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Advances in complement biology and therapy in rheumatic and immunologic diseases

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Disclosures: Alfred H.J. Kim, MD, PhD

I do have related financial interests to disclose

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  - Bristol Myers Squibb
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- Research grants
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  - NIH/NIAMS, NCATS

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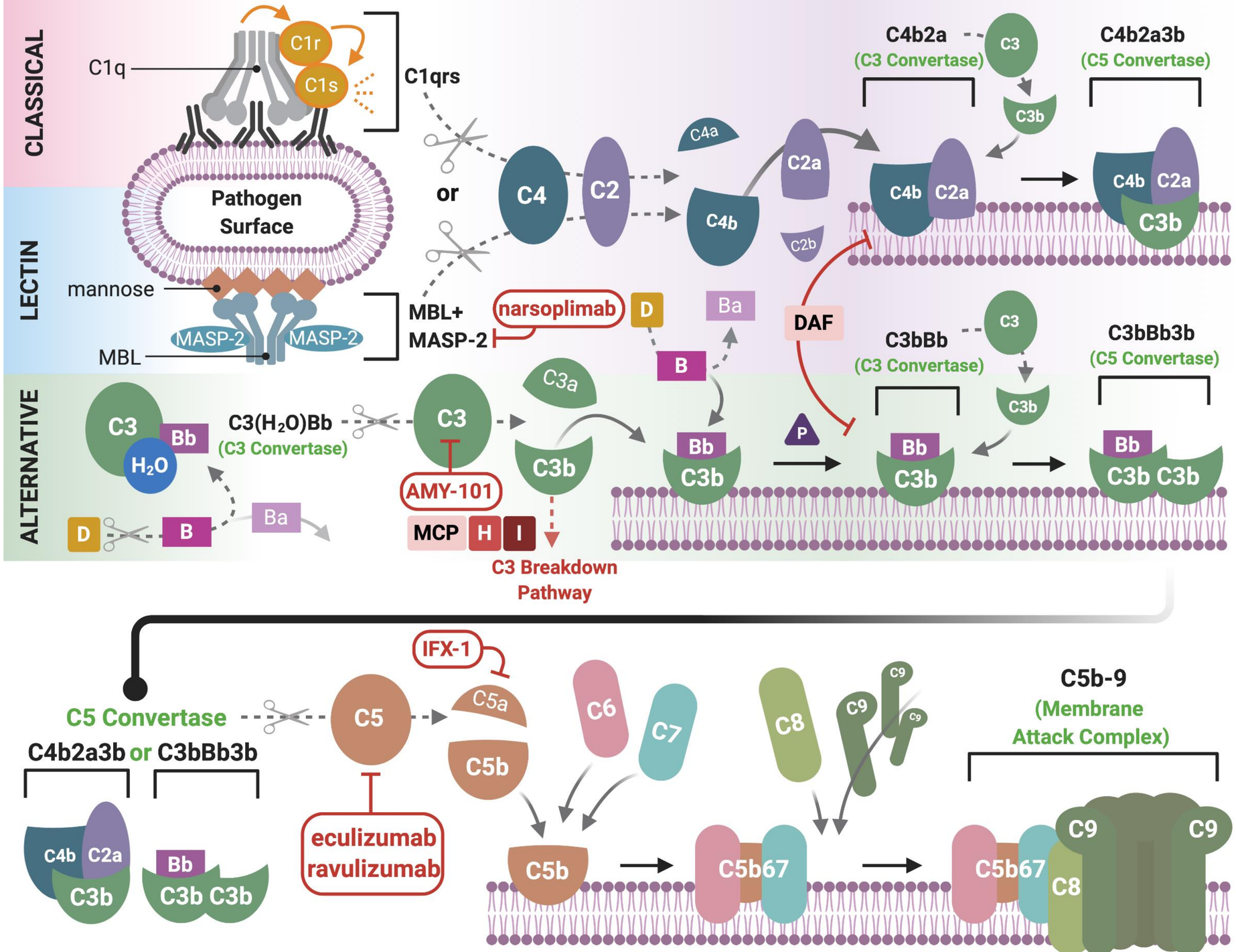
  - Alexion Pharmaceuticals
  - ANI Pharmaceuticals
  - AstraZeneca
  - Aurinia Pharmaceuticals
  - Exagen Diagnostics
  - GlaxoSmithKline
  - Kypha, Inc.
  - Pfizer, Inc.
  - UpToDate, Inc.
- Royalties/Patent Beneficiary
  - Kypha, Inc. (US Patent 11029318B2)



Java *et al.*, *JCI Insight*, 2020, PMID: 32554923

Outline

- Key concepts in complement biology
- Discussion of complement-dependent diseases & therapeutic approaches that provide mechanistic insights
  - Classical pathway activation by autoantibodies: Neuromyelitis optica (NMO)
  - Alternative pathway activation by genetic loss of function of regulators: paroxysmal nocturnal hemoglobinuria (PNH) (with a cameo from cold agglutinin disease), thrombotic microangiopathy (TMA)
  - Alternative pathway activation by neutrophils: antiphospholipid syndrome (APLS), systemic lupus erythematosus? (SLE), ANCA-associated vasculitis (AAV)
- Advances in complement testing

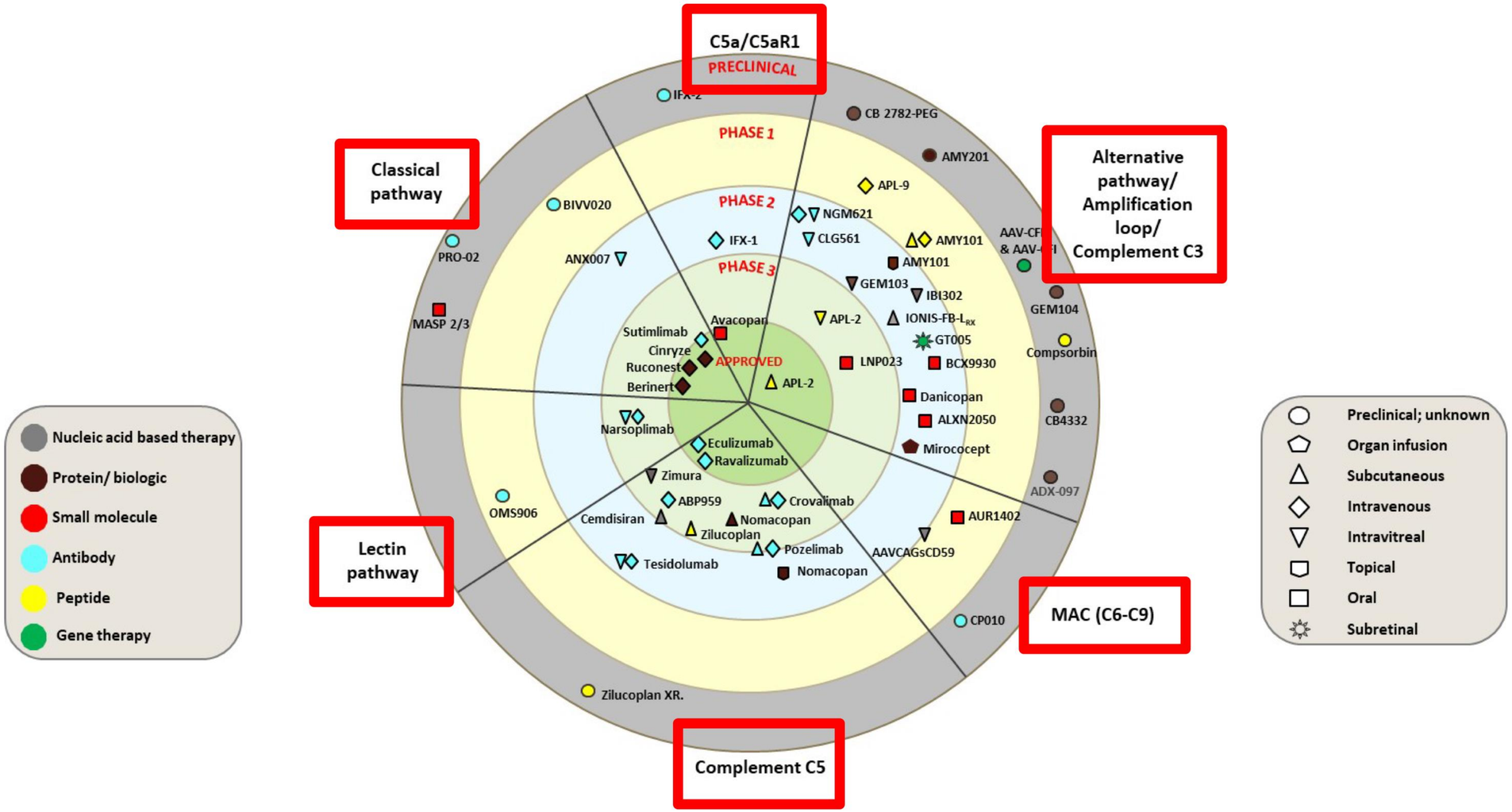
Complement therapeutics

Approved and potential indications

- Approved
  - Hereditary angioedema (C1-INH replacement)
  - Paroxysmal nocturnal hemoglobinuria (PNH) (anti-C5, C3 convertase inhibitor)
  - Atypical hemolytic uremic syndrome (aHUS) (anti-C5)
  - Neuromyelitis optica (NMO) (anti-C5)
  - Myasthenia gravis (anti-C5)
  - ANCA-associated vasculitis (C5aR antagonist)
  - Cold agglutinin disease (anti-C1s)
- Positive/supportive human clinical trials or pilots
  - Age-related macular degeneration
  - C3 glomerulopathy
  - IgA nephropathy
  - Lupus nephritis
  - Periodontitis
  - Antiphospholipid syndrome
- Positive data in preclinical models and patient biomarkers
  - Stroke, osteoarthritis, rheumatoid arthritis, myositis, bullous pemphigoid, multiple sclerosis, Alzheimer’s, etc.

Complement therapeutics pipeline is growing

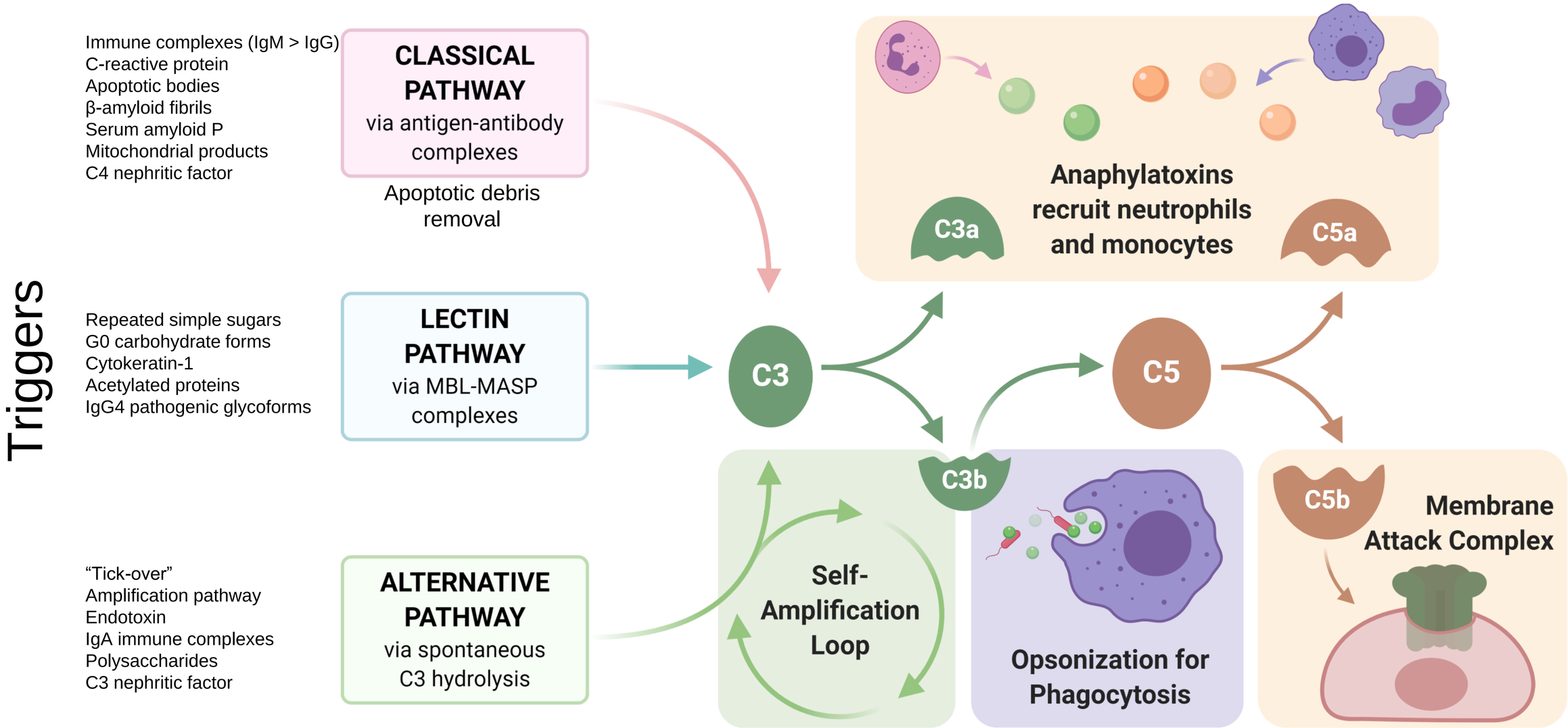
Functions as a toolkit to understand functional roles in human disease



Modified from Zelek *et al.*, *Mol Immunol,* 2019, PMID: 31446305

The complement system

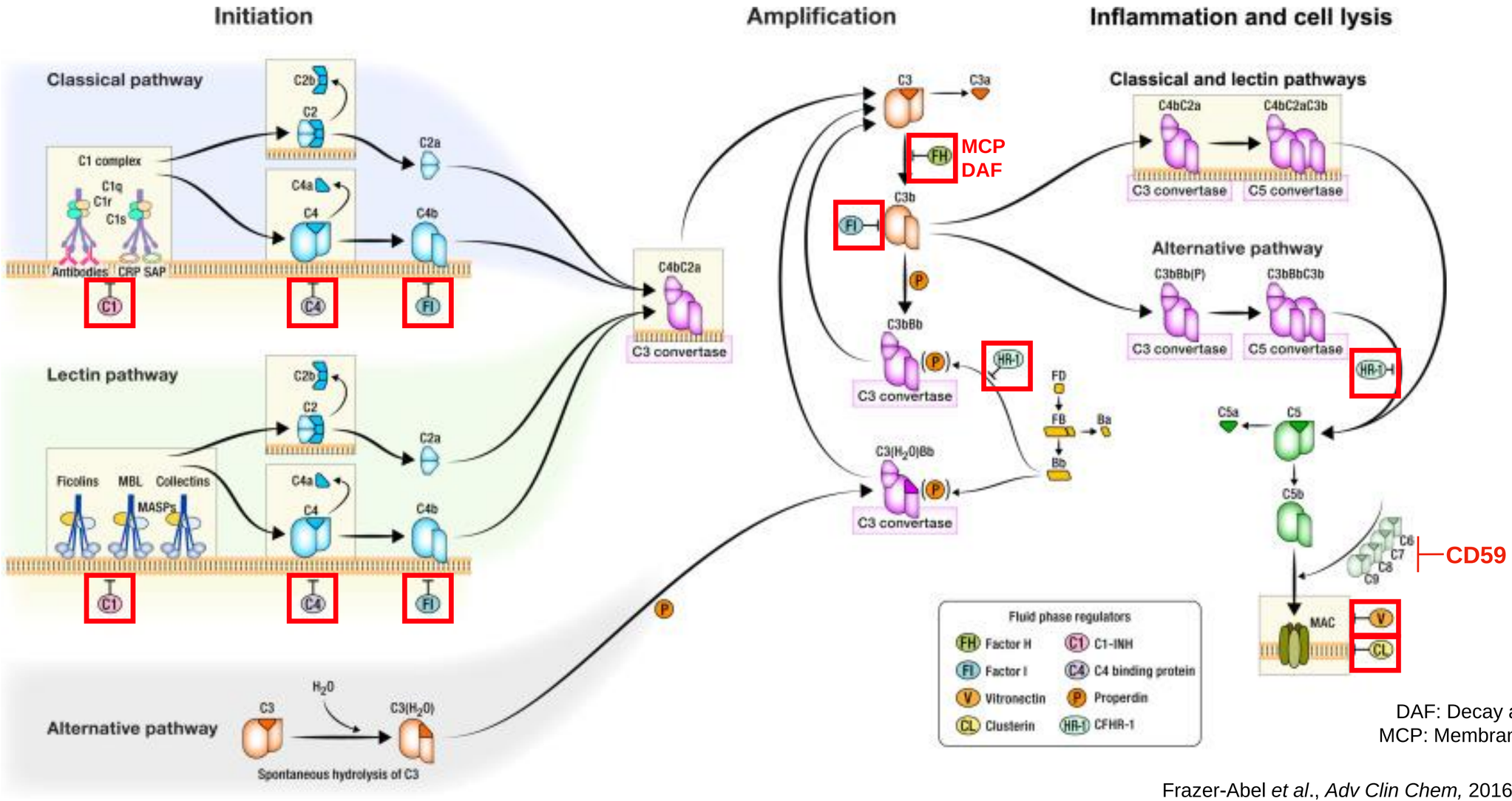
Purpose: to rapidly amplify upon microbial threats



