

# Complement system: from pathogenesis to clinical application

Ioannis Mitroulis


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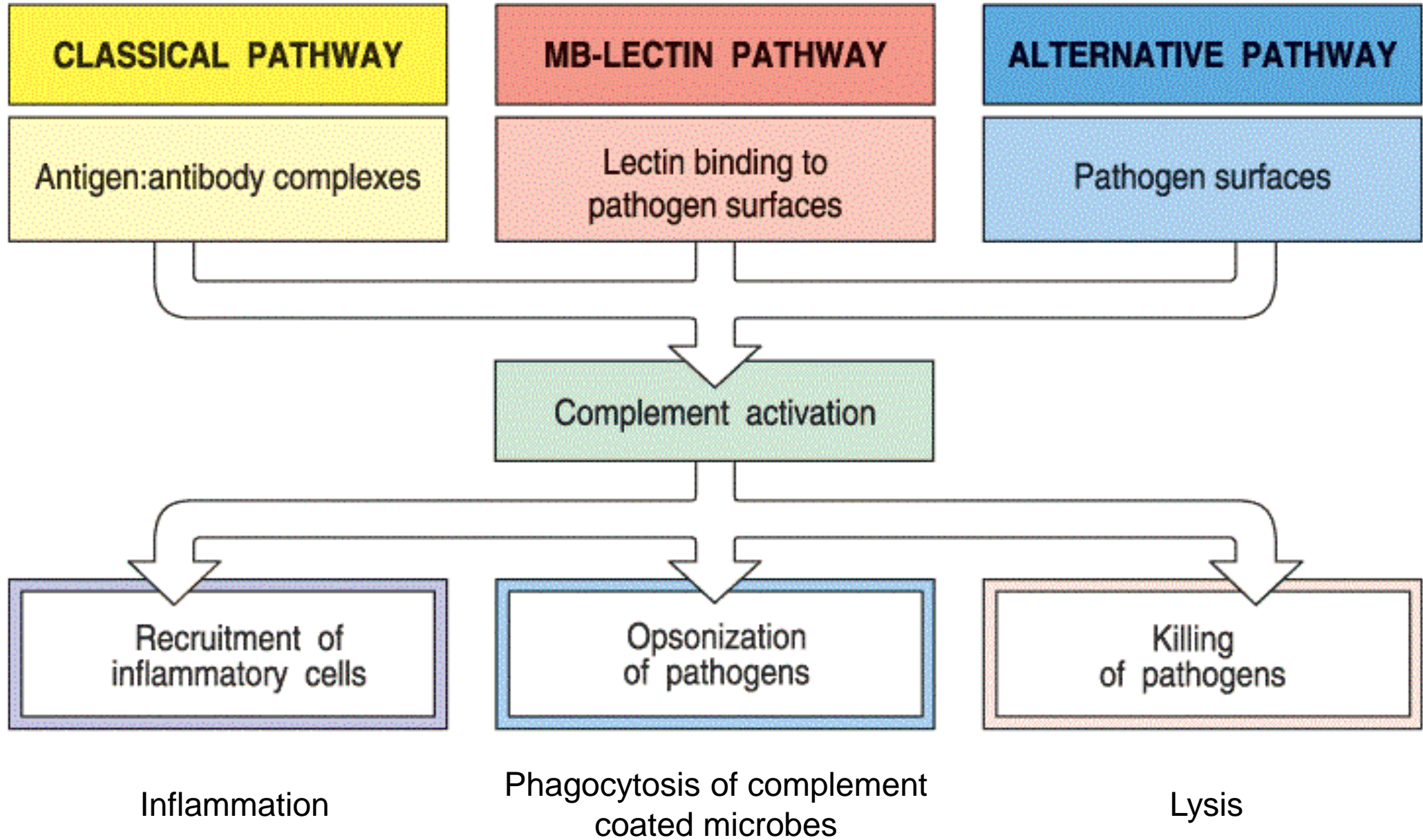
Associate Professor of Internal Medicine

