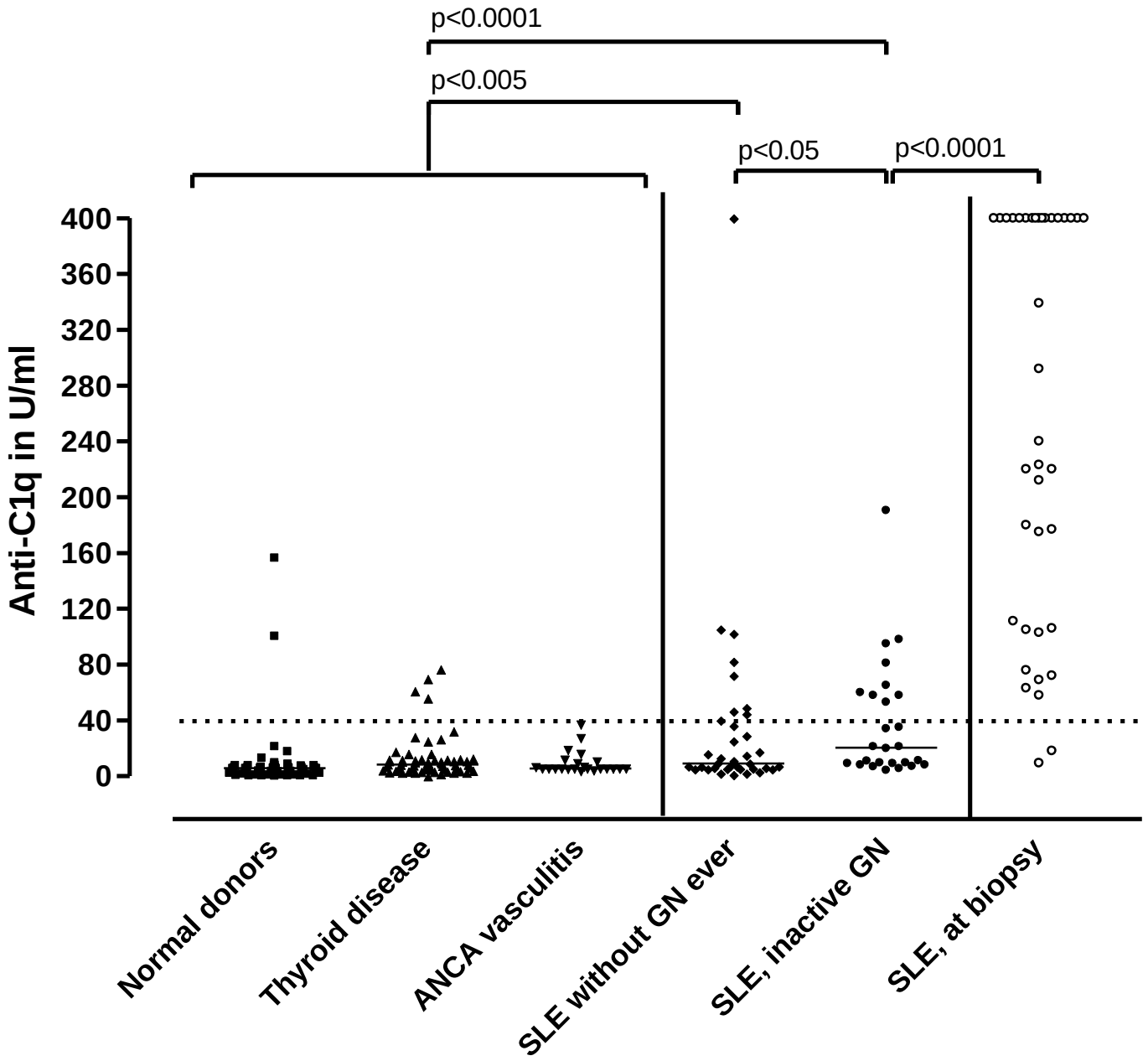
Low ‘complement’ as marker of disease activity

- Complement consumption does occur in SLE (e.g. as judged by C3dg/larger C3 molecules)
- Association with disease activity: C3 > CH50 > C4 (own data, unpublished)
- Low CH50, C3 or C4 partially correlate with the SLEDAI as they are part of it.
- C4 is strongly influenced by C4 gene copy numbers (but this seems not to be the major issue in SLE)
- C3 and C4 display an increase in synthetic rate in response to inflammatory stimuli, which may compensate for hypercatabolism.
- Measurement of complement levels in serum may not reflect accurately what is occurring in tissues
- Autoantibodies to complement proteins may be associated with profound activation of the complement pathway in vivo, and the level of complement activation may be associated with the levels of these autoantibodies rather than by disease per se.