Java *et al*., *JCI Insight,* 2020, PMID: 32554923

The complement system

Amplification balanced by regulation: key to appropriate functioning

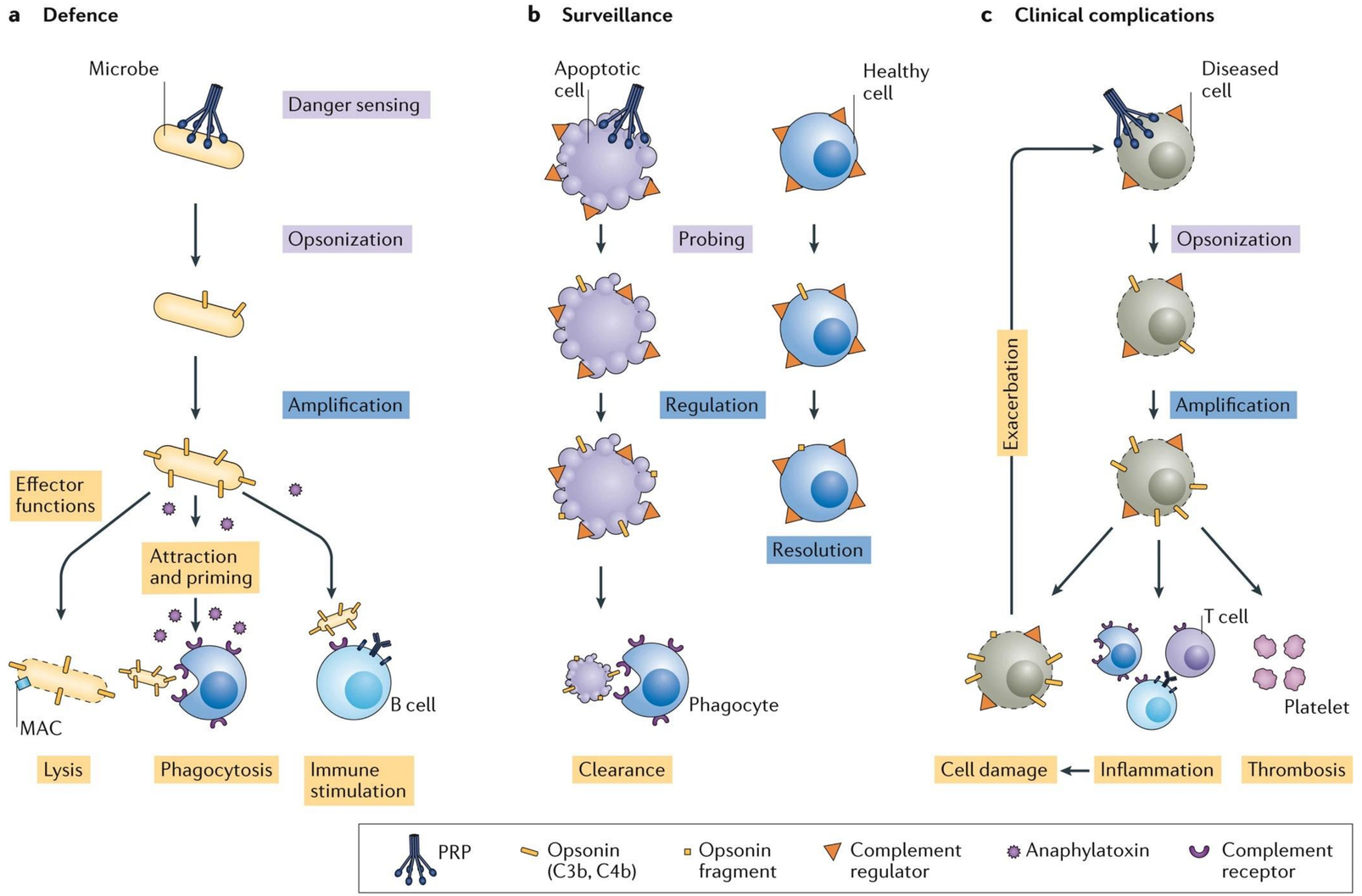


DAF: Decay accelerating factor
MCP: Membrane cofactor protein

Frazer-Abel *et al*., *Adv Clin Chem,* 2016, PMID: 27717414

The complement system

Collectively, complement plays three roles in human physiology



Ricklin *et al*., *Nat Rev Nephrol,* 2018, PMID: 29199277

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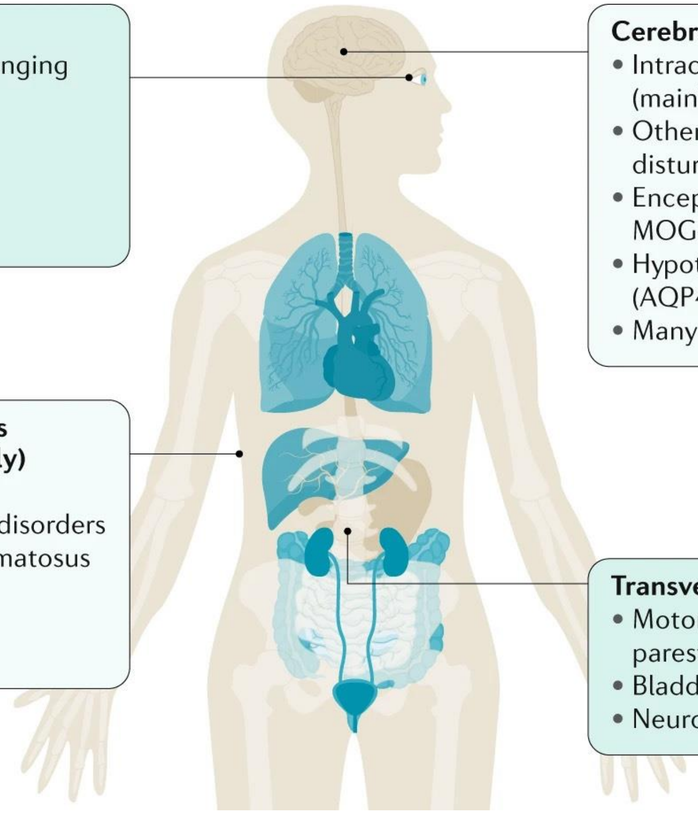
Neuromyelitis optica

Widespread neural inflammation resulting in optic neuritis and transverse myelitis

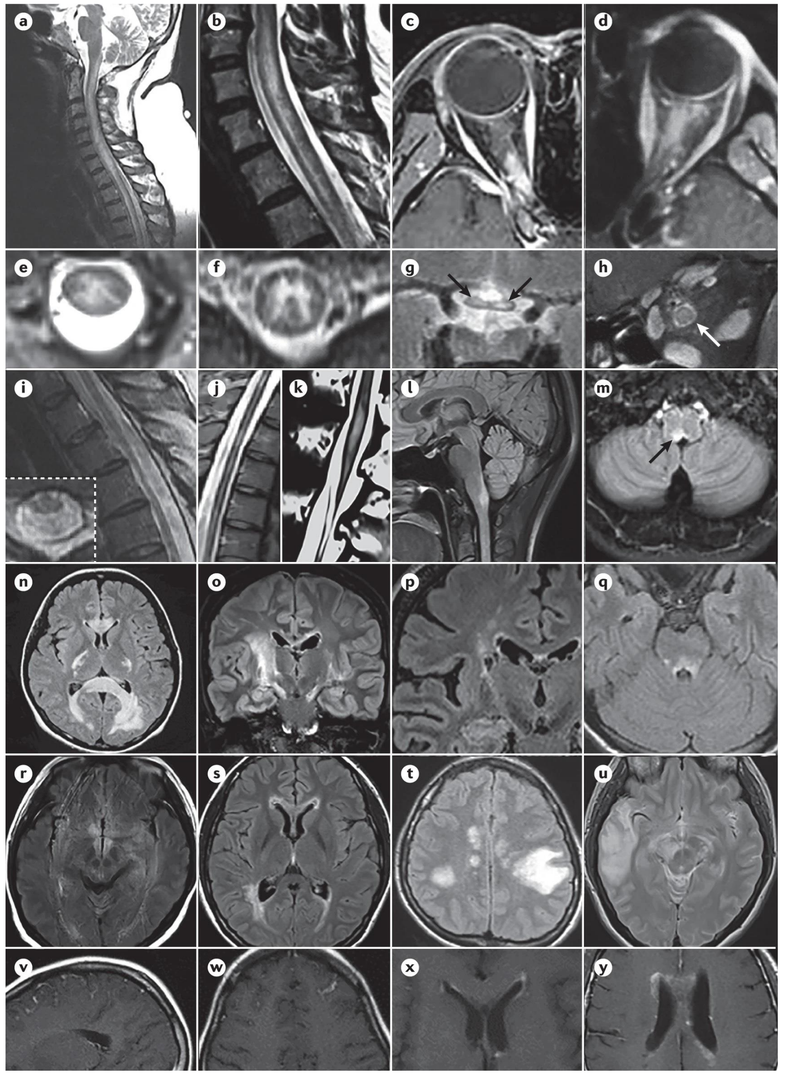
Optic neuritis
- Reduced visual acuity, ranging from mild to severe
- Colour desaturation
- Scotoma
- Ocular pain/pain upon eye movement

Cerebral involvement
- Intractable nausea, vomiting or hiccups (mainly AQP4-IgG disease)
- Other brainstem syndromes (e.g. oculomotor disturbances, facial numbness)
- Encephalopathy with seizures (mainly MOG-IgG disease)
- Hypothalamic or thalamic syndromes (AQP4-IgG disease; e.g. narcolepsy, SIADH)
- Many others



Extra-CNS complications (AQP4-positive NMO only)
- Myositis
- Comorbid autoimmune disorders
  - Systemic lupus erythematosus
  - Sjögren syndrome
  - Myasthenia gravis
  - Many others

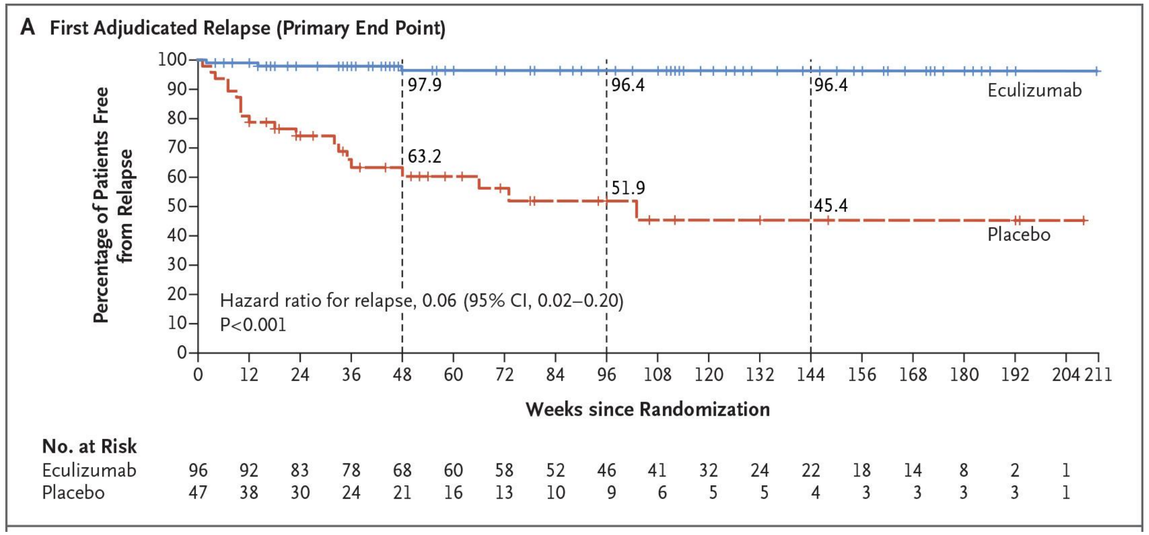
Transverse myelitis
- Motor and sensory deficits ranging from paresthesia to paresis
- Bladder, bowel and/or erectile dysfunction
- Neuropathic pain

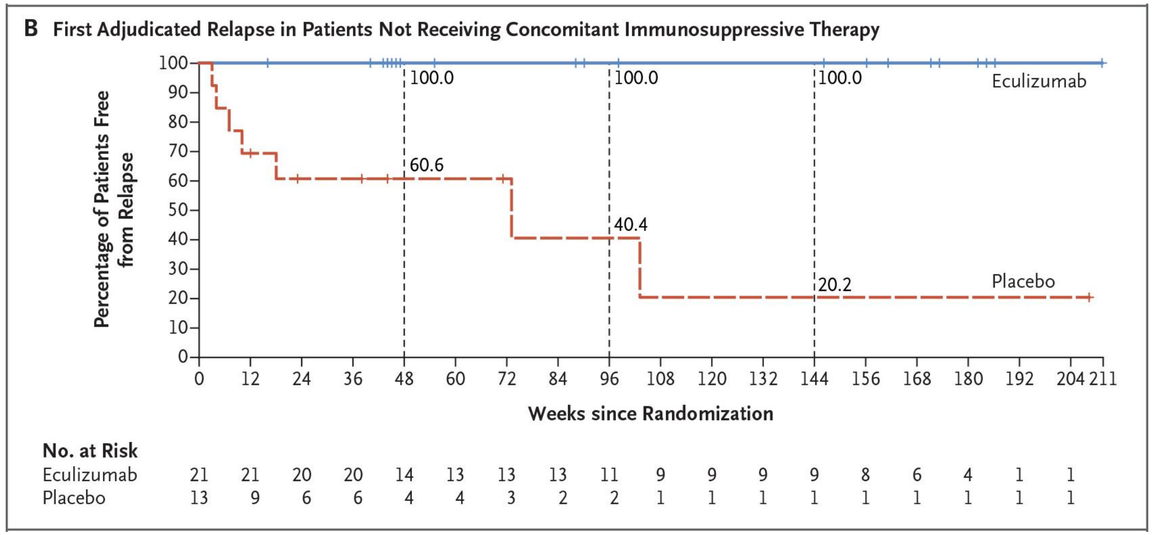


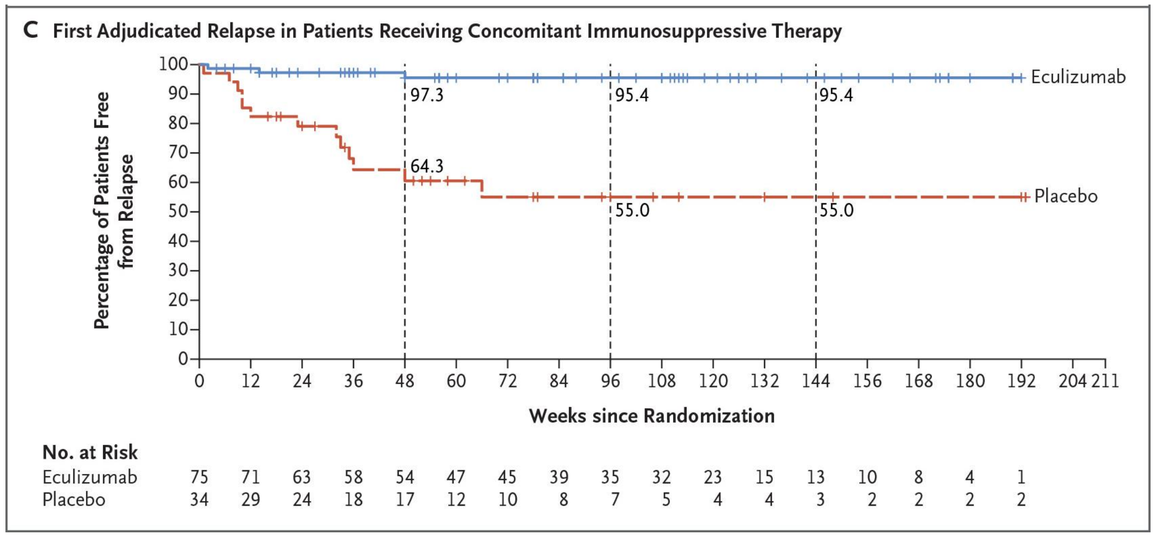
Jarius *et al*., *Nat Rev Dis Primers,* 2020, PMID: 33093467