Democritus University of Thrace

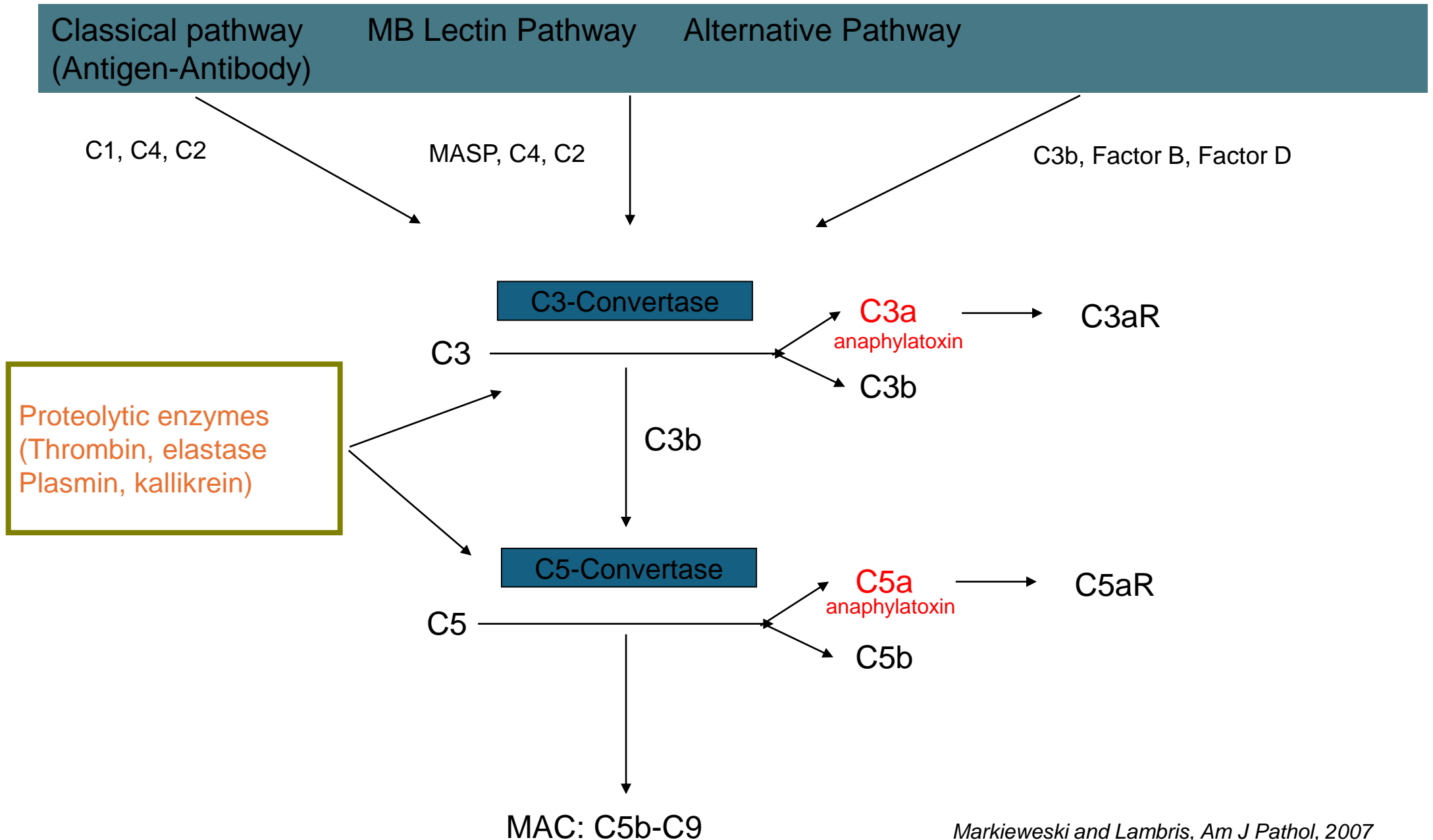


# The complement system

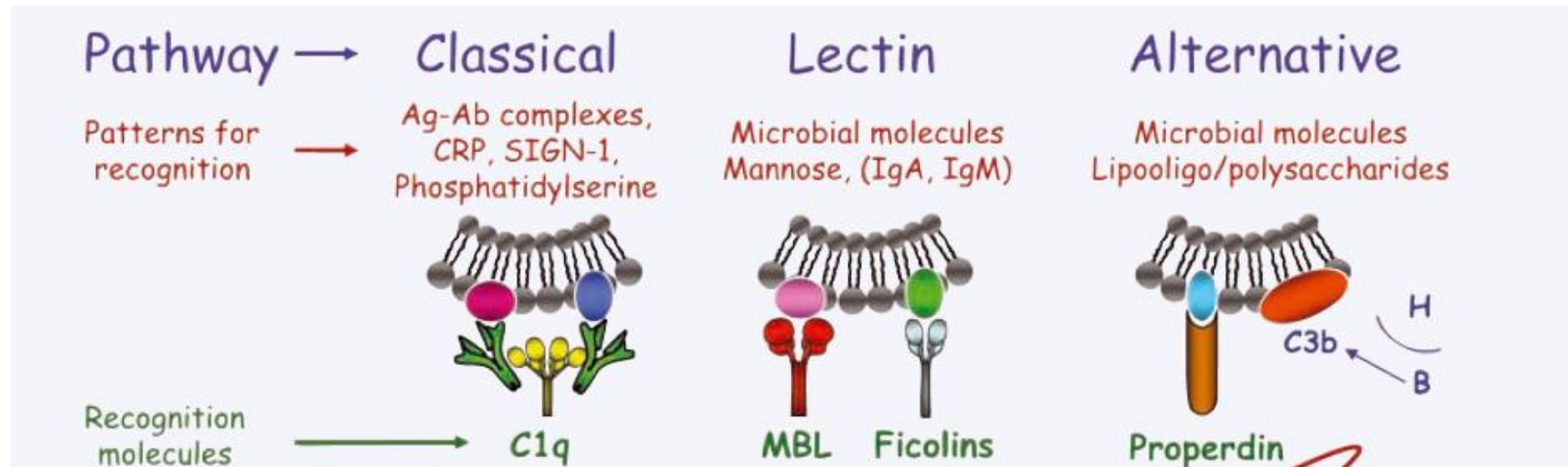
- 
- 30 enzymes circulating in serum in an inactive state
  - Indicated with letter (C) and number
  - Activation triggered via different pathways after pathogen recognition
  - Sequential activation of components by proteolysis