Autoantibodies against complement components

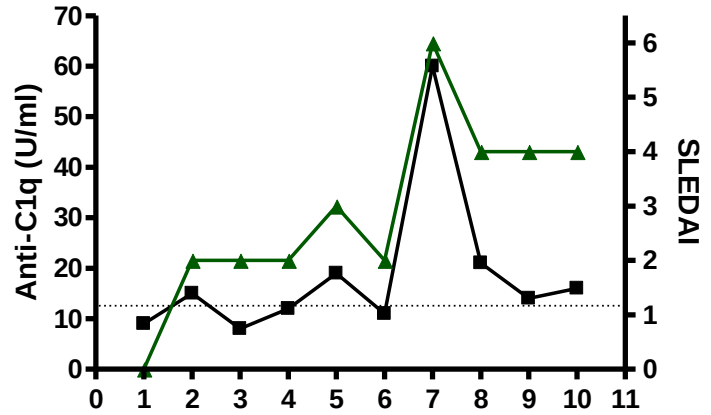
- Anti-C1q antibodies (SLE, maybe others)
- Anti-C1 inhibitor antibodies (acquired angioedema)
- Anti-Factor H antibodies (aHUS, AMD, C3 glomerulopathy)
- Anti-C3bBb antibodies (nephritic factor, C3 Nef): C3 glomerulopathy
- Others

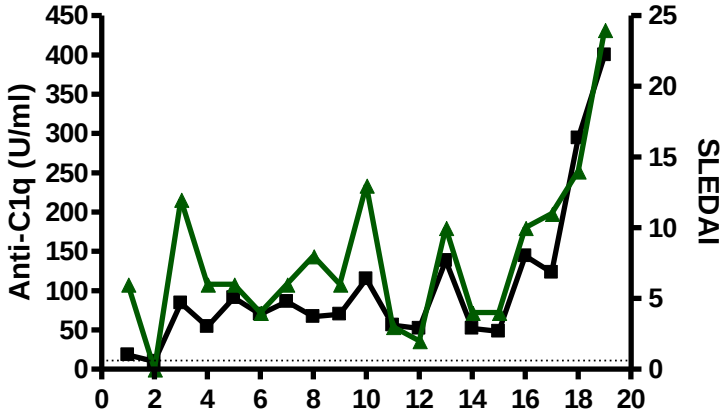


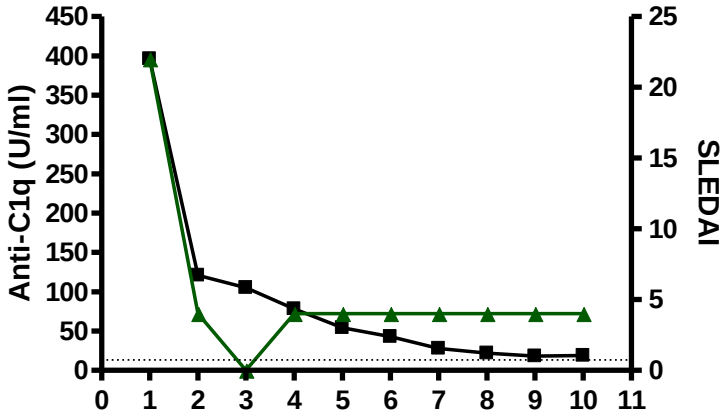


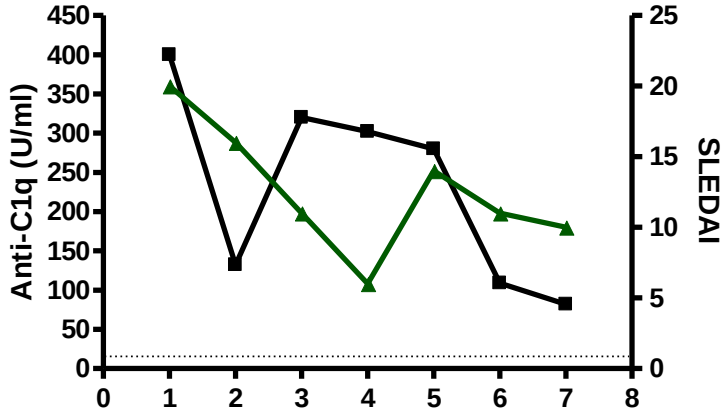
Trendelenburg M et al., Nephrol Dial Transpl 2006