Neuromyelitis optica

Reduced relapse rate with anti-C5 mAb



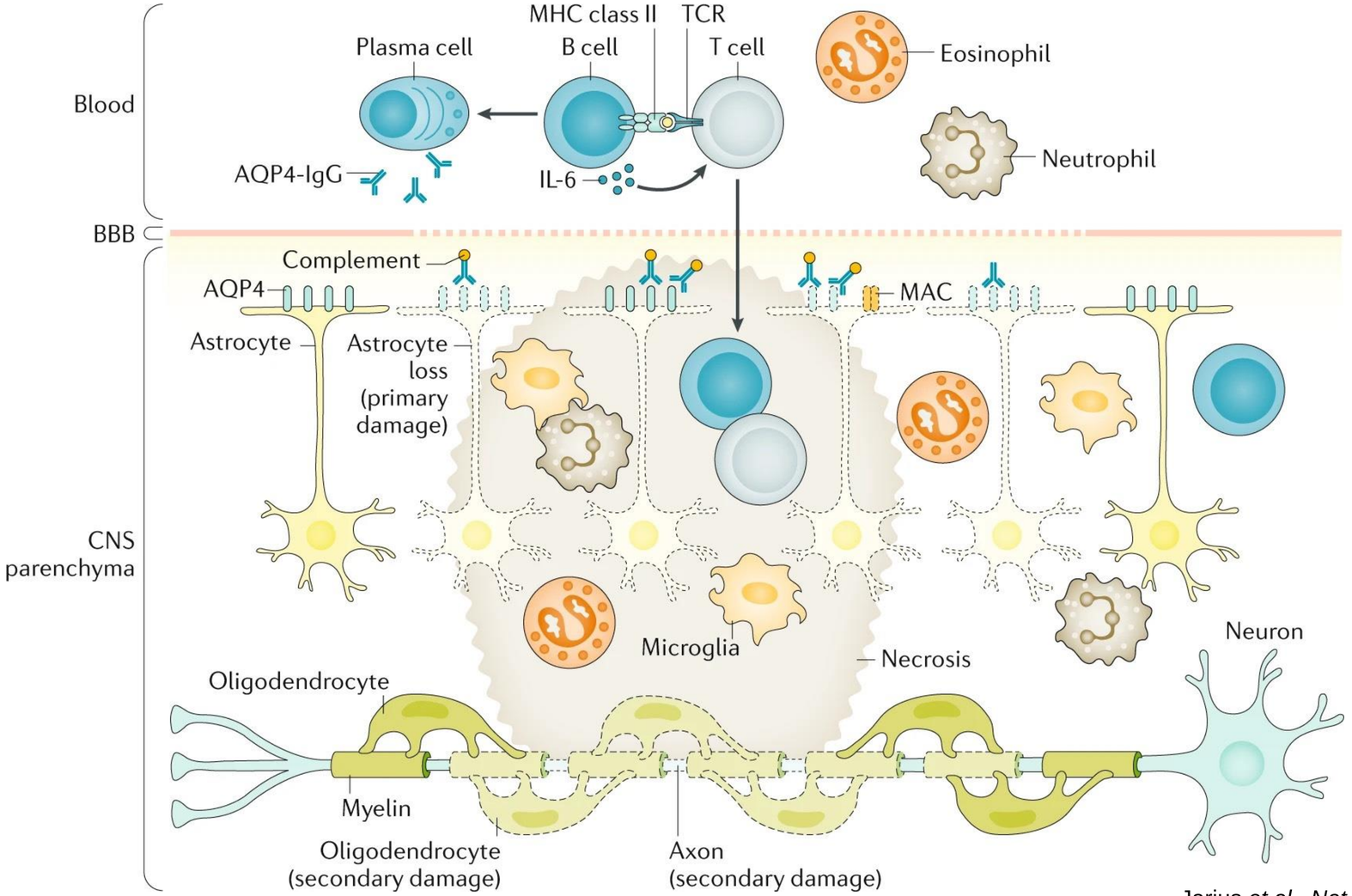




Pittock *et al.*, *New Engl J Med,* 2019, PMID: 31050279

Neuromyelitis optica

AutoAbs to astrocyte aquaporin 4 (AQP4) drives complement activation



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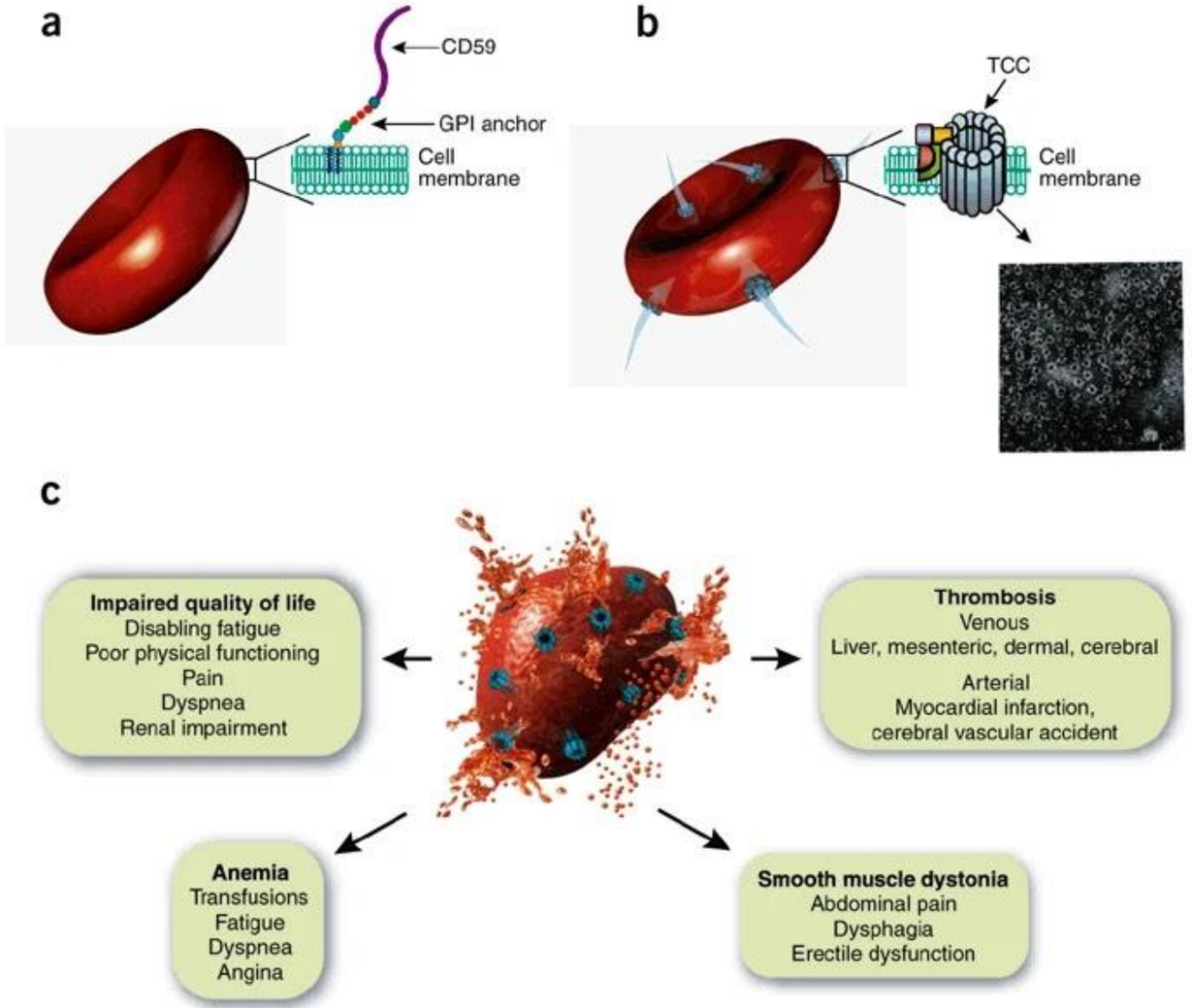
Paroxysmal nocturnal hemoglobinuria (PNH)

Disease of unregulated alternative pathway activation on RBCs

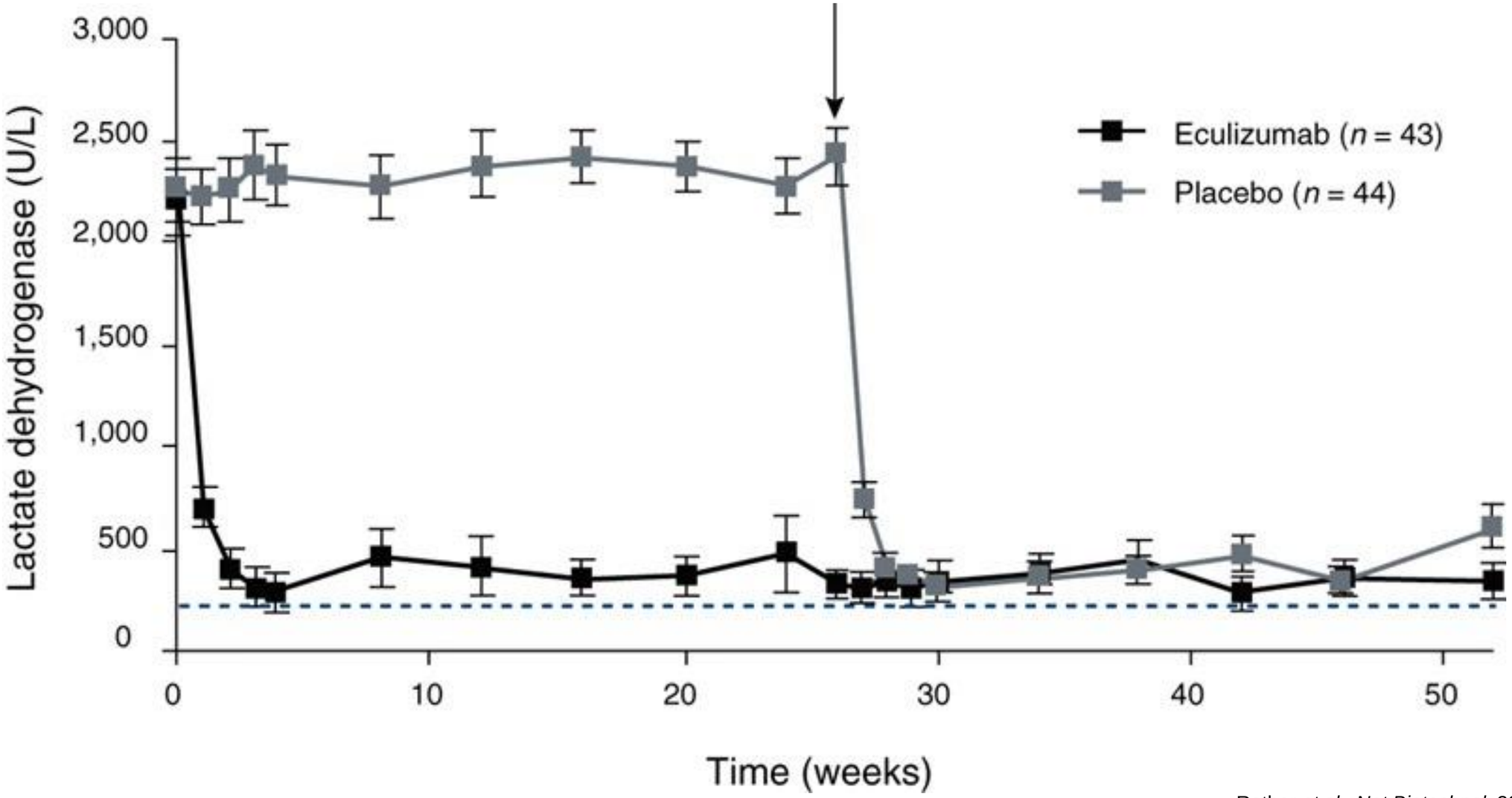
First disease to be targeted by complement inhibition



Rother *et al*., *Nat Biotechnol,* 2007, PMID: 17989688

Paroxysmal nocturnal hemoglobinuria (PNH)

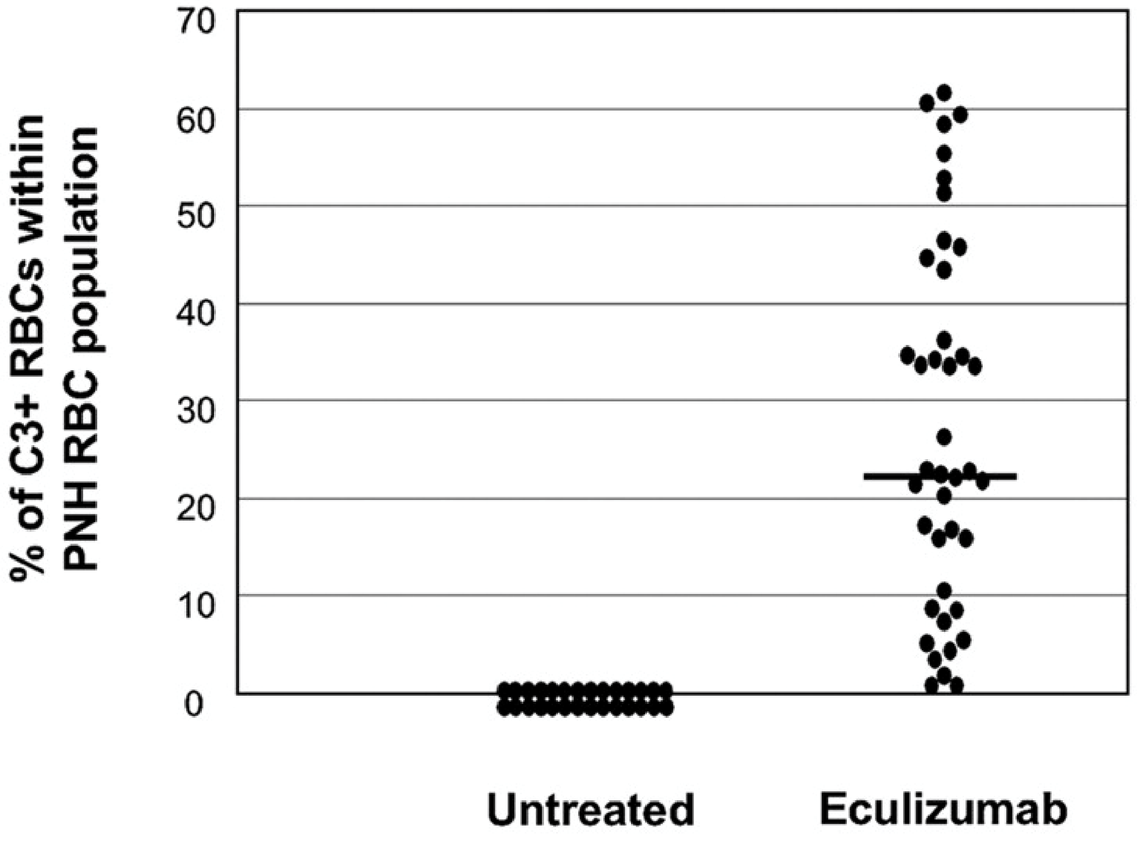
Anti-C5 mAb ameliorates intravascular hemolysis

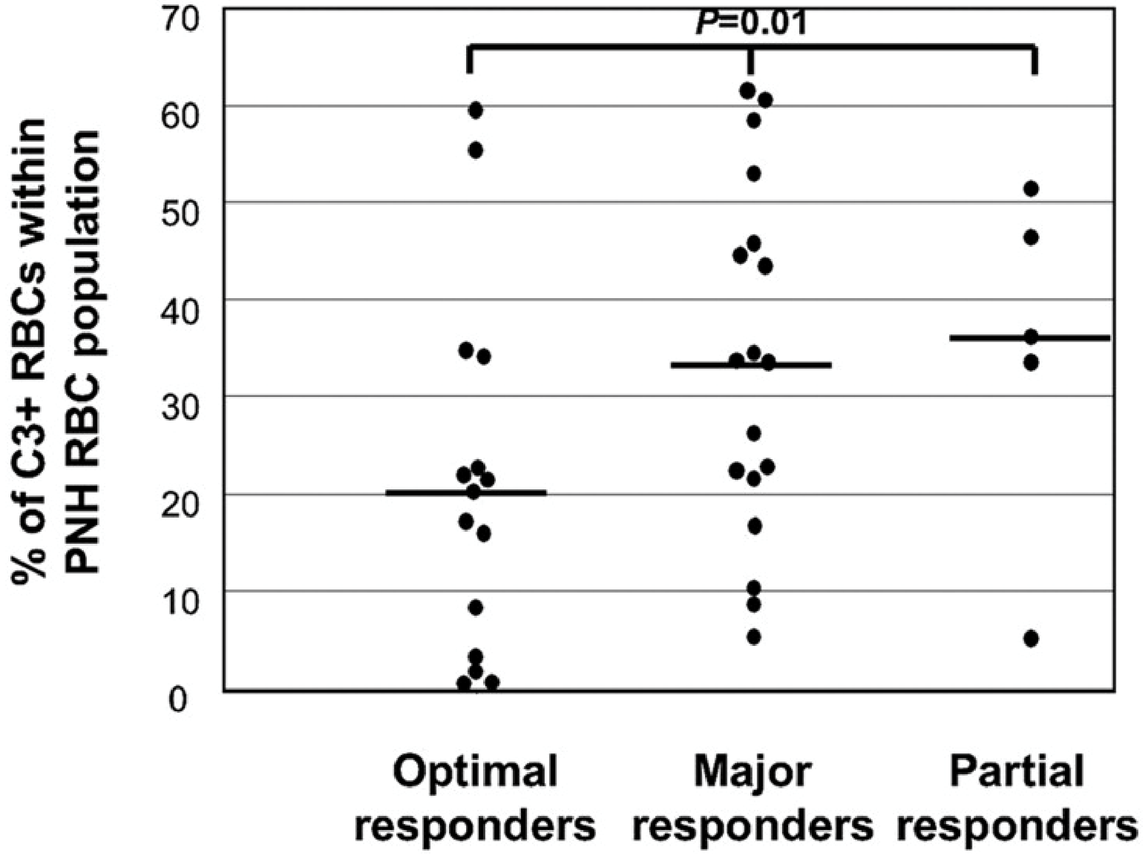


Rother *et al*., *Nat Biotechnol,* 2007, PMID: 17989688

Paroxysmal nocturnal hemoglobinuria (PNH)