# The complement system

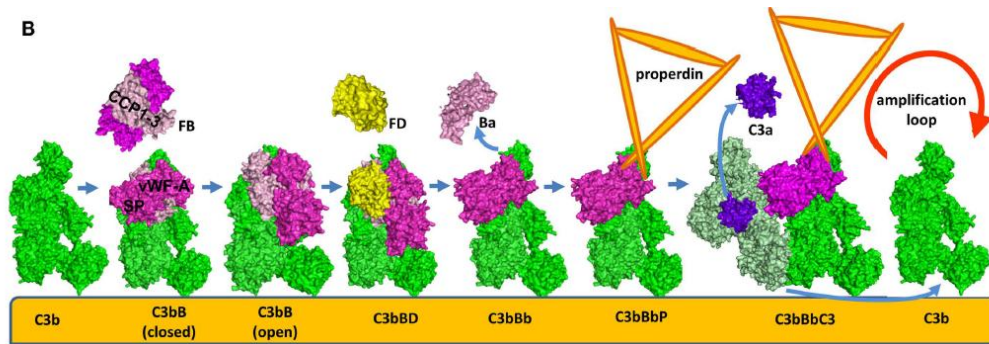


# Initial activation

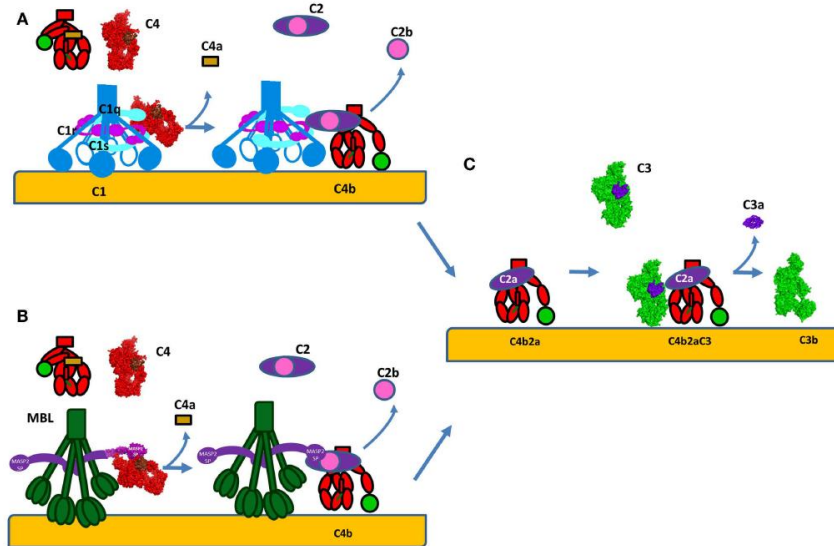


# C3 convertase

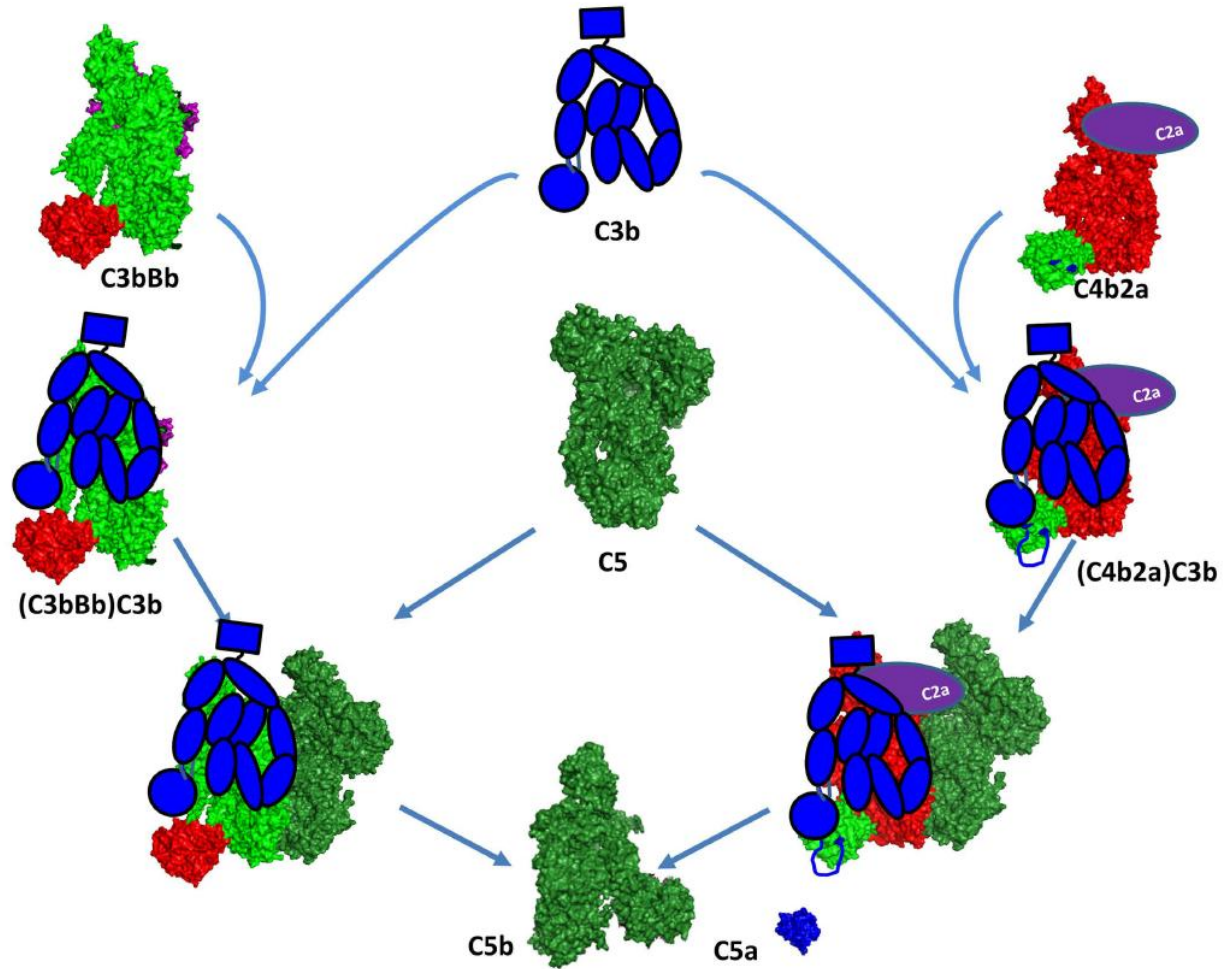
- Alternative pathway → C3(H2O)Bb



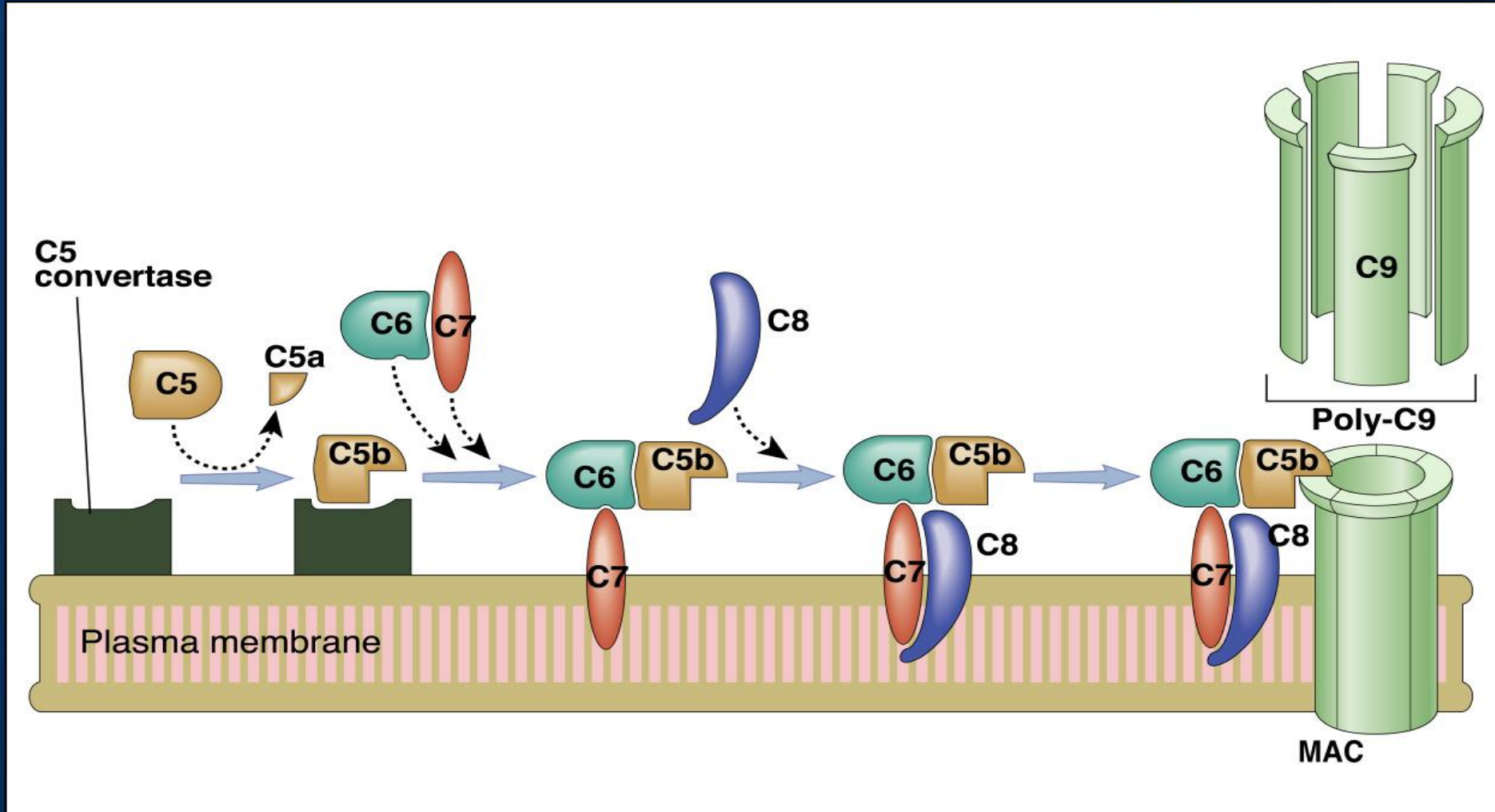
- Classical and lectin pathway → C4b2a

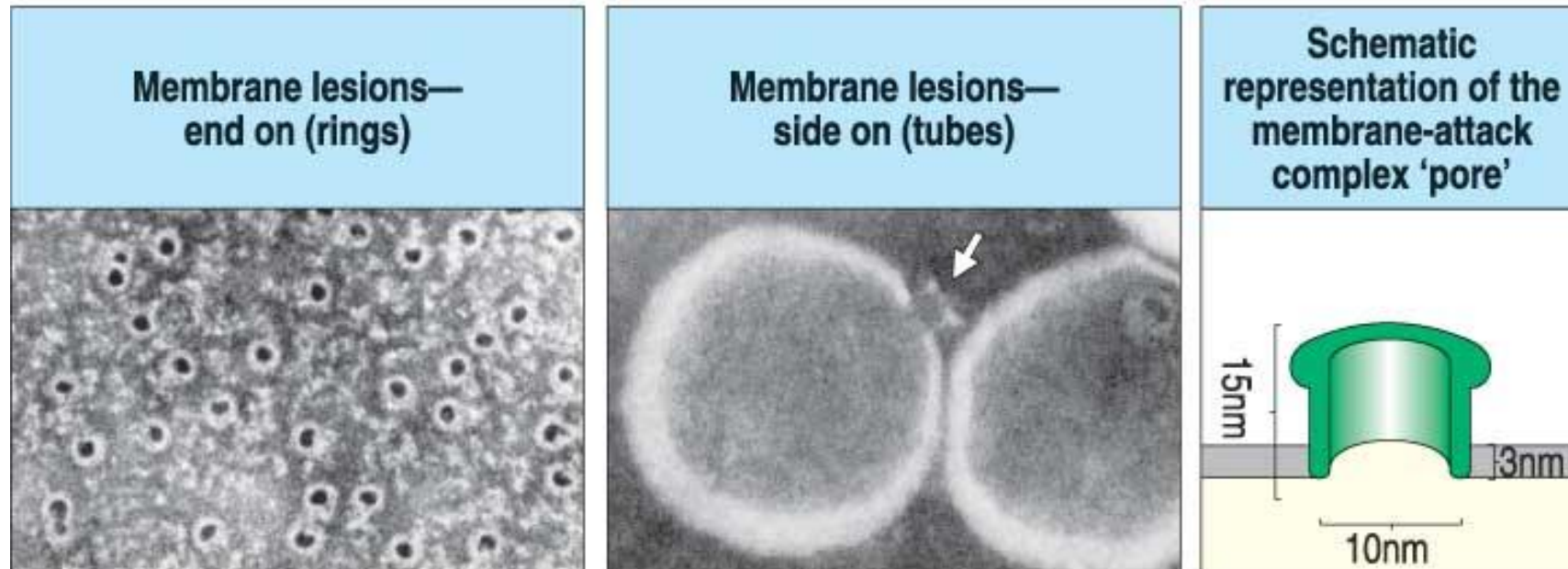
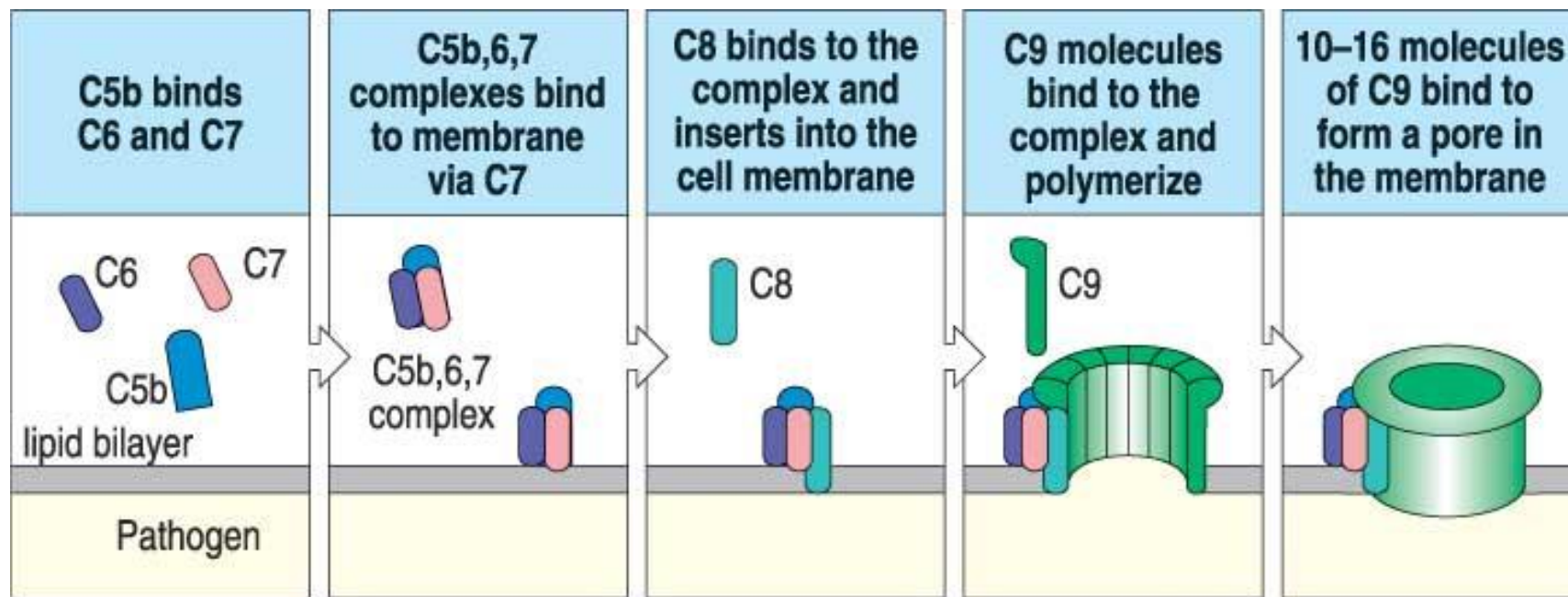