Anti-C1q in the follow-up







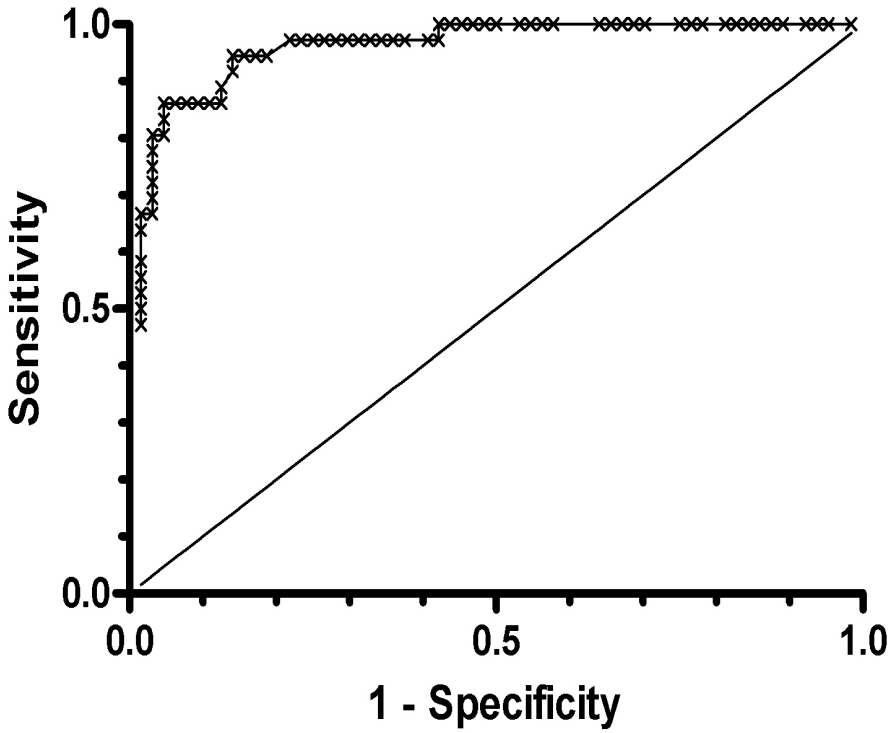


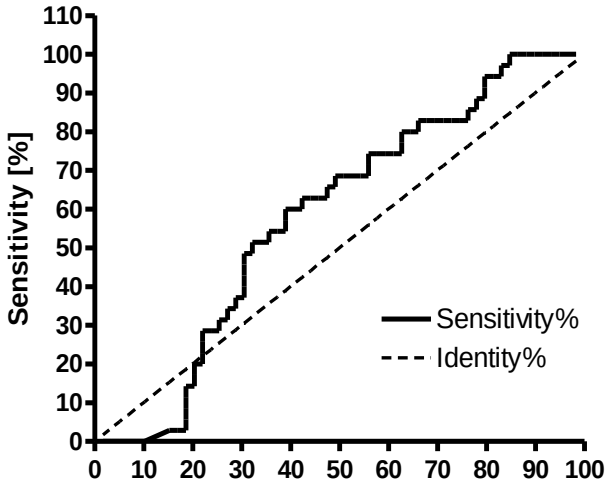
Bock M. et al., PLoS One 2015

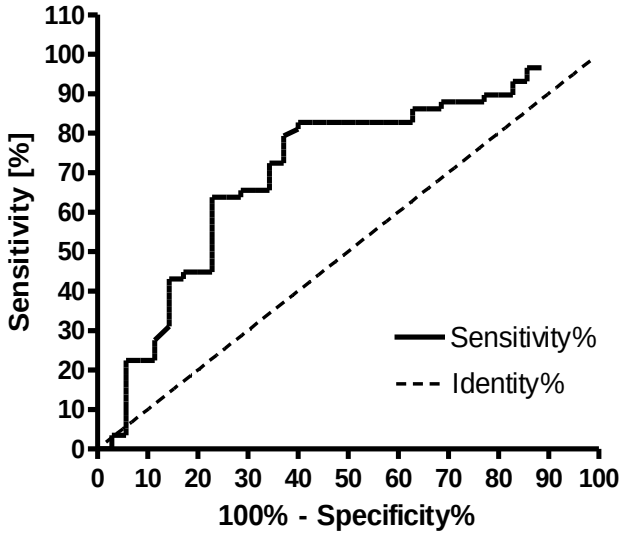
Conclusions

- Complement activation can occur by extrinsic triggers as well as due to intrinsic dysregulation.
- Complement is involved in many diseases. Its role is understood best in rare diseases but complement is likely to be of importance for frequent diseases as well (AMD, Alzheimer, schizophrenia, cardiovascular, …)
- Anti-C1q antibodies are an excellent marker of disease activity in patients with SLE

Receiver operating characteristics (ROC)