But…C3 fragments found on PNH RBCs on anti-C5 mAb inversely correlated with response

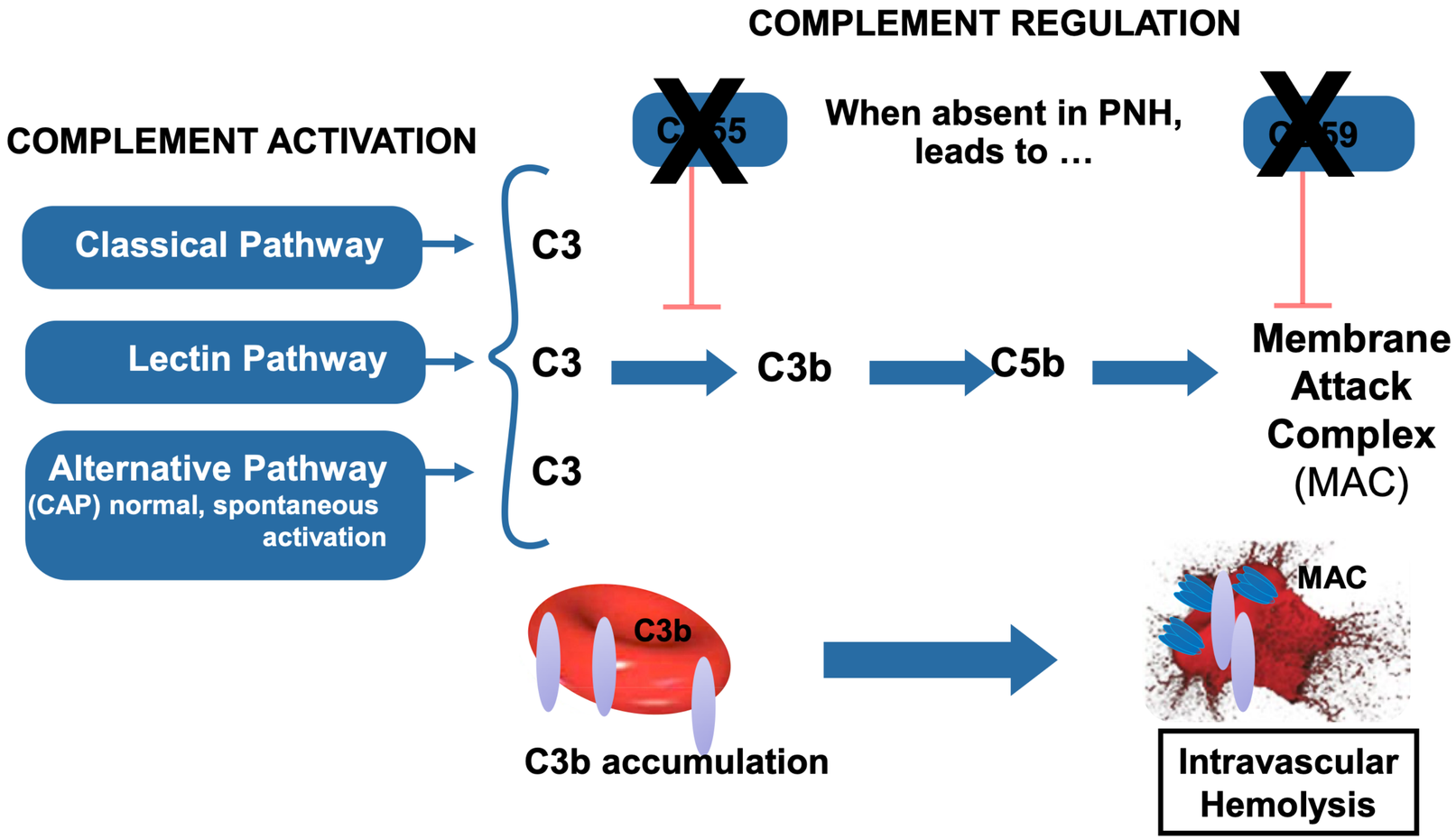




Risitano *et al*., *Blood,* 2009, PMID: 19179465

Paroxysmal nocturnal hemoglobinuria (PNH)

Anti-C5 mAb blocks intravascular hemolysis but leads to RBC C3b accumulation, driving extravascular hemolysis



Slide courtesy of Bill Lundberg

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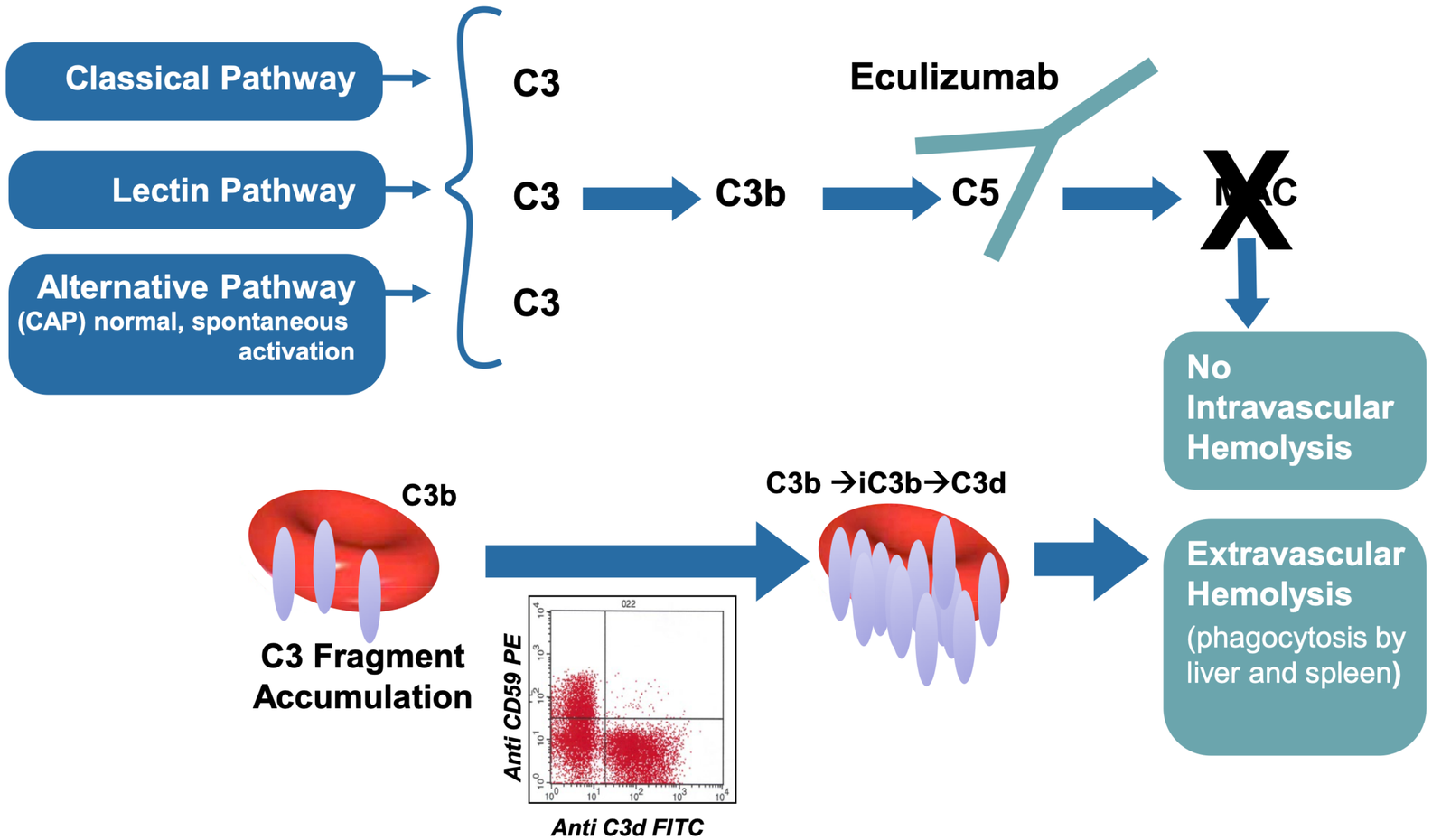
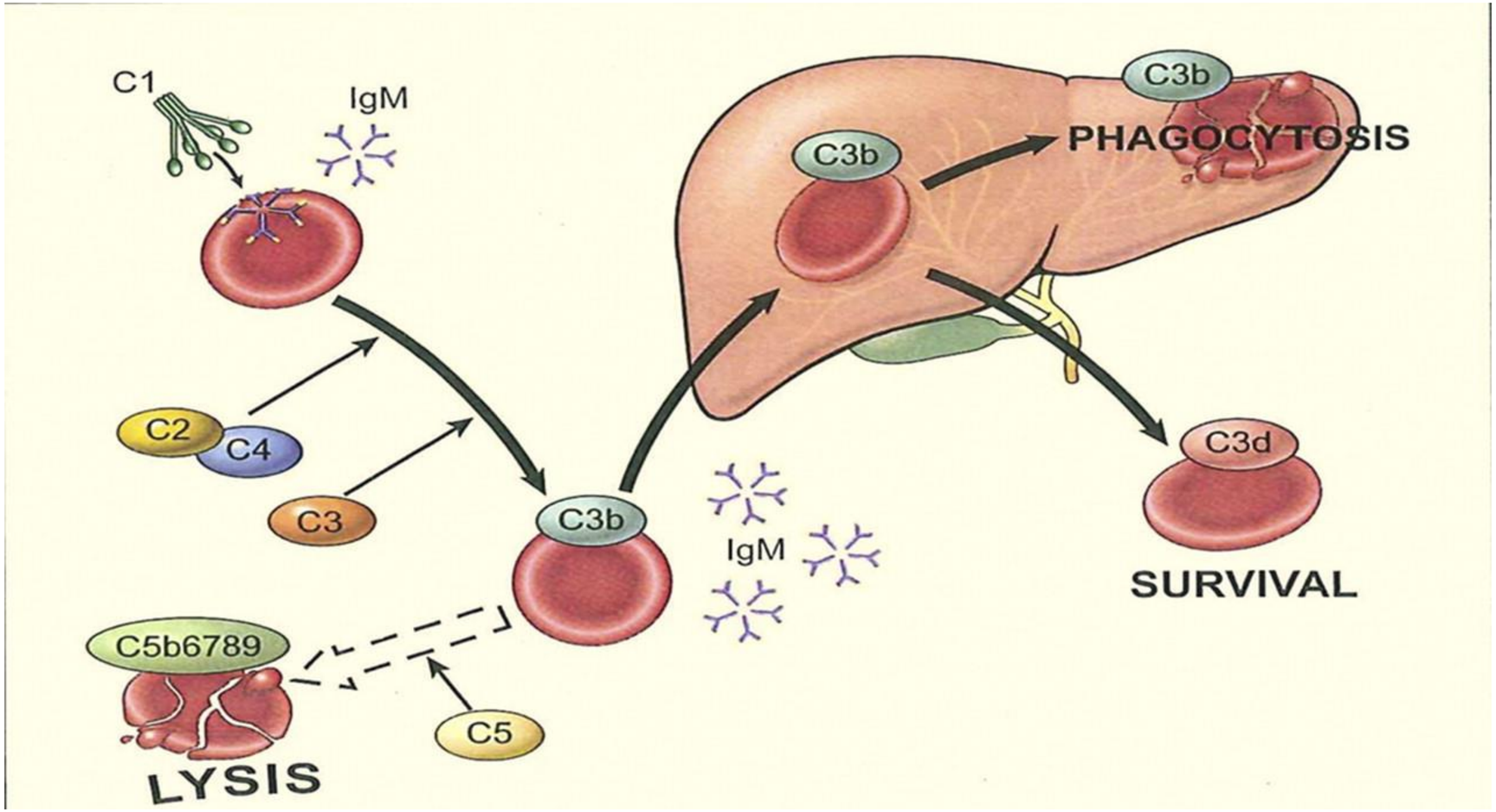


Risitano *et al*., *Blood,* 2008, PMID: 18606894
Risitano *et al*., *Blood,* 2009, PMID: 19179465
Hill *et al.*, *Haematologica*, 2010, PMID: 20145265

Slide courtesy of Bill Lundberg

Cold agglutinin disease

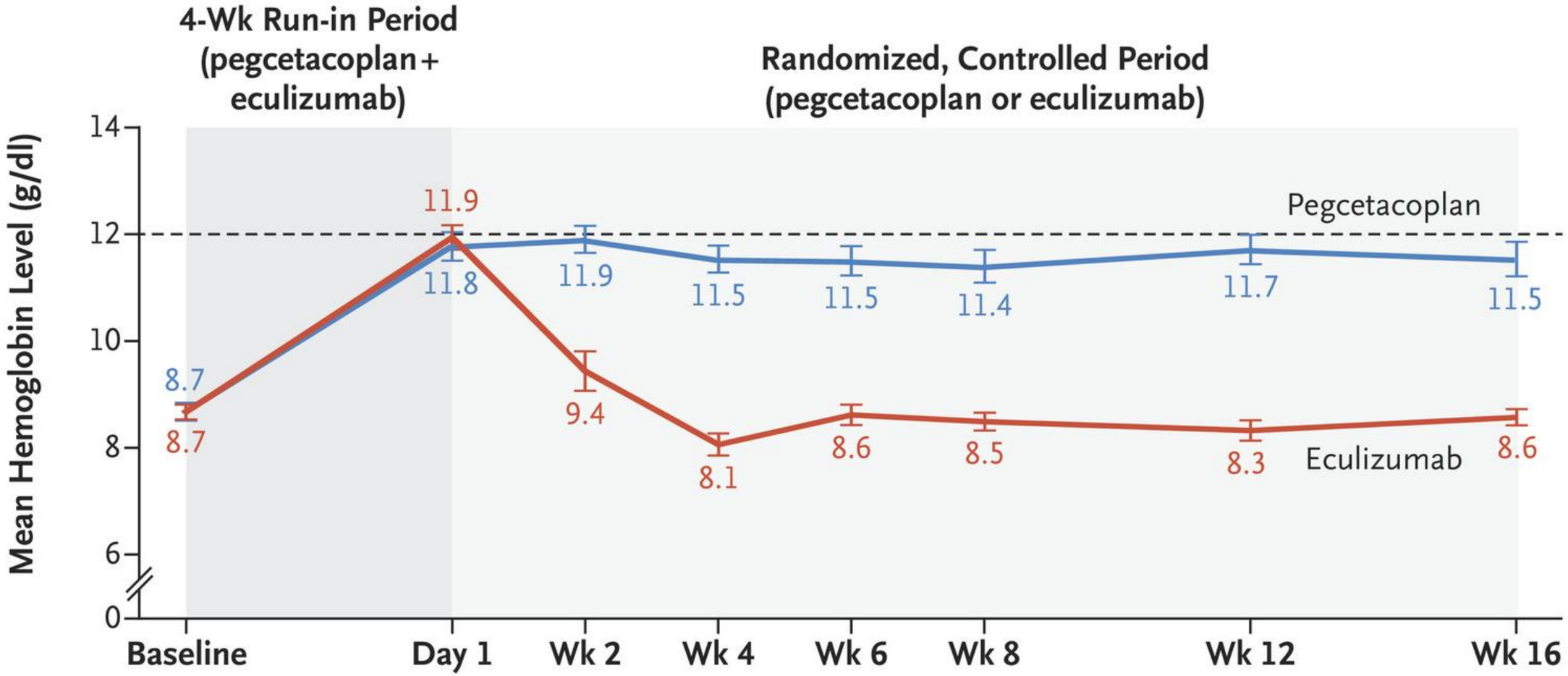
Mechanism of C3-mediated extravascular hemolysis revealed in cold agglutinin disease studies



Atkinson and Frank, *J Clin Invest,* 1974, **54**:339, PMID: N/A
Stone, *Blood*, 2010, PMID: 21030565