# C5 convertase



## Late steps of complement activation: formation of the membrane attack complex (MAC)

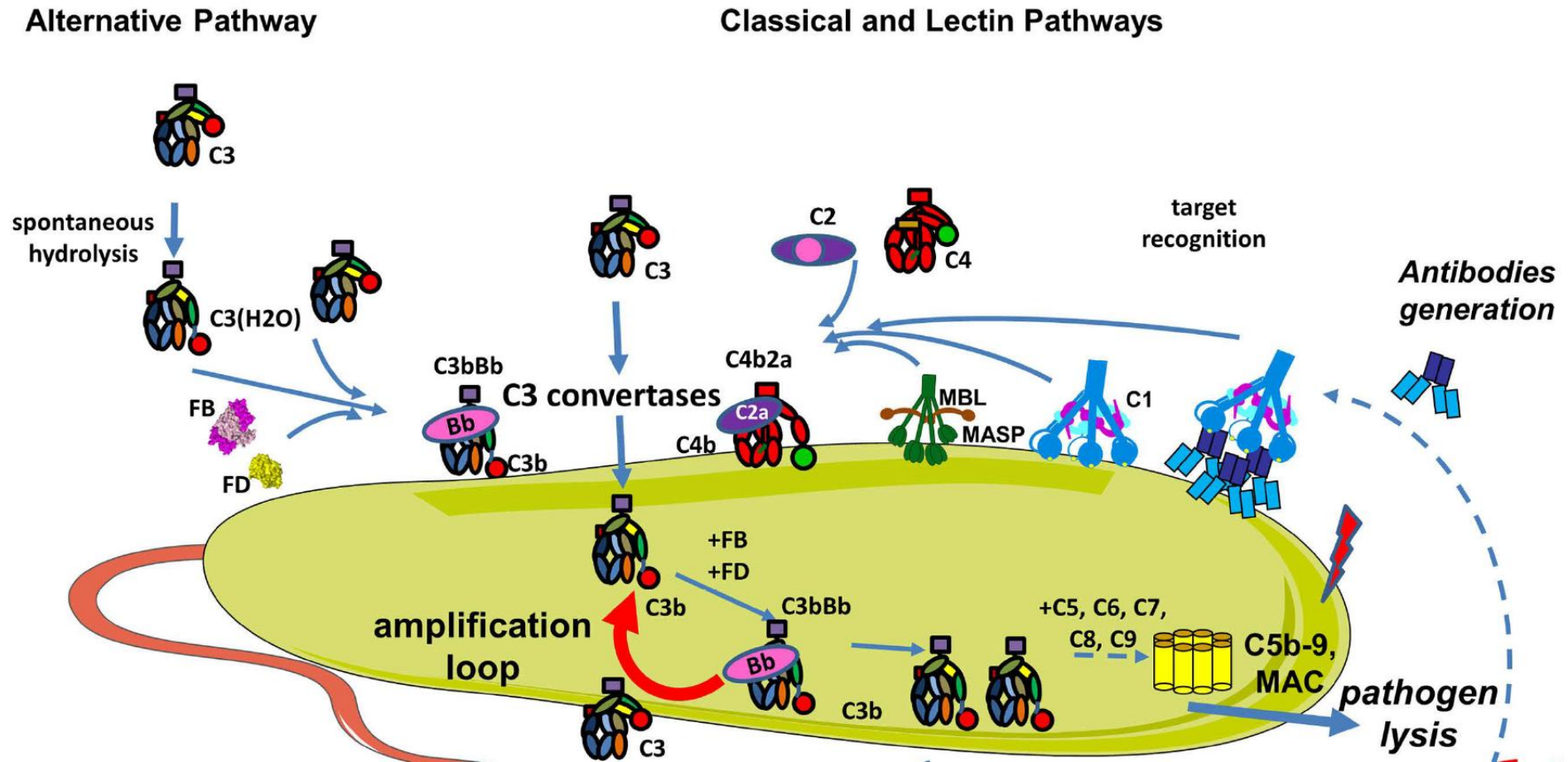




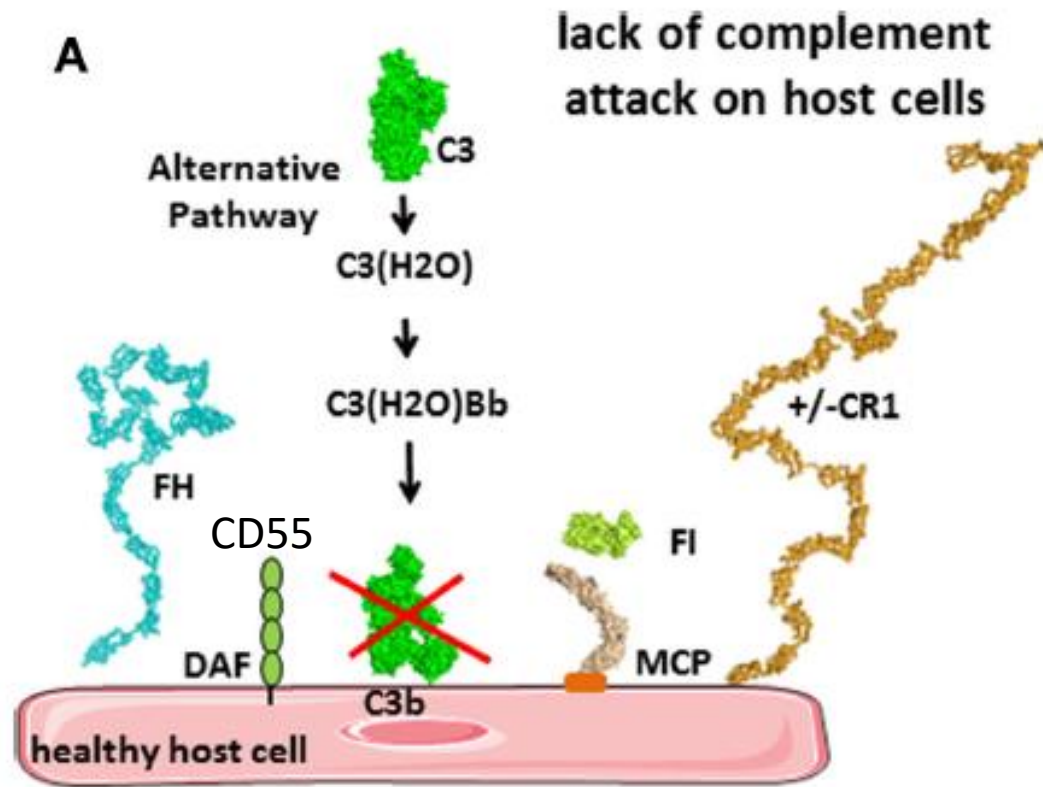
- Alternative Pathway is permanently active at low levels to survey for presence of pathogens.
- Healthy host cells are protected against complement.
- The three pathways are activated on the surface of apoptotic cells to ensure homeostasis.
- Complement is only fully activated during infection.