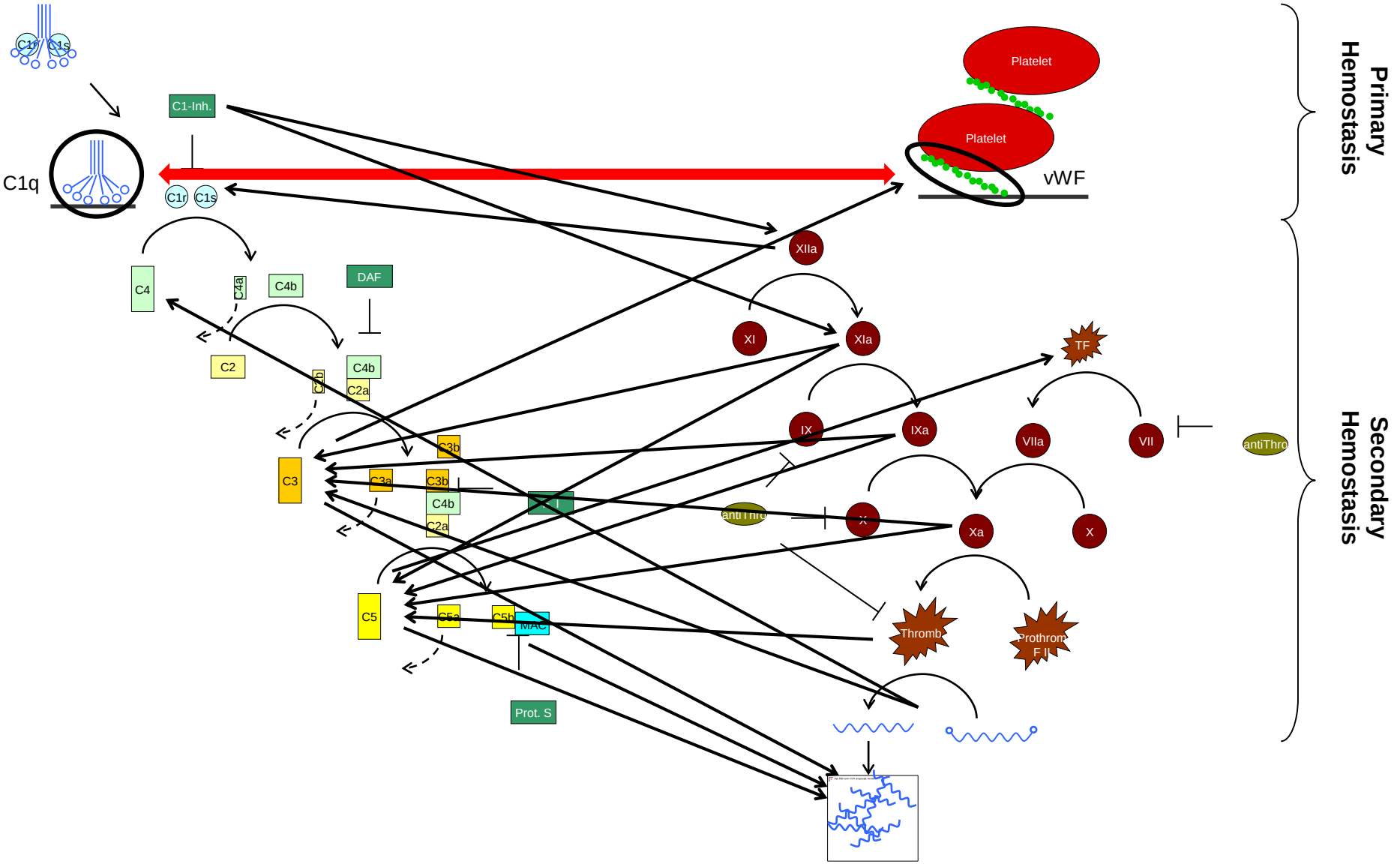


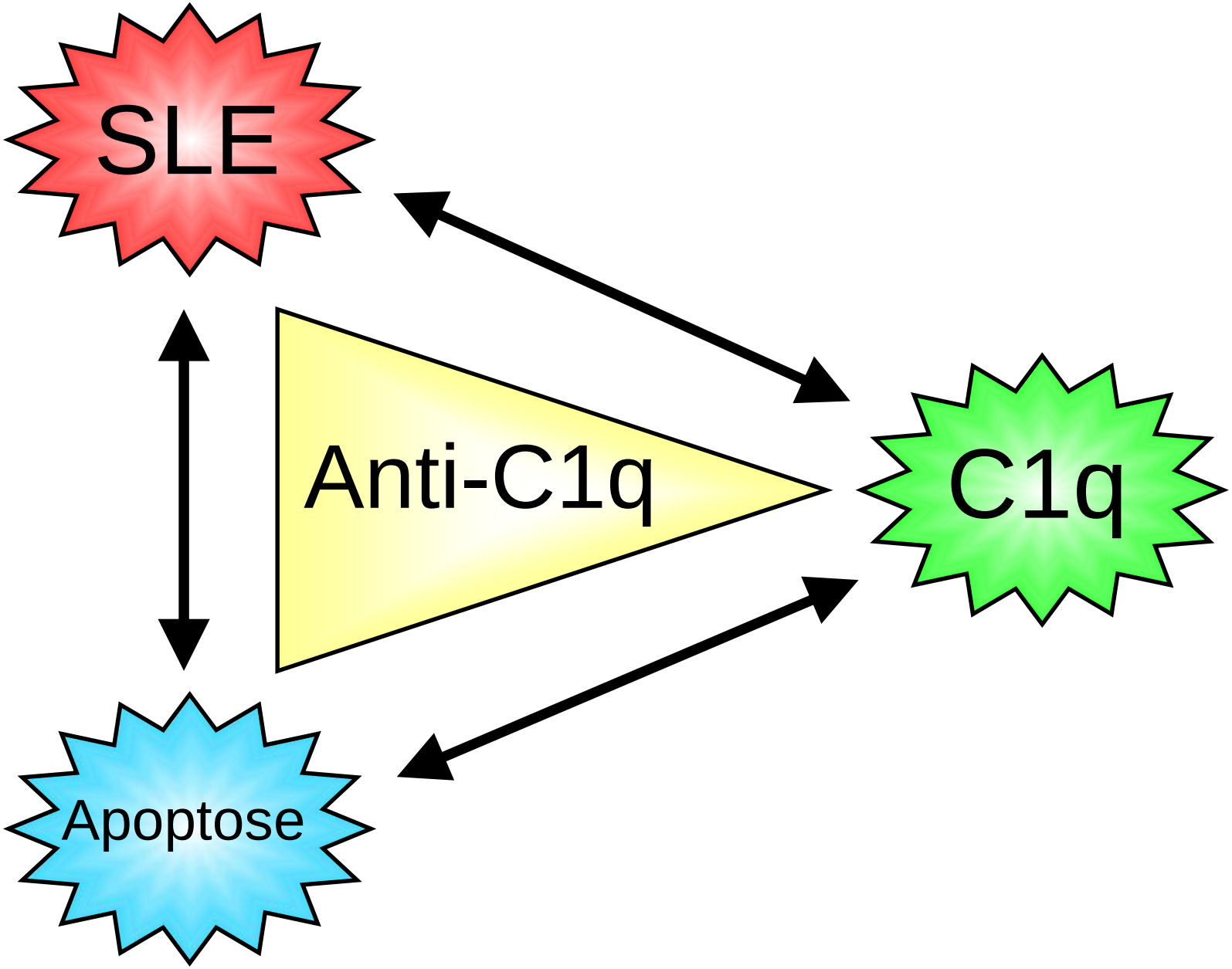




Trendelenburg M et al., Nephrol Dial Transpl 2006; Bigler C. et al., Am J Kidney Dis 2008

Complement and Hemostasis




SLE
Anti-C1q
C1q
Apoptose