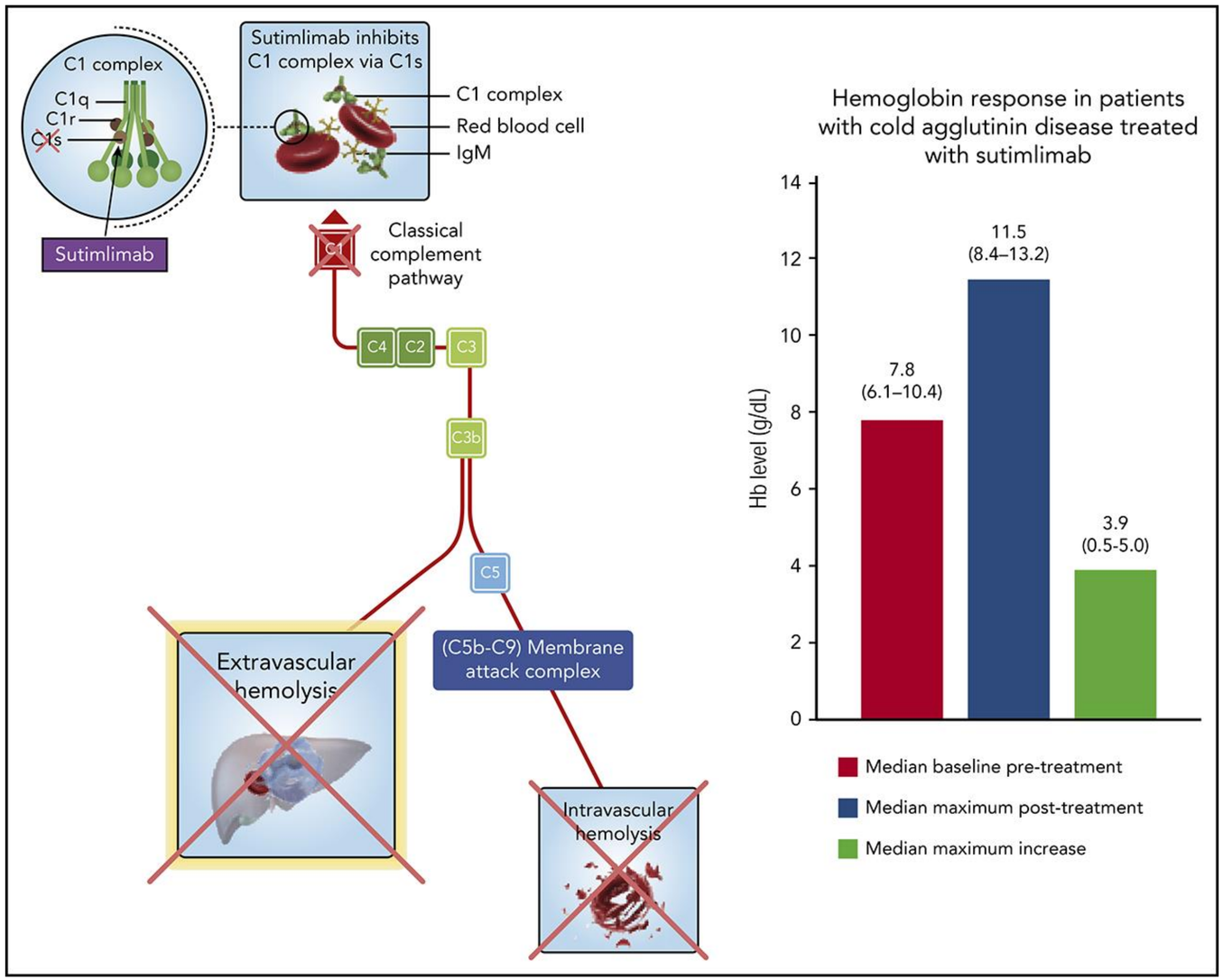
Paroxysmal nocturnal hemoglobinuria (PNH)

Treatment with C3 inhibitor abrogated both intravascular and extravascular hemolysis



Hillmen *et al*., *New Engl J Med,* 2021, PMID: 33730455

Cold agglutinin disease
Anti-C1s mAb also effective

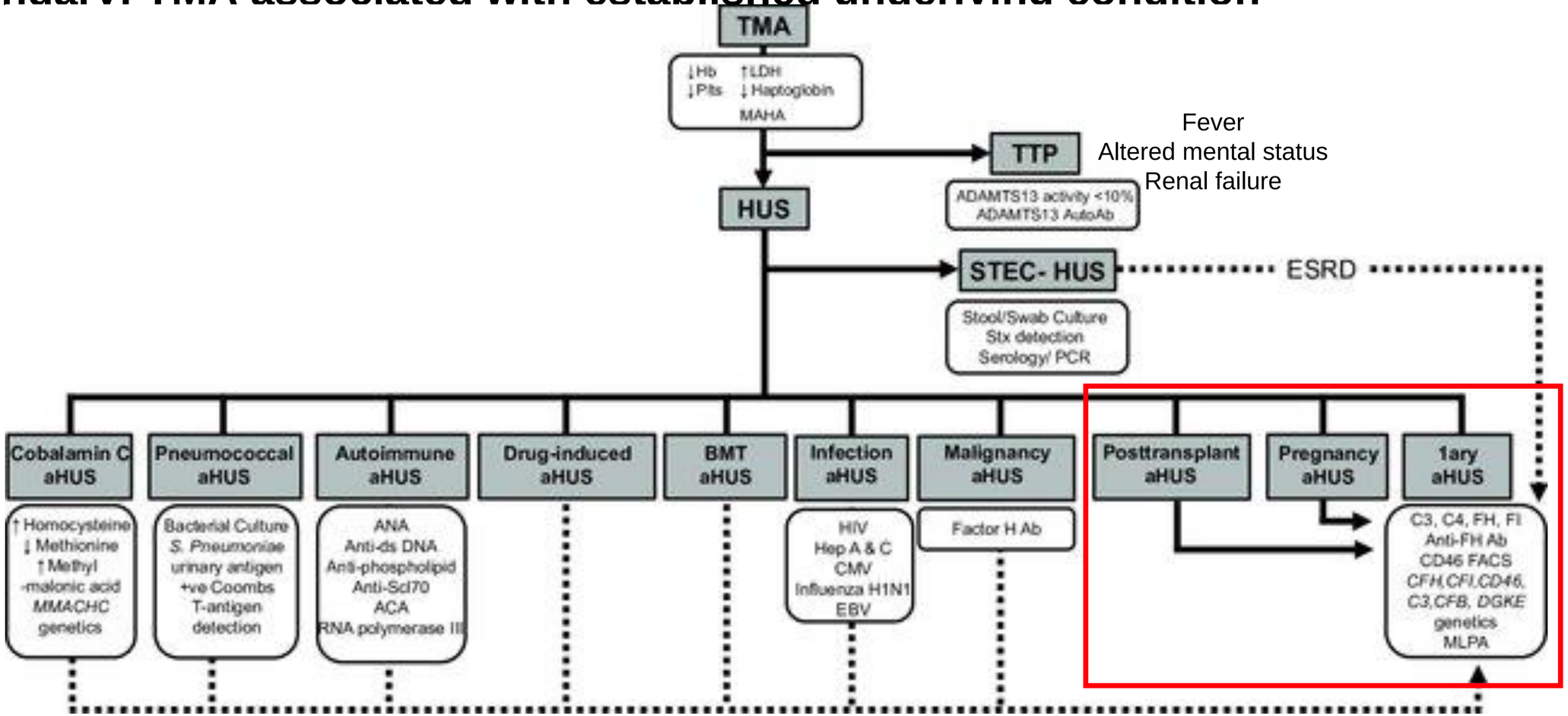


Jager *et al.*, *Blood*, 2019, PMID: 30559259

Thrombotic microangiopathy (TMA)

Primary: Mutations in complement regulatory proteins leading to excessive activation

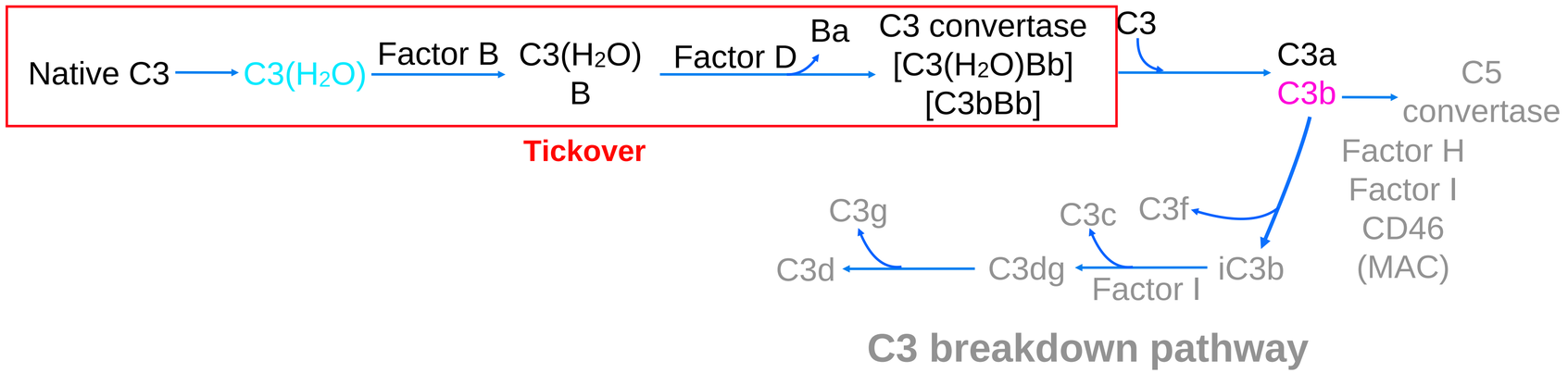
Secondary: TMA associated with established underlying condition



Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference, Dec 2016

Thrombotic microangiopathy (TMA)

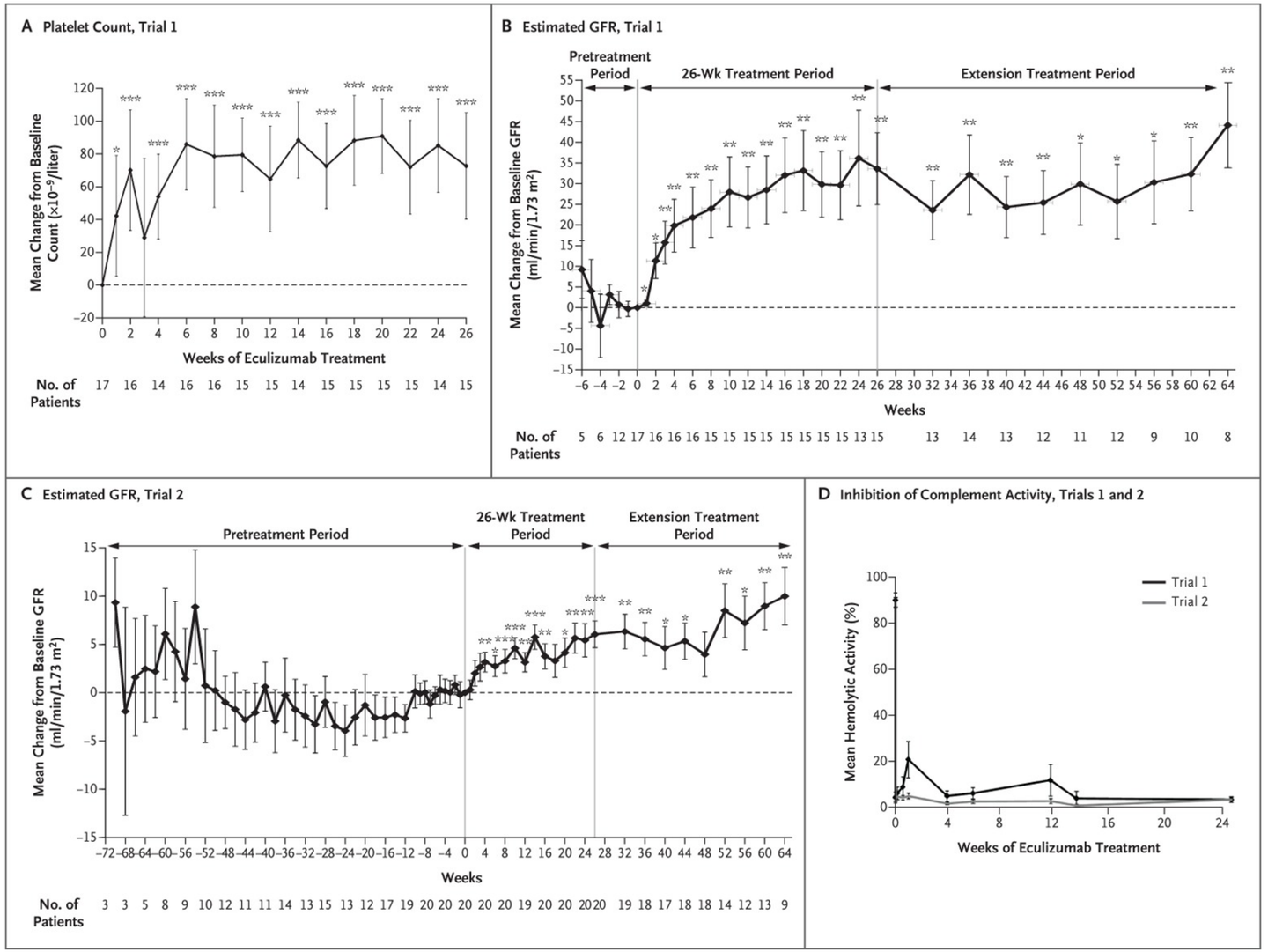
Variants in complement regulatory proteins drive excessive AP activation



- Loss of function mutations in Factor H
  - Cantsilieris *et al.*, *Proc Natl Acad Sci*, 2018, PMID: 29686068
- Inhibitory autoAbs to Factor H
  - Brocklebank *et al.*, *Kidney Intl*, 2017, PMID: 28750931
- Mutations of Factor I altering secretion or function
  - Nilsson *et al.*, *Eur J Immunol*, 2010, PMID: 19877009
- Rare mutations also found in CD46 and FH family proteins
  - Valoti *et al.*, *Front Immunol*, 2019, PMID: 31118930

Frazer-Abel *et al.*, *Adv Clin Chem,* 2016, PMID: 27717414

Thrombotic microangiopathy (TMA)
Anti-C5 mAb effective in aHUS

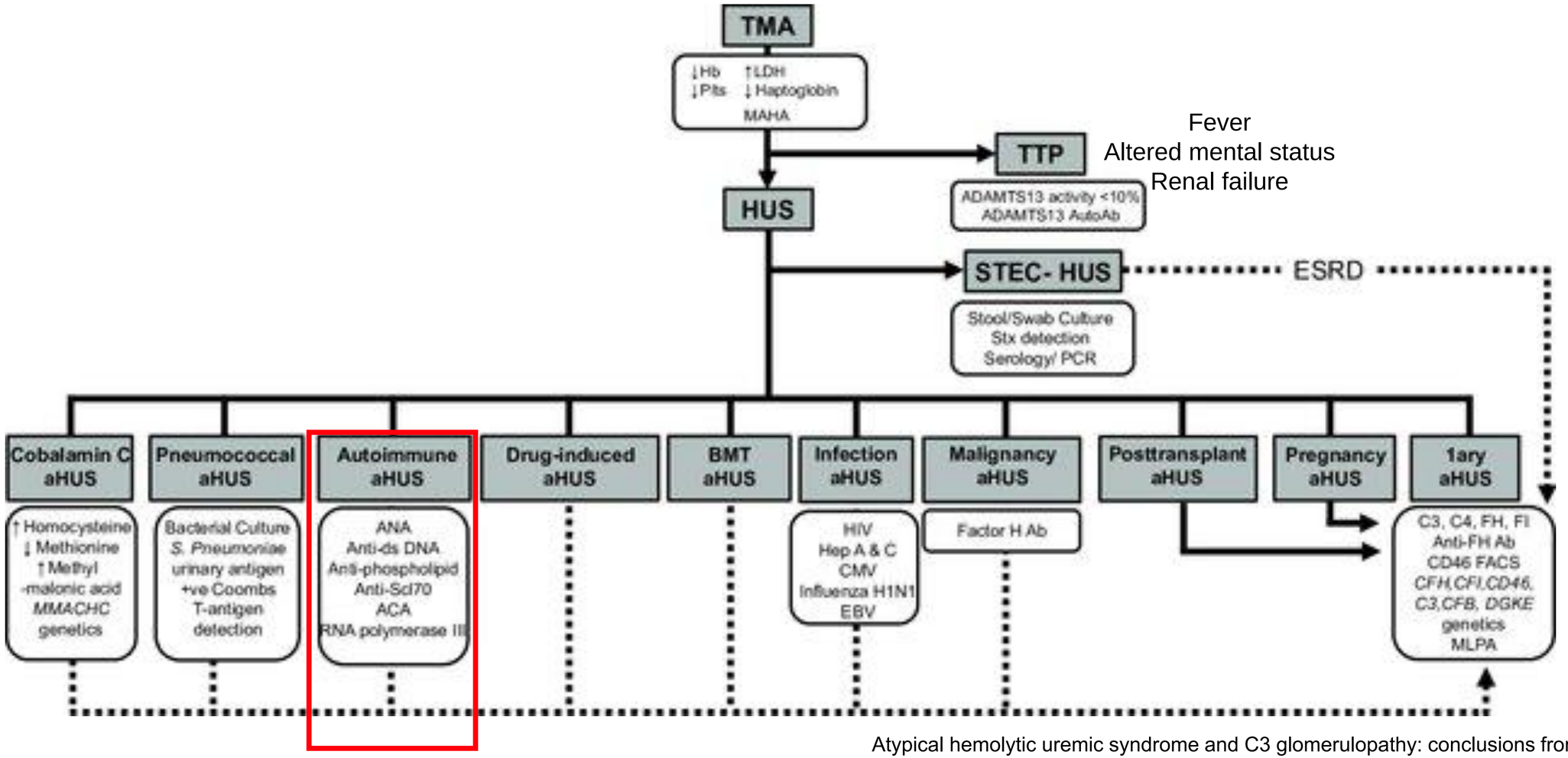


Legendre *et al.*, *New Engl J Med,* 2013, PMID: 23738544

Thrombotic microangiopathy (TMA)