# Pathogen recognition

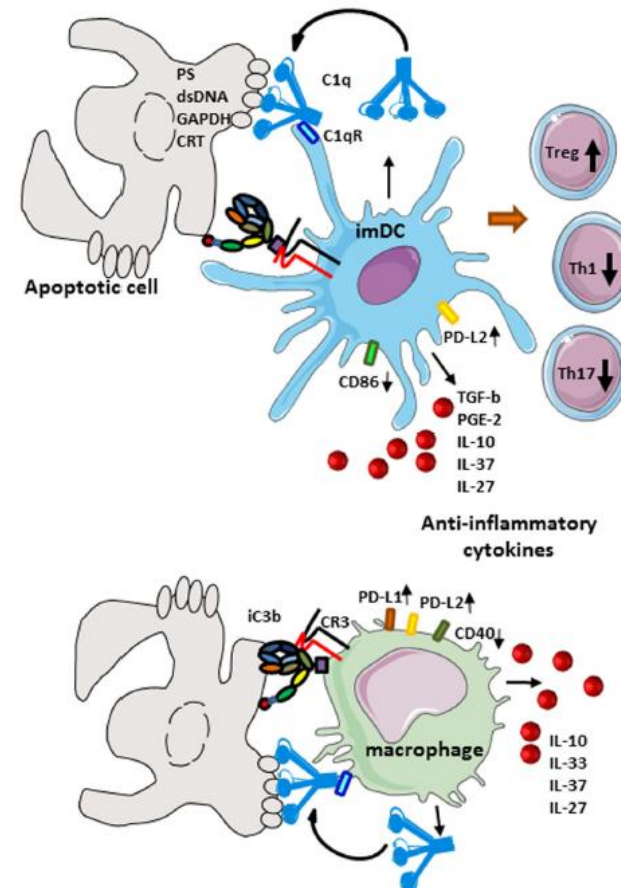
Merle et al., Frontiers Immunology 2015



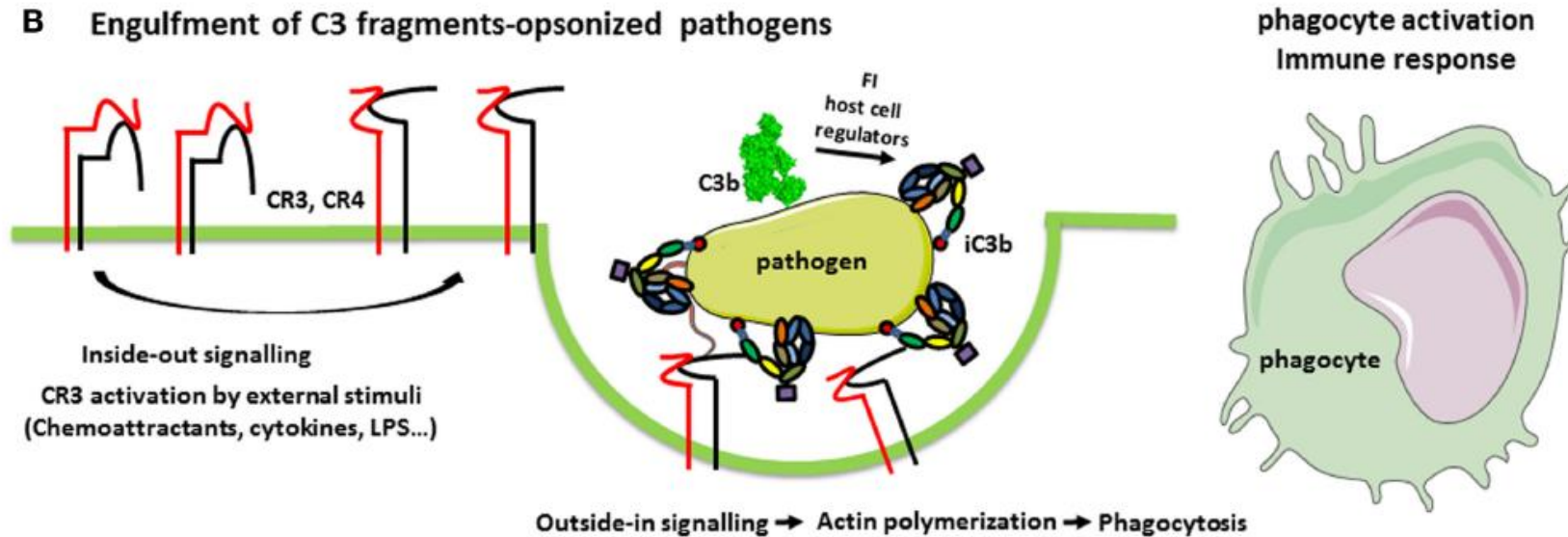
# Complement activation and inhibition in normal vs apoptotic cells



## Immunologically silent clearance of apoptotic cells



# Complement dependent phagocytosis



**a**

**Lectin pathway**

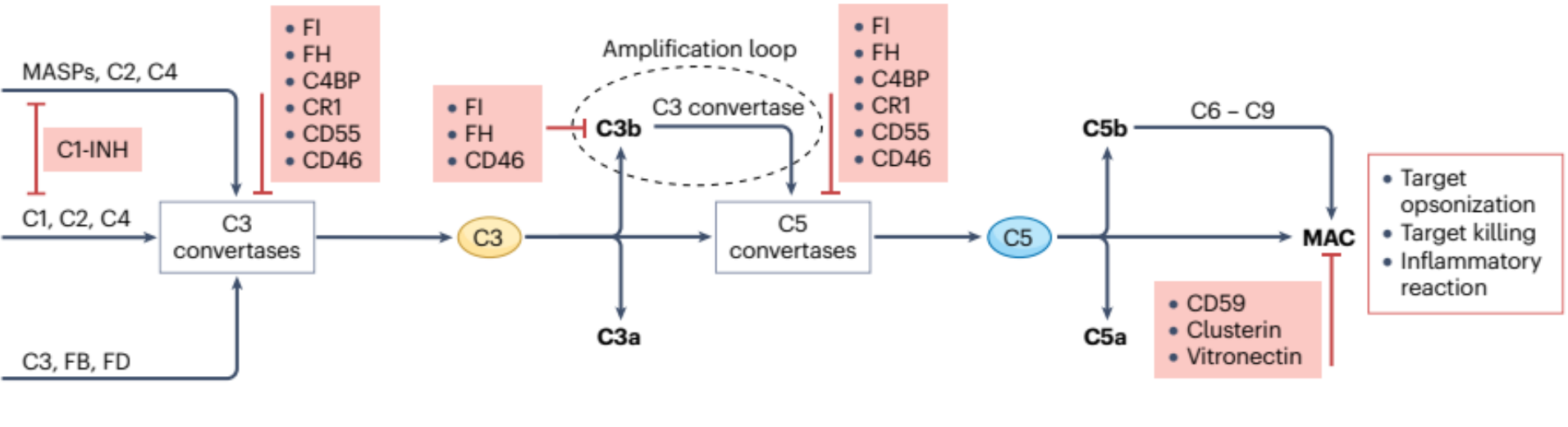
- MBL
- Ficolins
- Carbohydrates

**Classical pathway**

- Antibody or antigen
- C1q

**Alternative pathway**

- Pathogens
- Altered self
- 'Tick over'



# To sum up

West and Kemper, Nat Rev Nephrol. 2023

# Complement in disease pathogenesis

### Infection and infection-associated pathology

- Respiratory tract infections (C3, C3aR, CD46)
- Immunodeficiency (C3)
- SARS-CoV-2-induced lung pathology (C3)



### Cardiovascular disease

- Atherosclerosis (C5, C5aR1)
- Plaque destabilization (C5, C5aR1)



### Cancer

- Colon cancer (C1q, C1qBP)
- Bladder cancer (CD46)



### Kidney disease

- Renal endothelial dysfunction (FH)
- Injury-induced nephropathy (C5, C5aR1)
- Fibrosis (C5, C5aR1)
- Clear-cell renal cell carcinoma (FH, C1)



### Autoimmunity – arthritic disease

- Rheumatoid arthritis (C3, CD46)
- SLE (C1q, C3, C5, CD46, FH)
- Scleroderma (C3, C5, C5aR1, CD46)