Primary: Mutations in complement regulatory proteinsleading to excessive activation

Secondary: TMA due to established underlying condition



Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference, Dec 2016

TMA in autoimmune diseases: Java & Kim, *J Rheumatol*, 2023, PMID: 36642429

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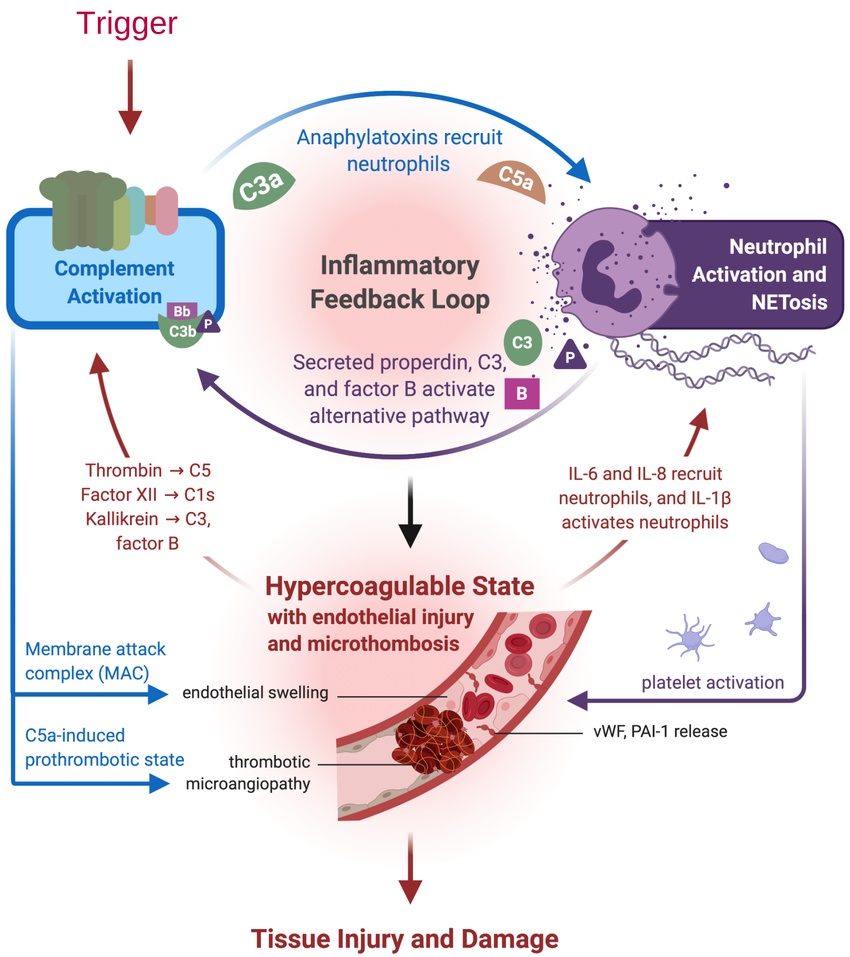
Antiphospholipid syndrome (APLS)

Classic “endotheliopathy”: neutrophil and complement activation driving endothelial cell activation and subsequent clotting

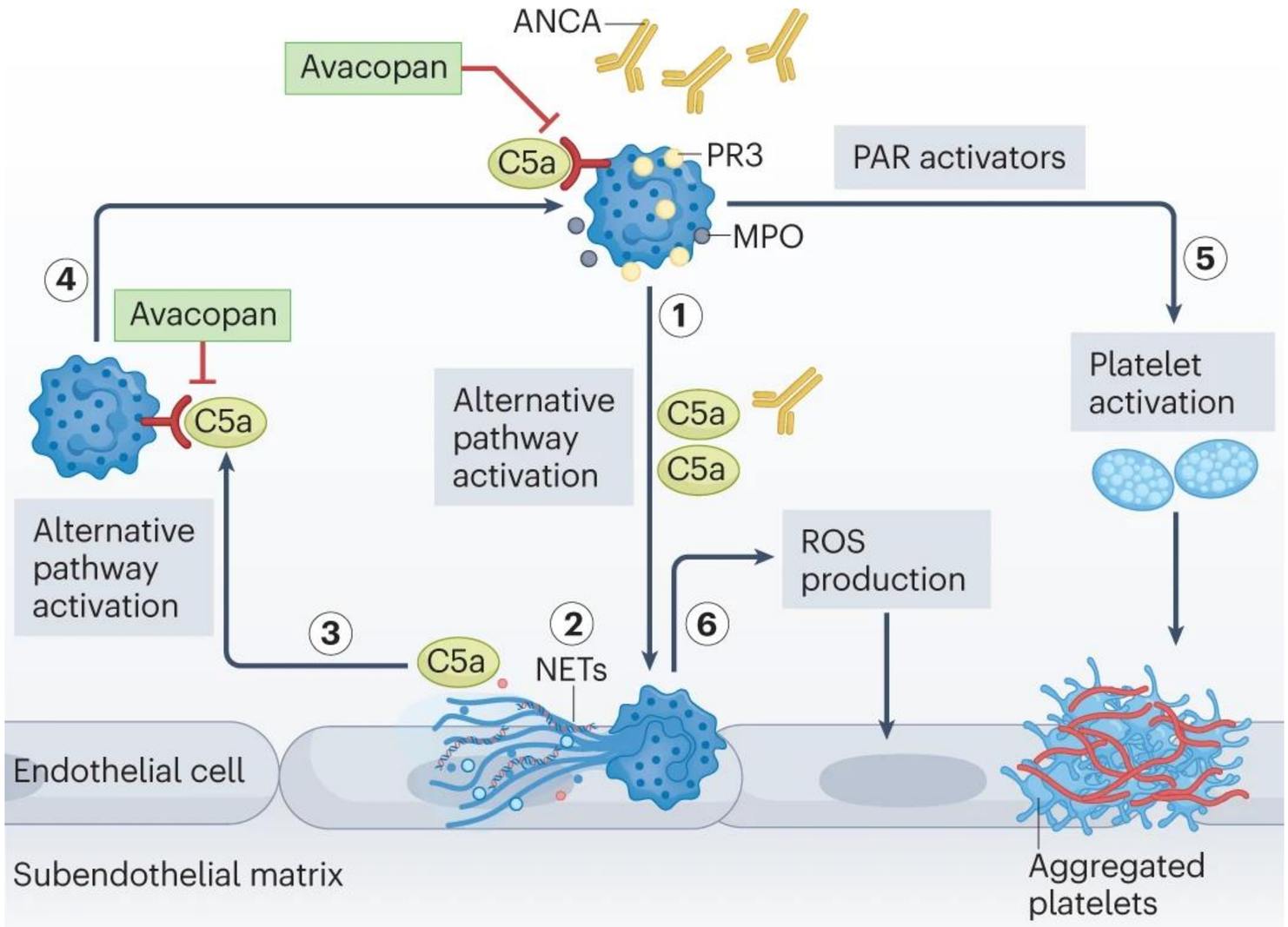


- C3 & C5 activation required for fetal loss in mouse model of APLS
  - Holers *et al.*, *J Exp Med*, 2002, PMID: 11805148
  - Girardi *et al.*, *J Clin Invest*, 2003, PMID: 14660741
- Complement regulatory gene mutations found in pts with APLS (PROMISSE)
  - Salmon *et al.*, *PLoS Med*, 2011, PMID: 21445332
- Hypocomplementemia and complement activation (Bb, sC5b-9) found in active pts with APLS
  - Ramos-Casals *et al.*, *Lupus*, 2010, PMID: 15540510
  - Kim *et al.*, *Ann Rheum Dis*, 2018, PMID: 29371202
- Anti-C5 mAb stabilized disease in 4/5 reports
  - Tinti *et al.*, *Clin Exp Med*, 2019, PMID: 31214910

Java *et al.*, *JCI Insight,* 2020, PMID: 32554923

ANCA-associated vasculitis (AAV)

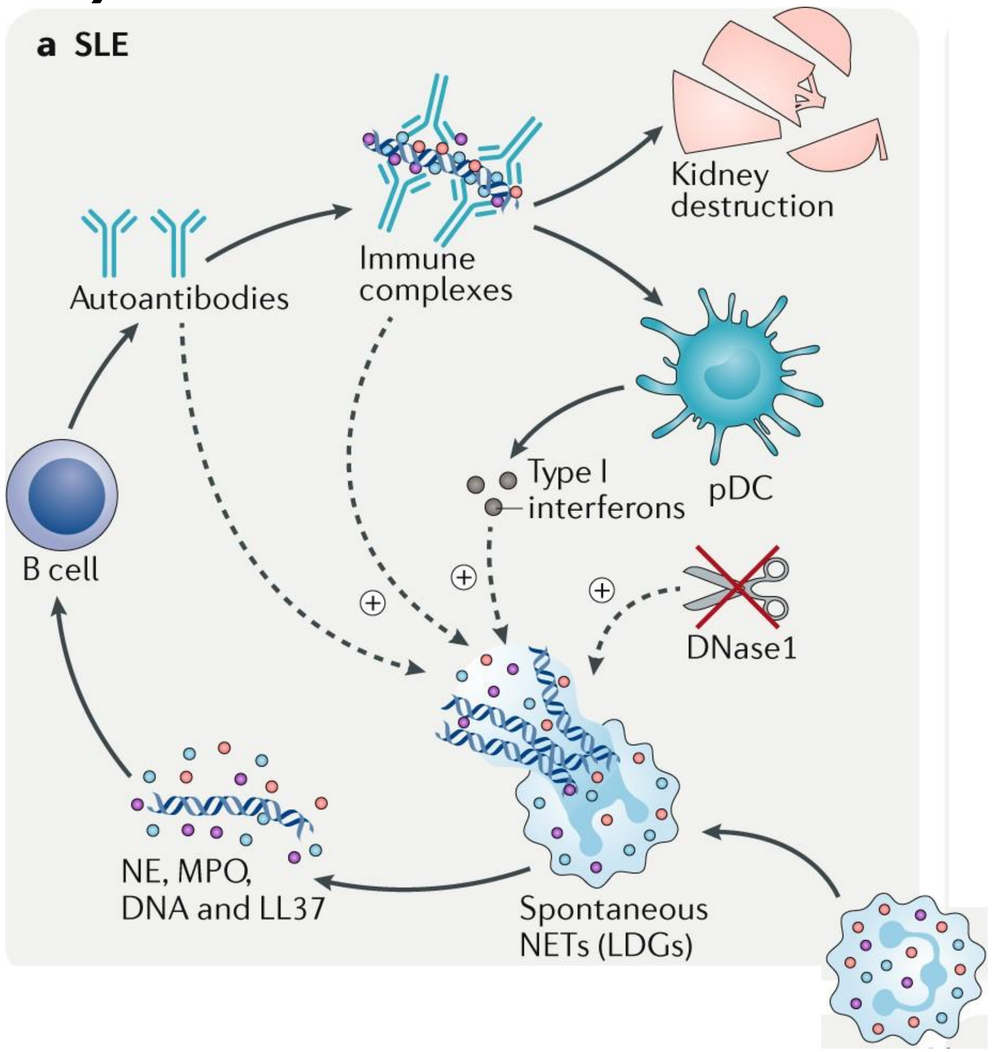
Minimally, unregulated generation of C5a important

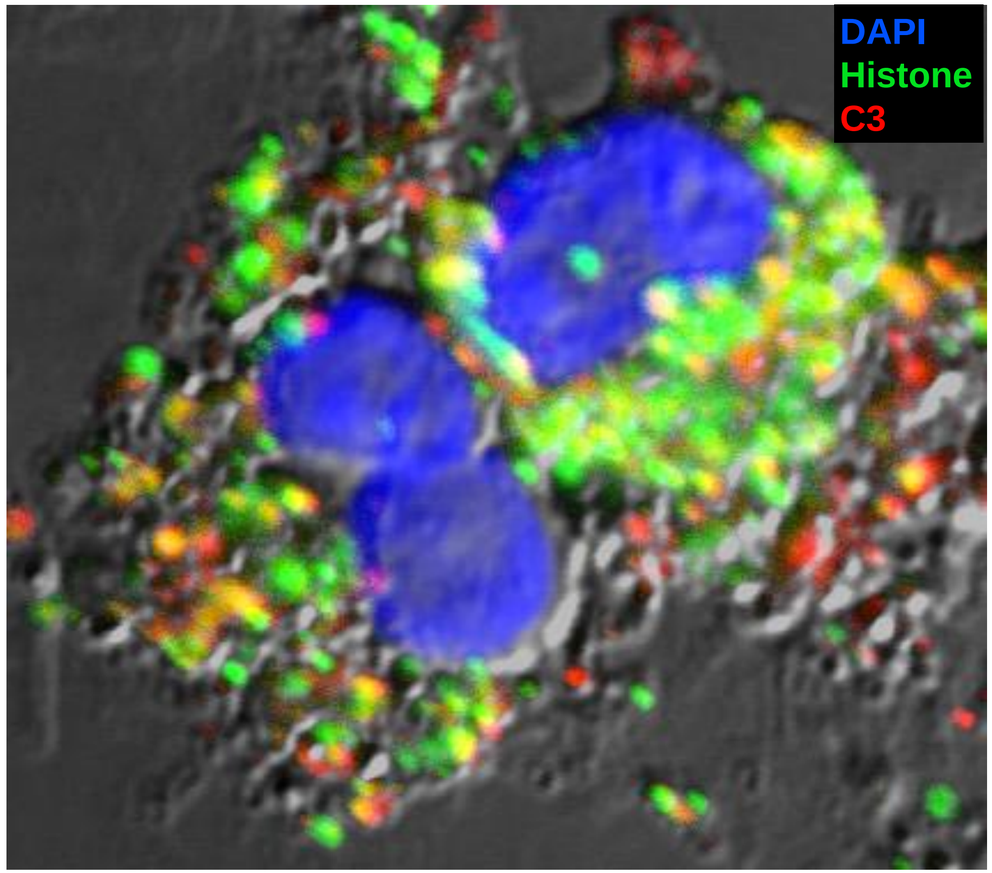


Holers, *Nat Rev Rheumatol,* 2023, PMID: 37337038

Neutrophils & C3: trigger for alternative pathway?

NETosis a prominent feature of several autoimmune diseases (APLS, SLE, AAV)



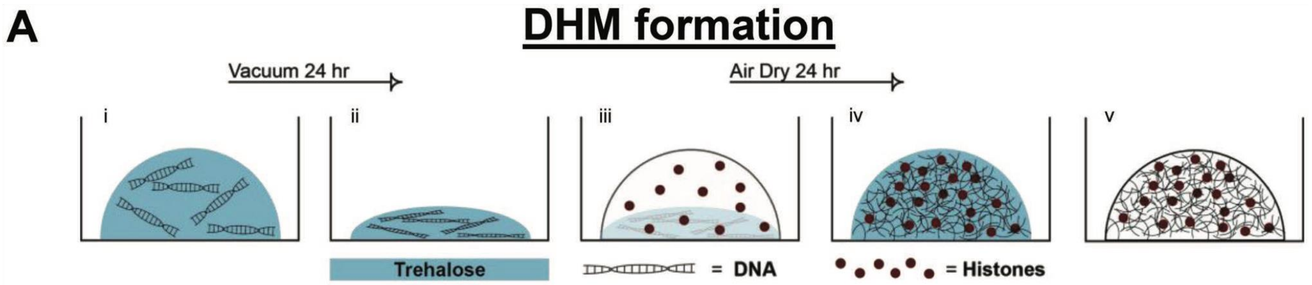


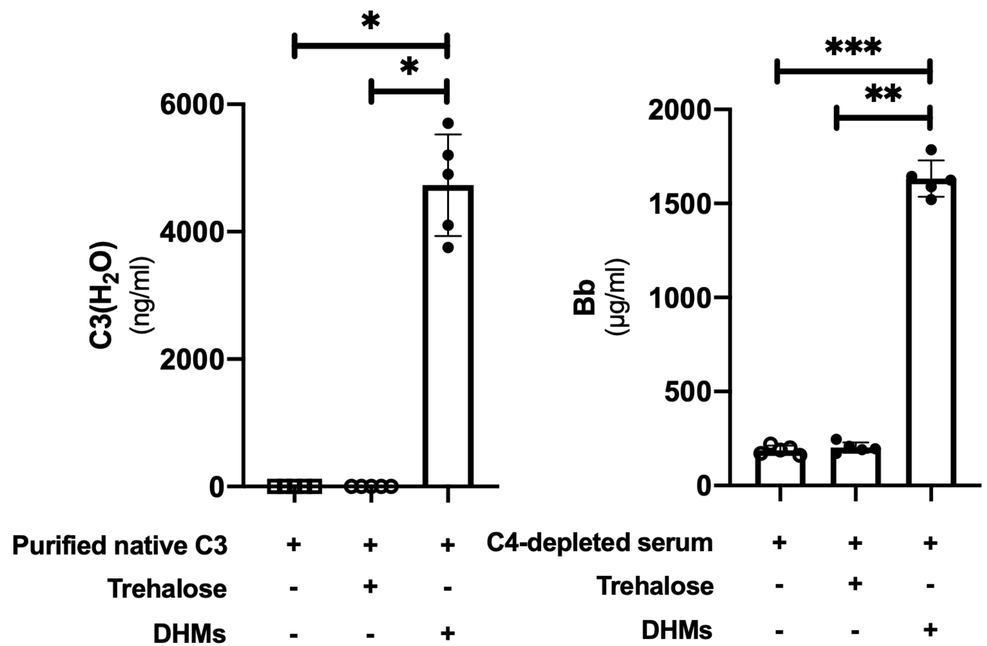
Can NETs promote the formation of C3(H_2O)?