### Diabetes and metabolic syndrome

- Diabetes (C3, CD59)
- Non-alcoholic fatty liver disease (C3)



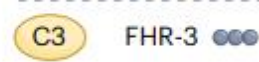
### IBD

- Crohn's disease (C3, C3aR)



### Potential complosome-driven disease

- AMD (FHR-3)
- Ageing-related pathological conditions of tissue
- COPD, asthma
- C3 glomerulopathies, lupus nephritis
- Chronic neuroinflammation (for example, AD and MS)
- Diseases driven by defects in haematopoiesis



# Complement in disease

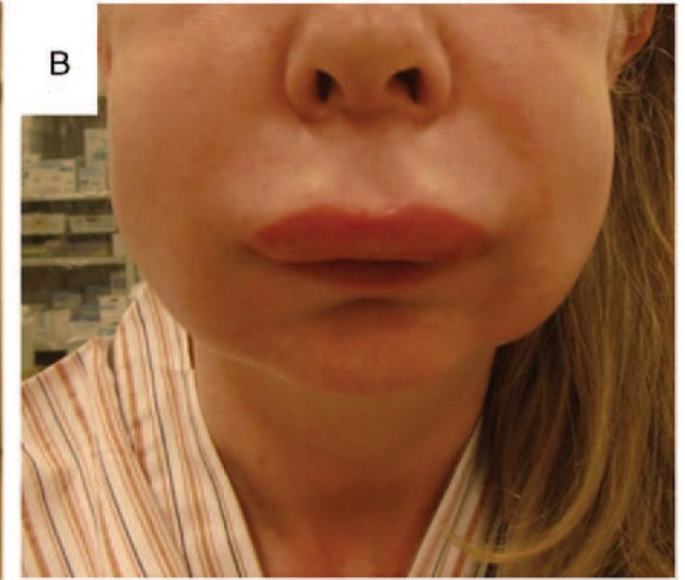
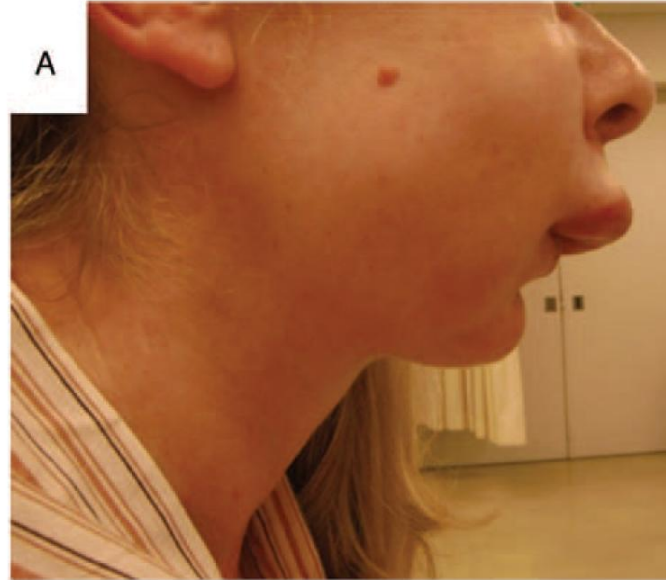
# Genetics of complement deficiencies

Table 3   Summary of complement deficiencies in humans			
Complement component involved	Frequency	Main disease association(s)	Reference(s)
C1q	50–100 reported cases	SLE; glomerulonephritis; infections	Skattum <i>et al.</i> <sup>7</sup>
C1r or C1s	10–50 reported cases	SLE; glomerulonephritis	Wu <i>et al.</i> <sup>106</sup>
C2	Estimated prevalence 1/20,000*	SLE; infections	Skattum <i>et al.</i> <sup>7</sup>
C3	20–50 reported cases	SLE; glomerulonephritis; recurrent infections	
C4	20–50 reported cases	SLE; glomerulonephritis; infections	
MBL	Estimated prevalence 1/10*	Susceptibility to infections	
Factor D	<20 reported cases	Neisserial infections	
Properdin	50–100 reported cases	Meningococcal disease	Fijen <i>et al.</i> <sup>107</sup>
C5, C6, C7 or C8	20–100 reported cases	Usually healthy; recurrent neisserial infections	Skattum <i>et al.</i> <sup>7</sup>
C9	<10 reported cases Estimated prevalence 1/1,000‡	Usually healthy	Skattum <i>et al.</i> <sup>7</sup> Witzel-Schlömp <i>et al.</i> <sup>108</sup>
C1Inh	Estimated prevalence 1/50,000§	Hereditary angioedema	Skattum <i>et al.</i> <sup>7</sup>

\*Estimated prevalence in white populations. †Rare deficiency in white populations, but common in the Japanese population (prevalence of about 0.1%).

‡Heterozygous deficiency. Abbreviations: C1Inh, plasma protease C1 inhibitor; MBL, mannose-binding lectin; SLE, systemic lupus erythematosus.

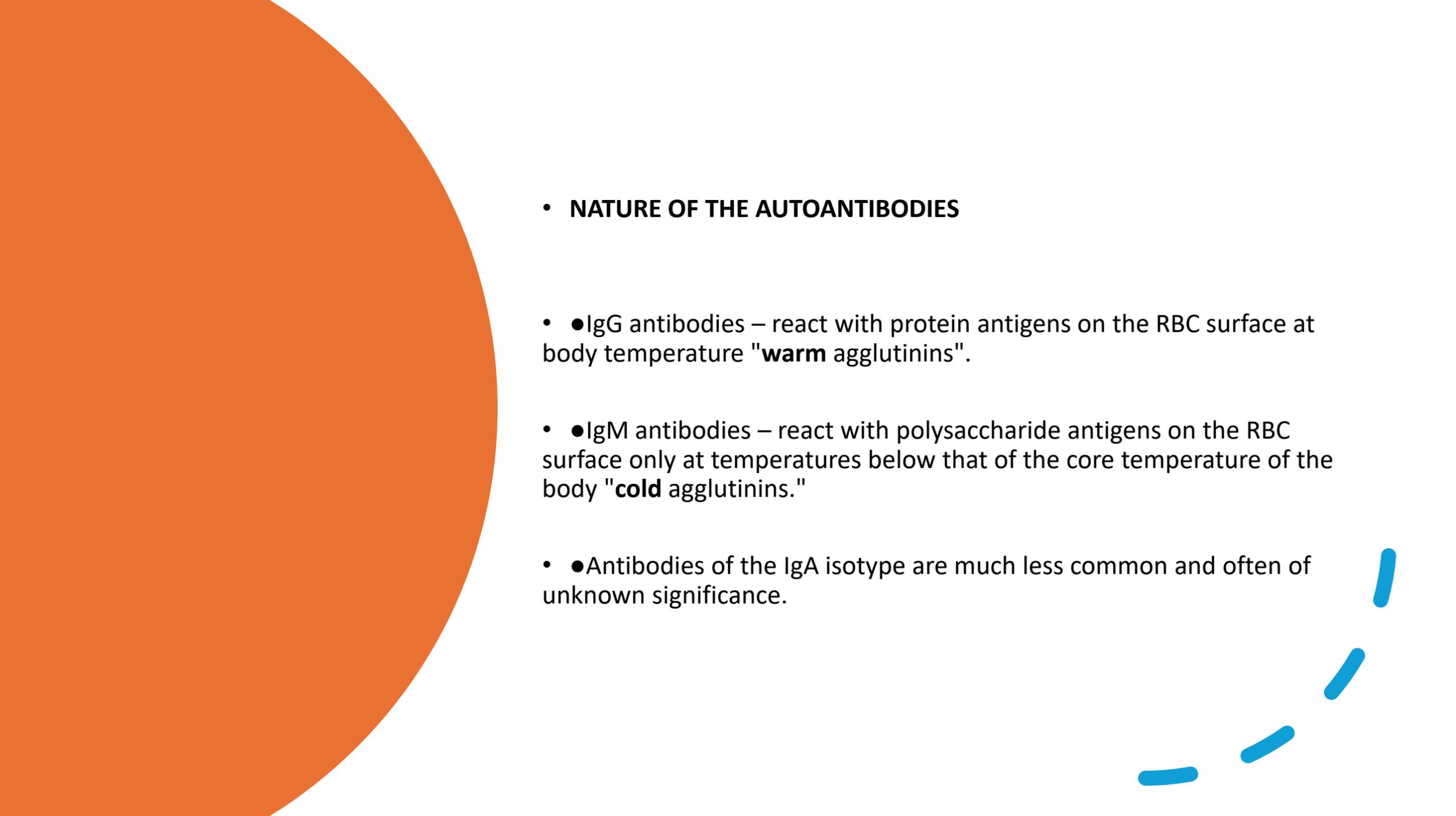
# Hereditary Angioedema





# AUTOIMMUNE HEMOLYTIC ANEMIA

- Acute extravascular hemolysis
- Autoantibodies are directed against RBC components (eg, Kell antigen)
- May be warm-reacting (IgG) or cold-reacting (IgM) antibody



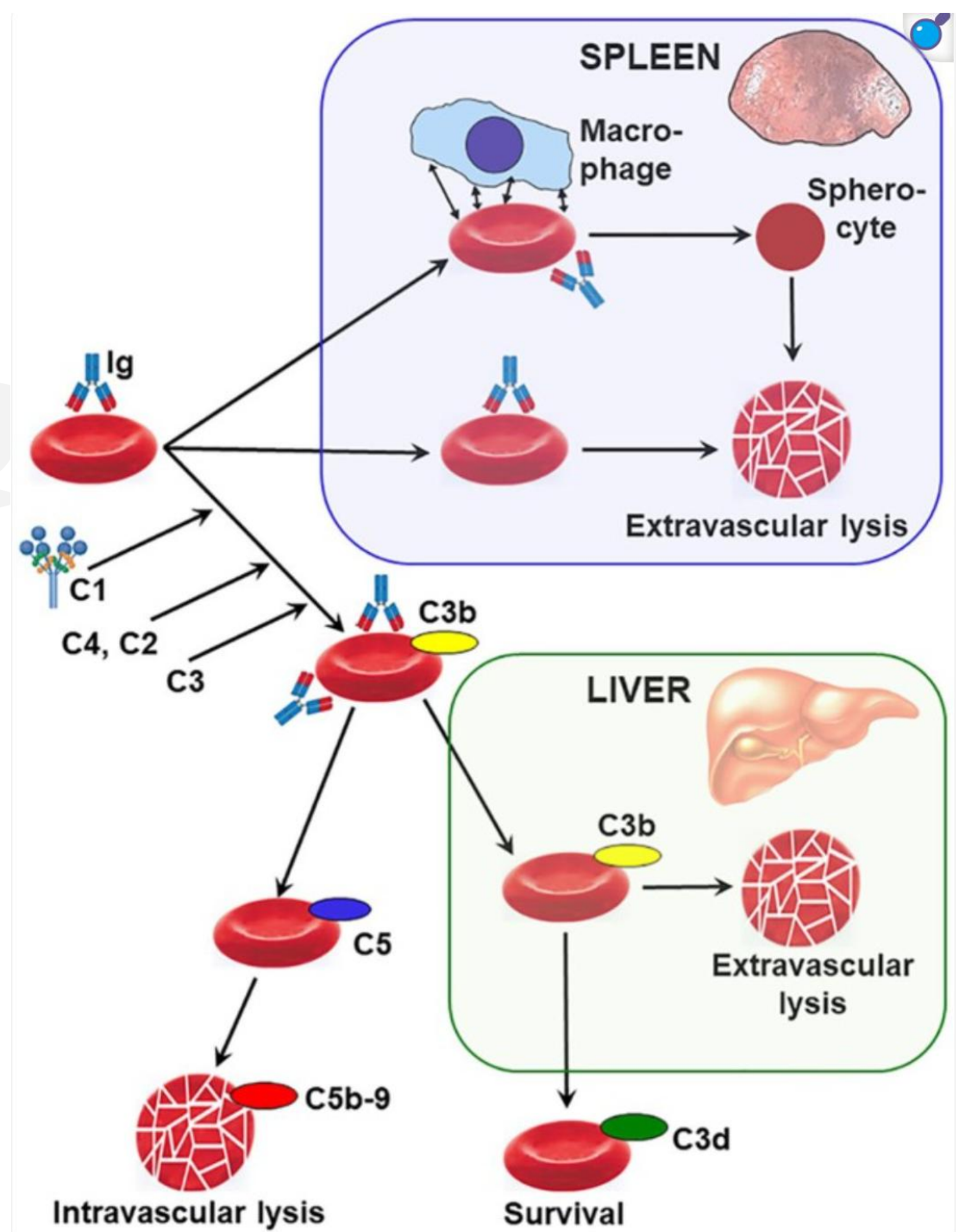
- **NATURE OF THE AUTOANTIBODIES**

- •IgG antibodies – react with protein antigens on the RBC surface at body temperature "**warm** agglutinins".
- •IgM antibodies – react with polysaccharide antigens on the RBC surface only at temperatures below that of the core temperature of the body "**cold** agglutinins."
- •Antibodies of the IgA isotype are much less common and often of unknown significance.