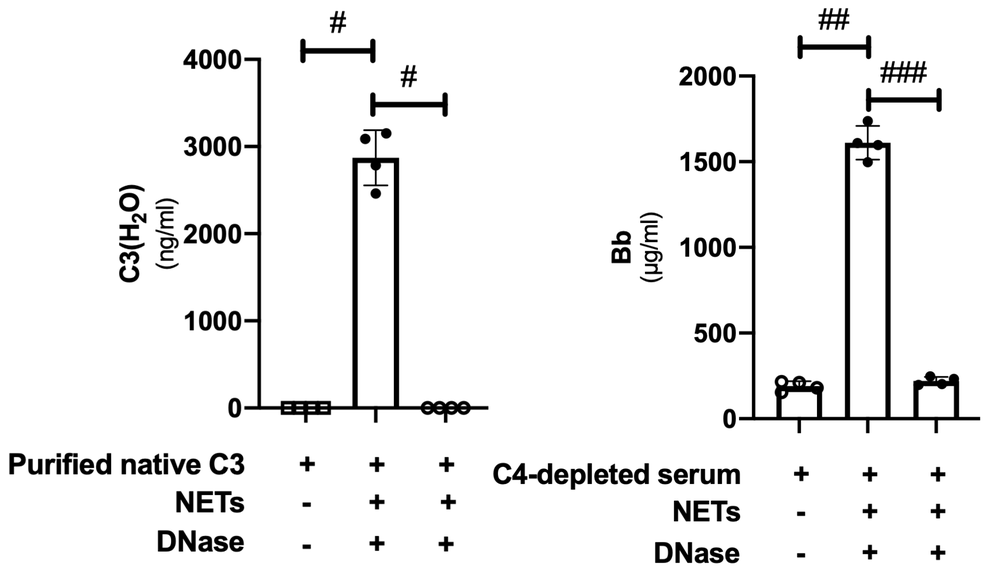
Apel et al., *Nat Rev Rheumatol*, 2018, PMID: 29930301

Neutrophils & C3: trigger for alternative pathway?

NETs sufficient to drive C3(H_2O) formation, AP activation







Weerappuli et al., *Adv Healthc Mater*, 2019, PMID: 31614077

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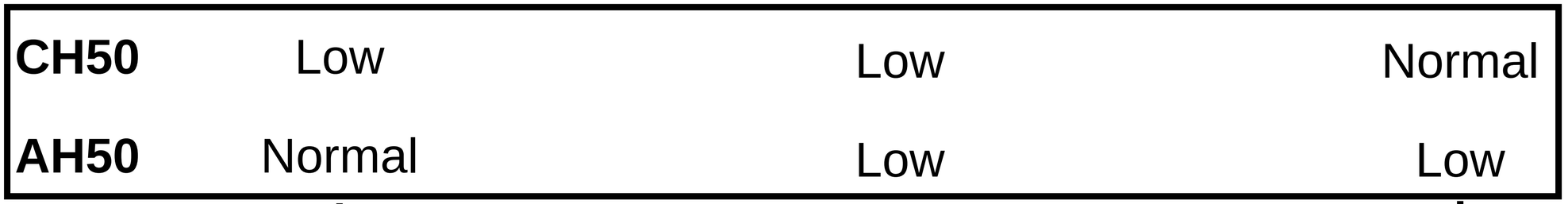
Screening for complement pathway *function*

Classical: CH50
Alternative: AH50



Test classical pathway
C1q, r, s
C4
C2

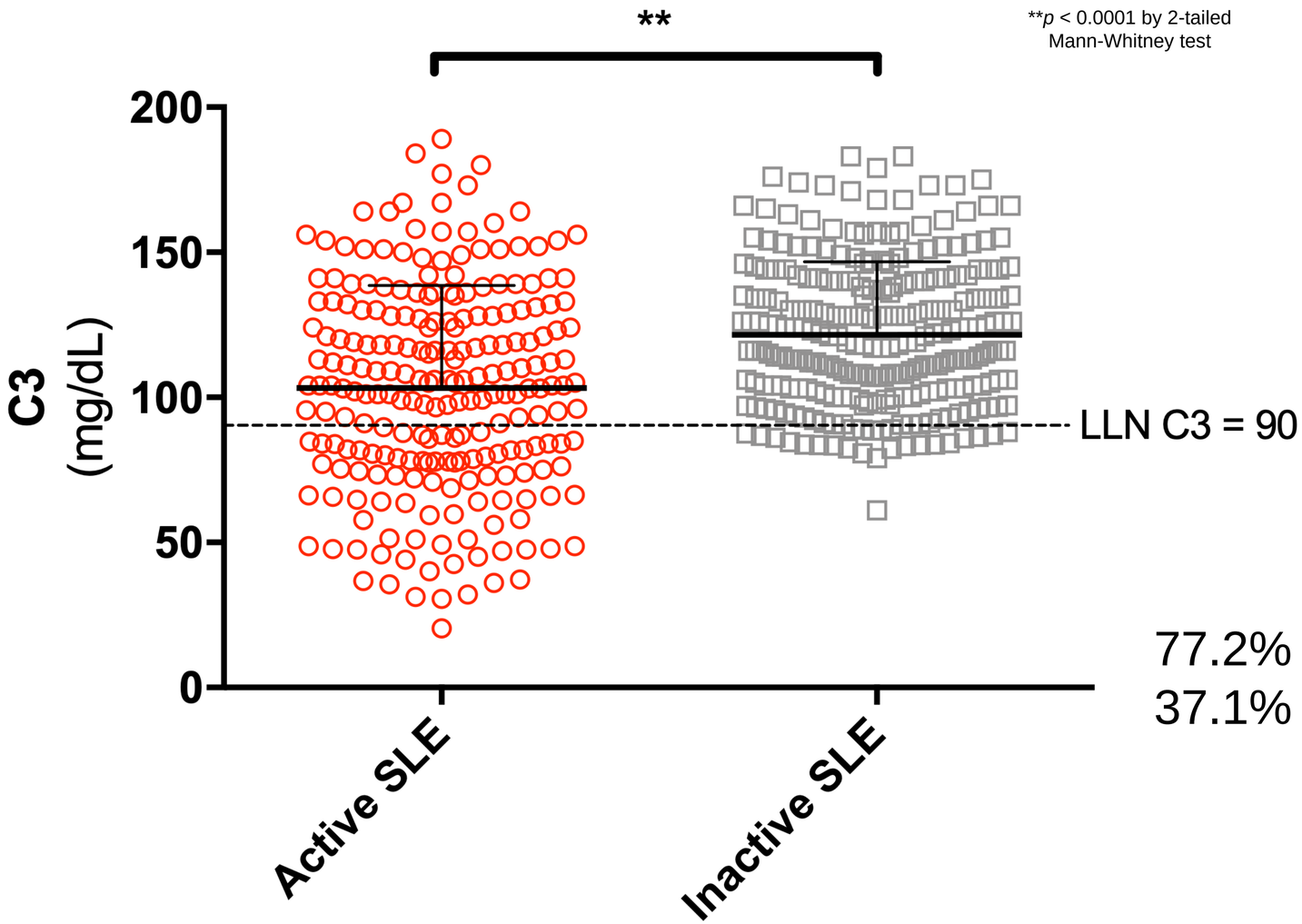
Test terminal pathway
C3
C5
C6
C7
C8
C9

Test alternative pathway
Factor B
Factor D

Fraser-Abel *et al*., *Adv Clin Chem,* 2016, PMID: 27717414

Testing for complement pathway *activation*

C3 & C4 as surrogates for SLE disease activity have substantial limitations

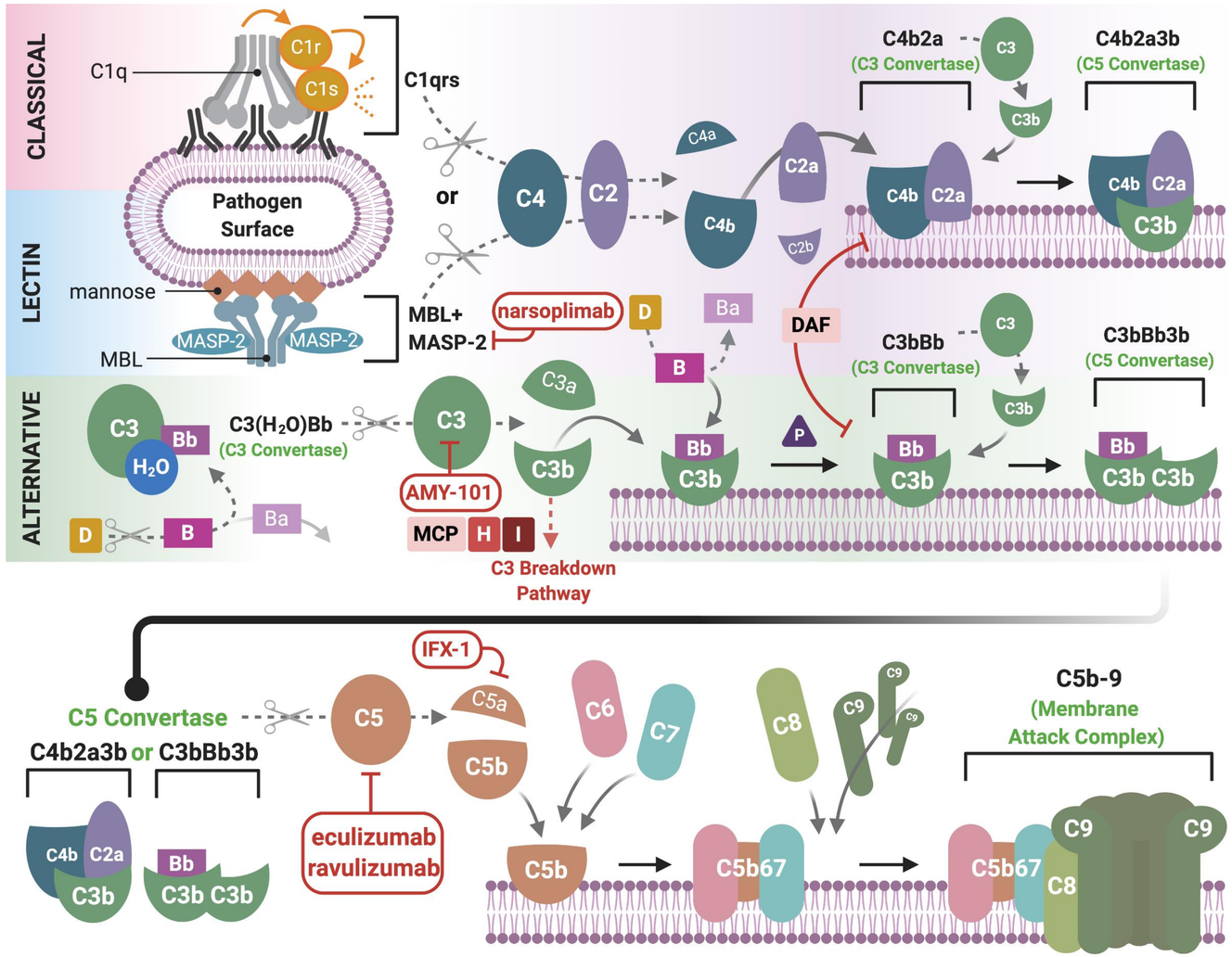


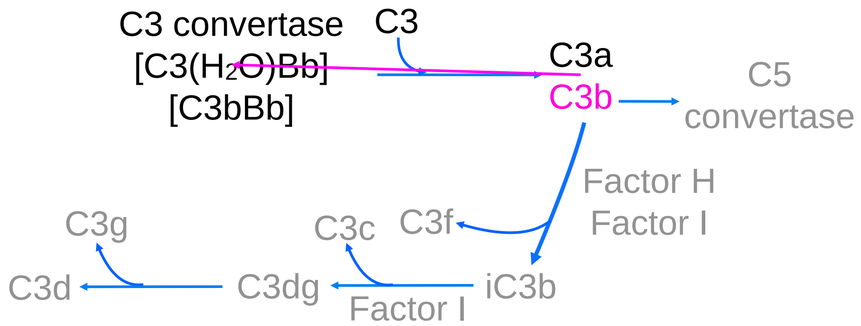
77.2% with low C3 have active disease
37.1% with active disease have low C3

Kim *et al*., *Arthritis Rheumatol,* 2019, PMID: 30294950

Testing for complement pathway *activation*

Complement activation products (CAPs) provide much higher resolution for assessing which pathway is activated





C3 breakdown pathway

Java *et al*., *JCI Insight,* 2020, PMID: 32554923

Testing for complement pathway *activation*

Cell-bound C4d may be useful for SLE diagnosis

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Measurement of Cell-Bound Complement Activation Products Enhances Diagnostic Performance in Systemic Lupus Erythematosus

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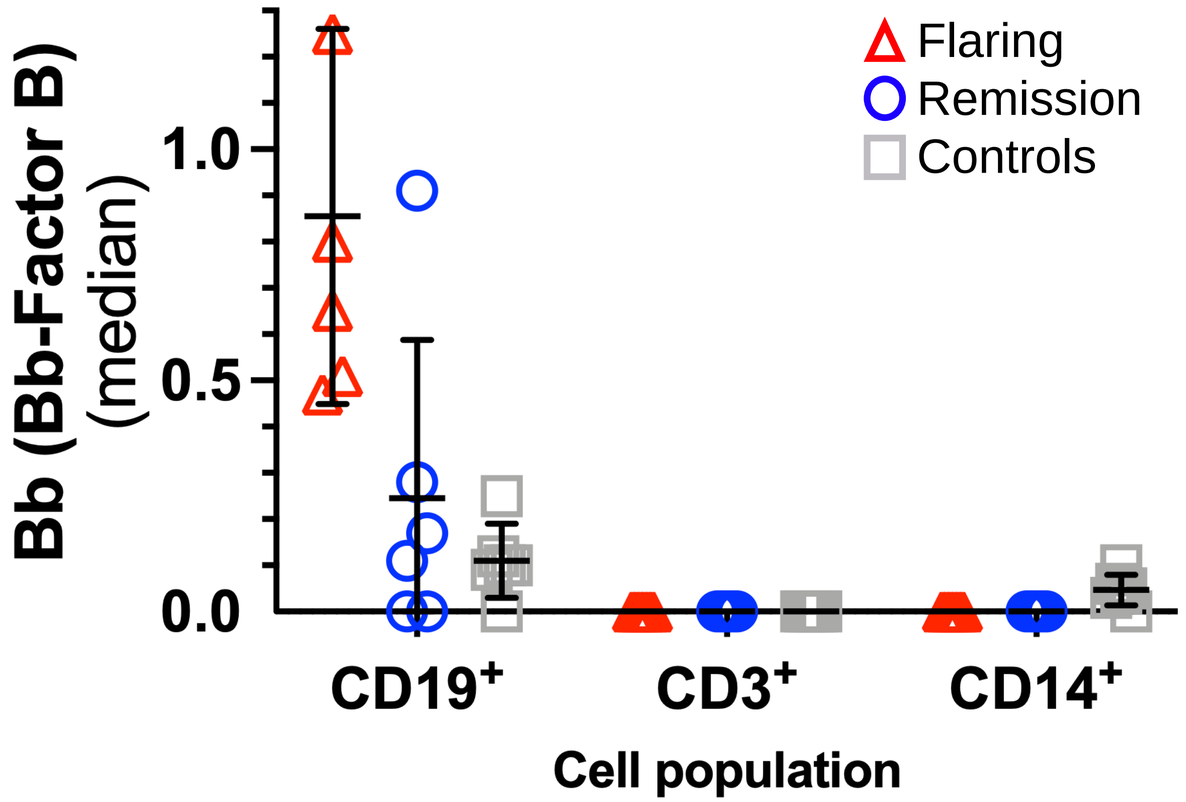
	ANA ≥20 units/ml	ANA ≥20 units/ml + logEC4d net MFI	ANA ≥20 units/ml + logEC4d net MFI + logBC4d net MFI
Sensitivity for SLE	84.5 (125/148)	65.5 (97/148)	68.2 (101/148)
Specificity against other rheumatic diseases	60.8 (104/171)	80.1 (137/171)	86.0 (147/171)
Specificity against healthy controls	90.7 (185/204)	97.5 (199/204)	99.0 (202/204)
ROC AUC, mean ± SEM	0.808 ± 0.0185	0.887 ± 0.0165	0.903 ± 0.0159

Presence of CAPs may associate with pathogenic cells in SLE

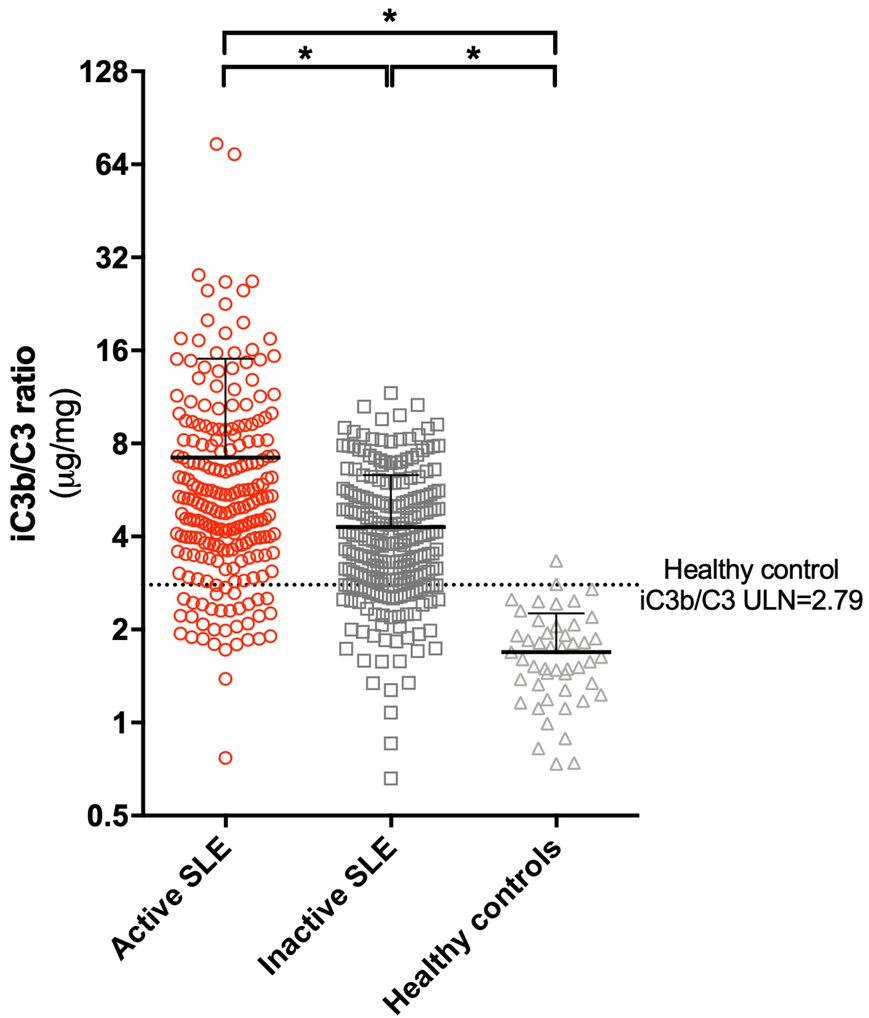
Bb-positive SLE B cells possess pathogenic inflammatory signatures

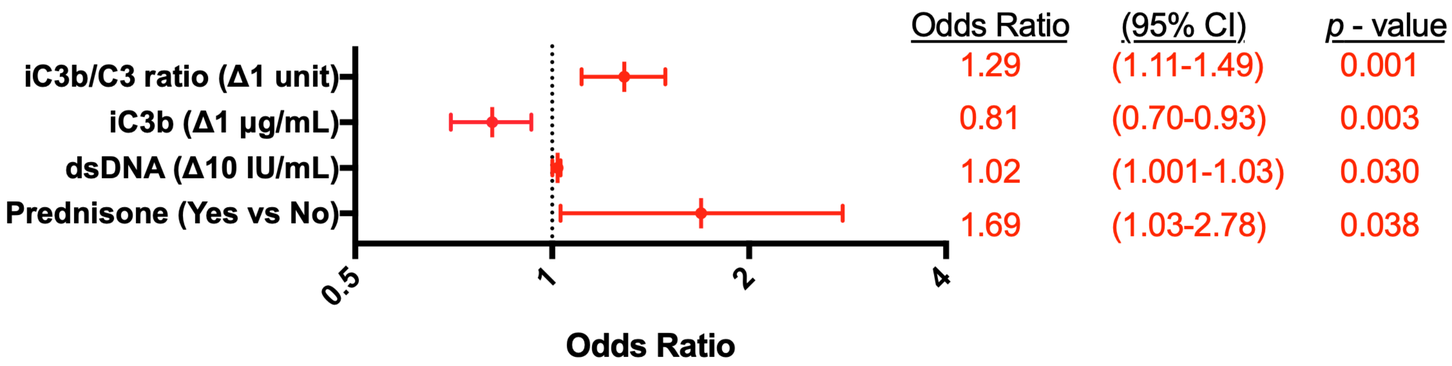


Pathway	Adjusted p-value
TNF-alpha signaling pathway	1.804E-03
Canonical NF-kB pathway	2.406E-03
T-cell receptor signaling pathway	6.253E-03
protease binding	8.229E-03
IL-18 signaling pathway	8.288E-03
RNA polymerase II transcription repressor complex	1.314E-02
B cell receptor signaling pathway	1.716E-02
STING pathway in Kawasaki-like disease and COVID-19	1.794E-02
hsa-miR-337-3p	1.811E-02
hsa-miR-202-5p	2.244E-02
C-C chemokine receptor activity	2.564E-02
positive regulation of miRNA transcription	2.641E-02
C-C chemokine binding	2.797E-02
aspartic-type endopeptidase inhibitor activity	2.873E-02
G protein-coupled chemoattractant receptor activity	3.292E-02
chemokine receptor activity	3.292E-02
Factor: NFKB2; motif: NGGGGAWTCCCCN	3.932E-02
Factor: NFKB2; motif: NGGGGAWTCCCCN; match class: 1	3.932E-02
positive regulation of miRNA metabolic process	4.173E-02

Testing for complement pathway *activation*

Soluble iC3b/C3 ratios correlate with SLE disease activity





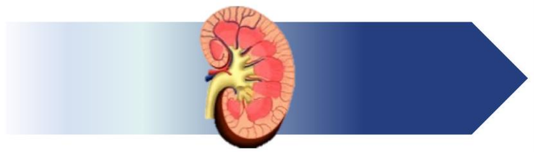
	Odds Ratio	(95% CI)	*p* - value
iC3b/C3 ratio (Δ1 unit)	1.29	(1.11-1.49)	0.001
iC3b (Δ1 µg/mL)	0.81	(0.70-0.93)	0.003
dsDNA (Δ10 IU/mL)	1.02	(1.001-1.03)	0.030
Prednisone (Yes vs No)	1.69	(1.03-2.78)	0.038

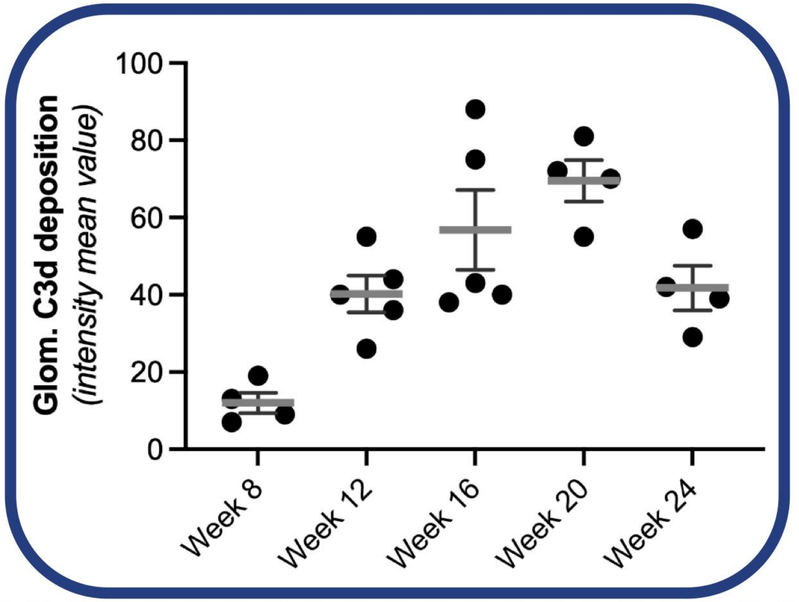
Kim *et al*., *Arthritis Rheumatol,* 2019, PMID: 30294950

Testing for complement pathway *activation*

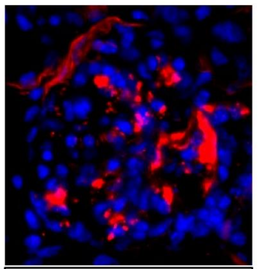
Can leverage deposition in tissues to *image* complement activation

Lupus-prone
MRL/lpr mice

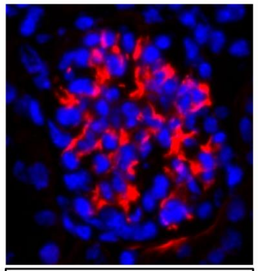




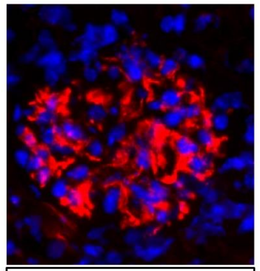
Representative images:



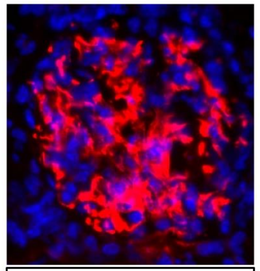
Week 8



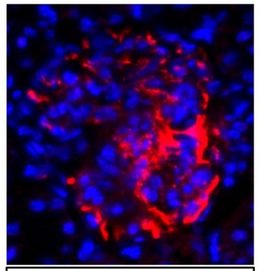
Week 12



Week 16



Week 20

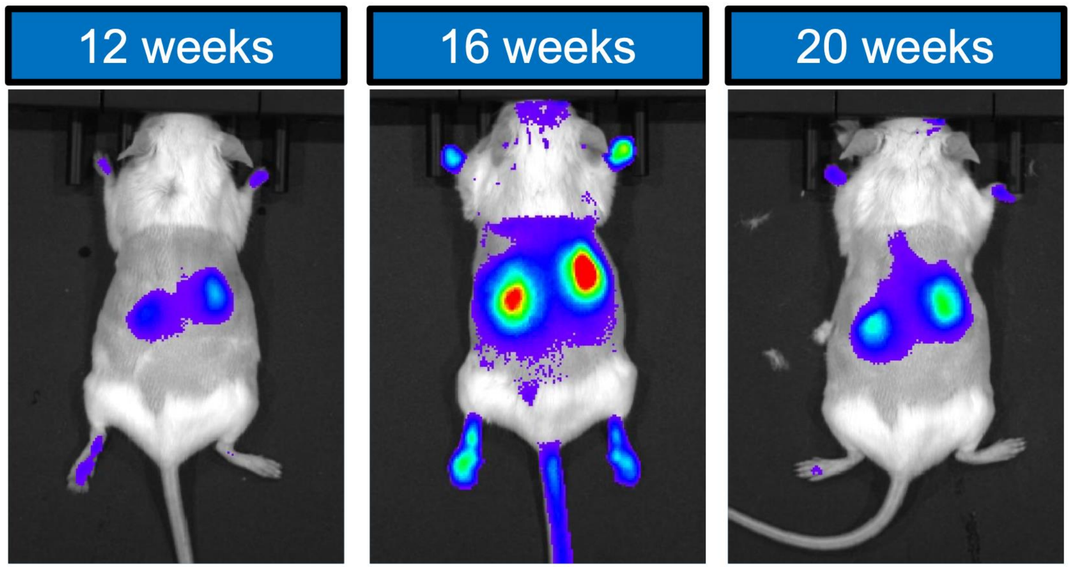


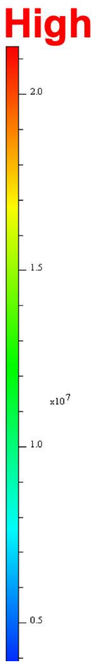
Week 24

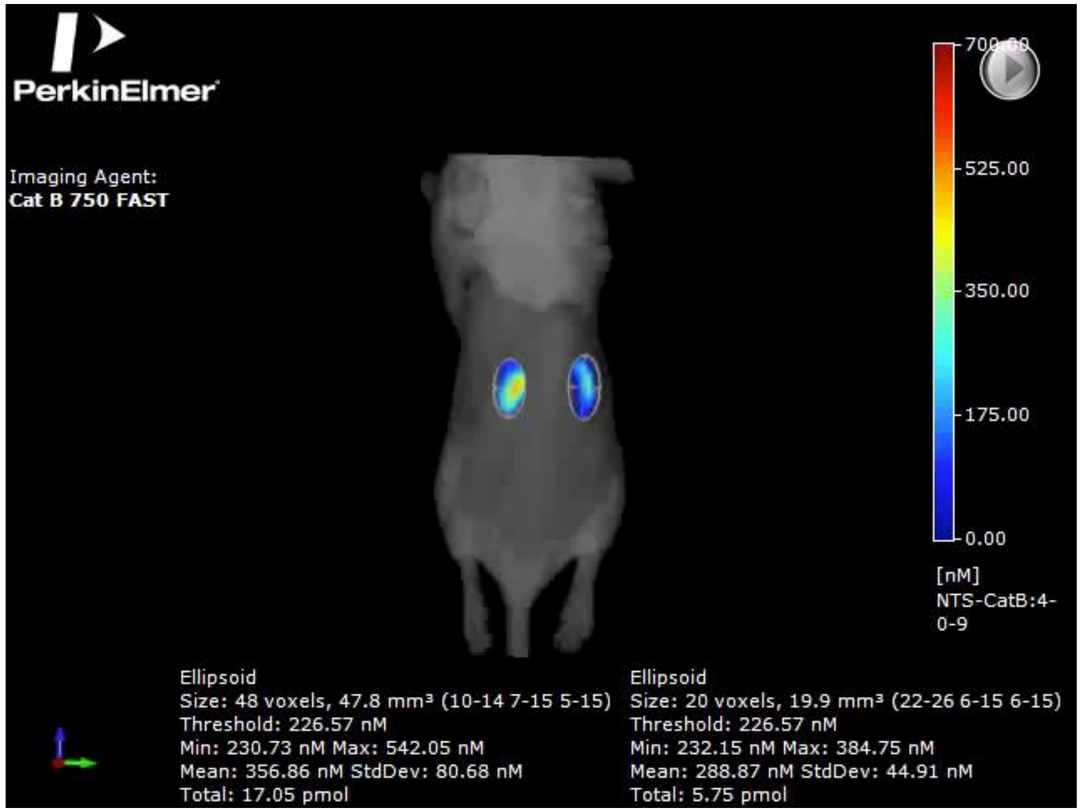
Renner *et al*., *J Am Soc Nephrol,* 2023, PMID: 36995143
Additional unpublished data courtesy of Josh Thurman

Testing for complement pathway *activation*

Can leverage deposition in tissues to *image* complement activation







Courtesy of Josh Thurman
Matthew Cheung

Conclusions

- Complement therapeutics pipeline is growing at a rapid pace
- Classical and alternative pathway activation contributes to the pathophysiology of several diseases
  - Classical pathway activation by autoantibodies: Neuromyelitis optica (NMO)
  - Alternative pathway activation by genetic loss of function of regulators: paroxysmal nocturnal hemoglobinuria (PNH) (with a cameo from cold agglutinin disease), thrombotic microangiopathy (TMA)
  - Alternative pathway activation by neutrophils: antiphospholipid syndrome (APLS), systemic lupus erythematosus? (SLE), ANCA-associated vasculitis (AAV)
- Advances in complement diagnostics are slowly moving, but offer high potential

- Topic for future talks: Intracellular complement activation (complosome)

nature reviews rheumatology

https://doi.org/10.1038/s41584-023-00981-x

Review article

Check for updates

Complement therapeutics are coming of age in rheumatology

V. Michael Holers