# Pathogenesis of Autoimmune Hemolytic Anemia

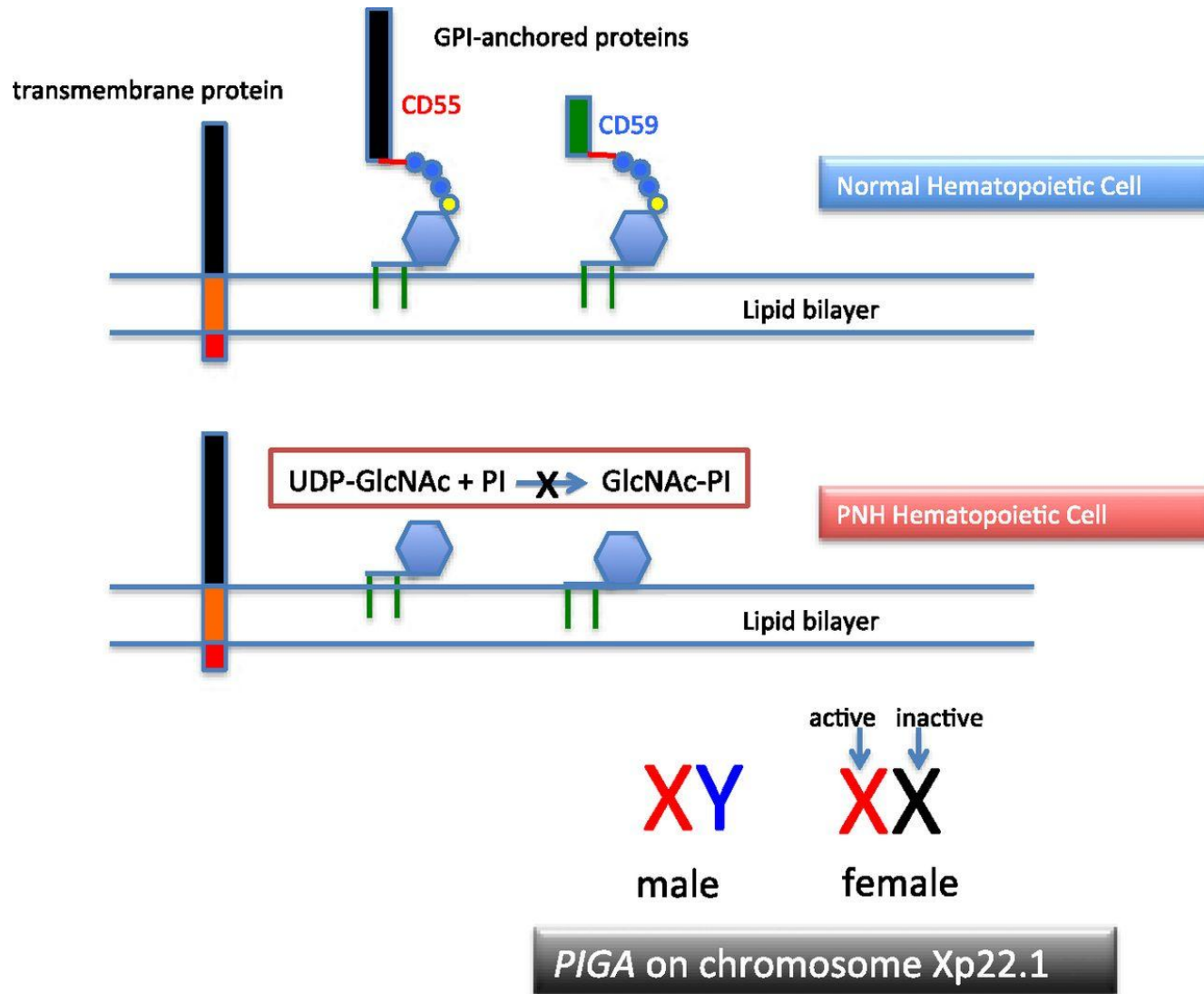
Berentsen et al, Ther Adv Hematol, 2019

6/10/2025



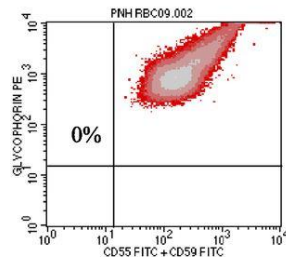
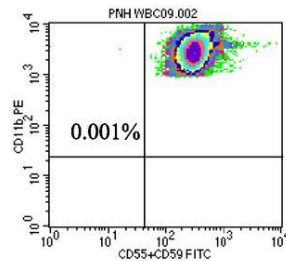
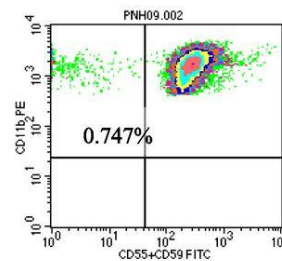
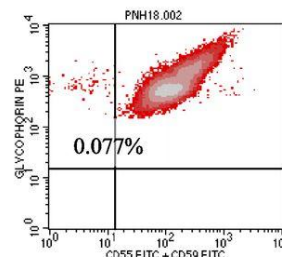
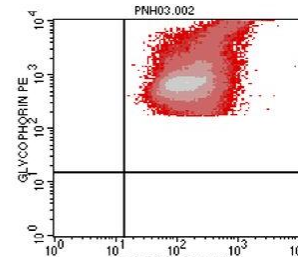
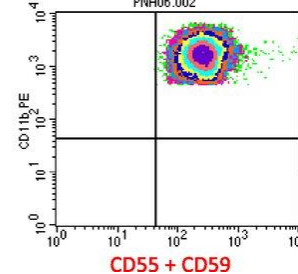
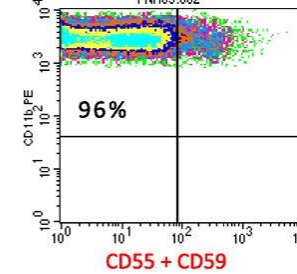
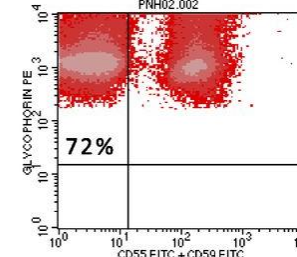
# Paroxysmal Nocturnal Hemoglobinuria

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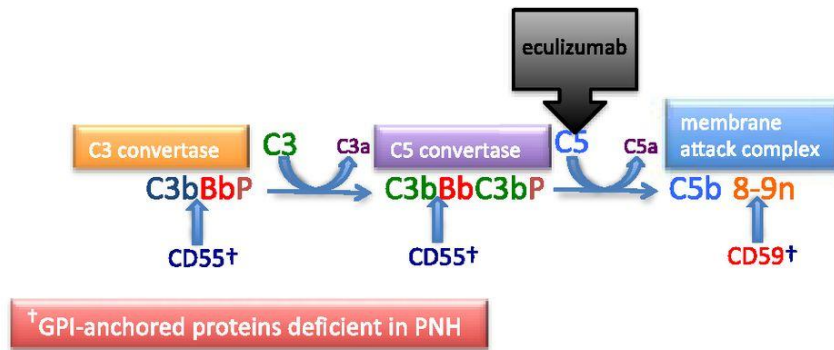
# Genetics of PNH

Charles J. Parker,  
Hematology Am Soc  
Hematol Educ Program,  
2016.

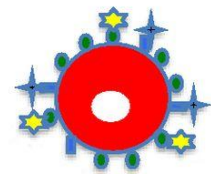
**A****Normal Control****RBCs****PMNs****Subclinical PNH****B****Normal Control****RBCs****PMNs****Classic PNH**

# Diagnosis of PNH

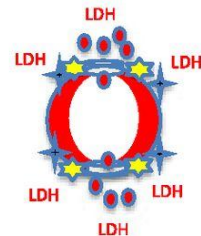
Charles J. Parker,  
Hematology Am Soc  
Hematol Educ Program,  
2016.



### Complement-Mediated Hemolysis



Normal RBC



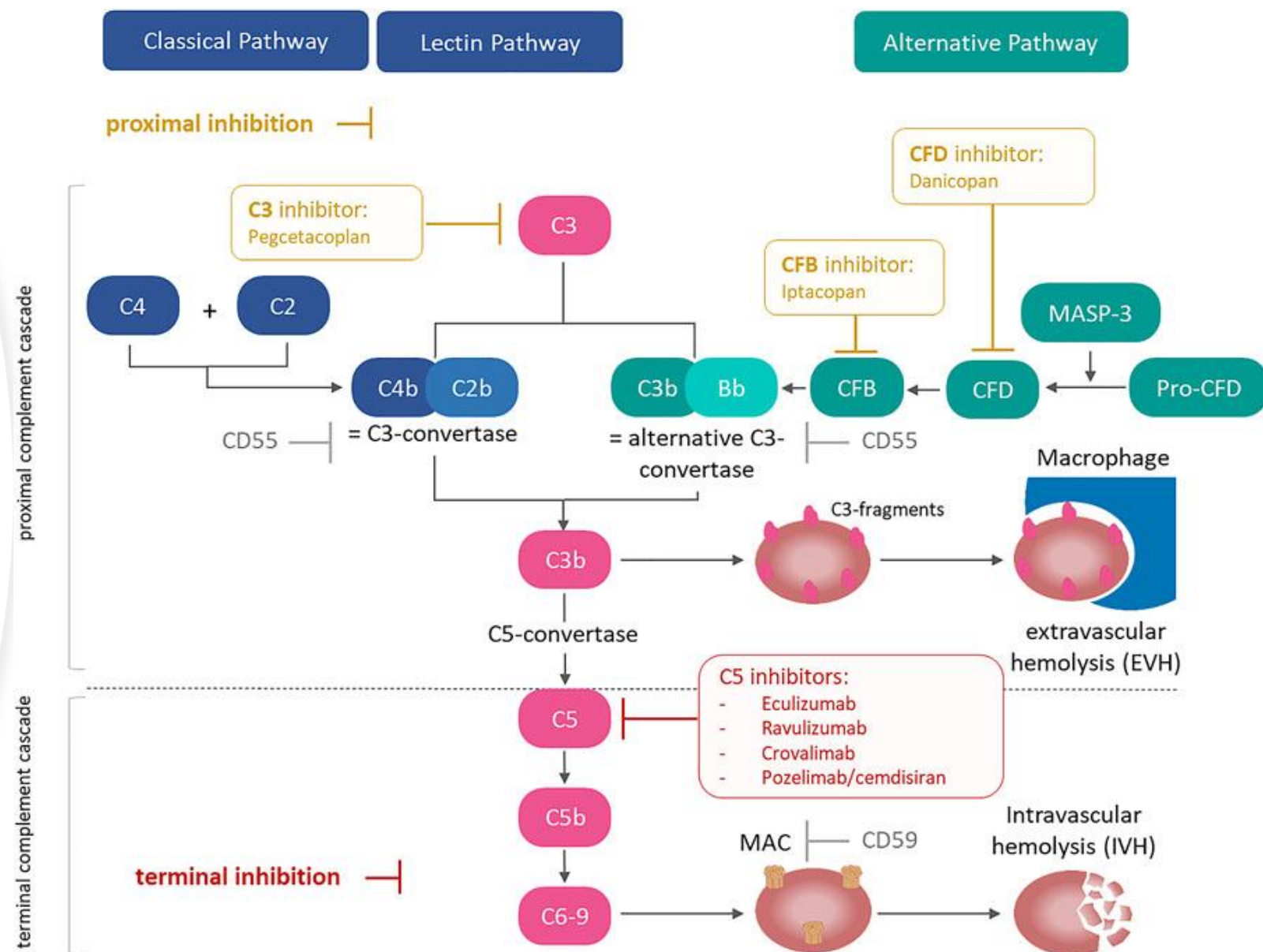
PNH RBC

Charles J. Parker, Hematology Am Soc Hematol Educ Program, 2016.

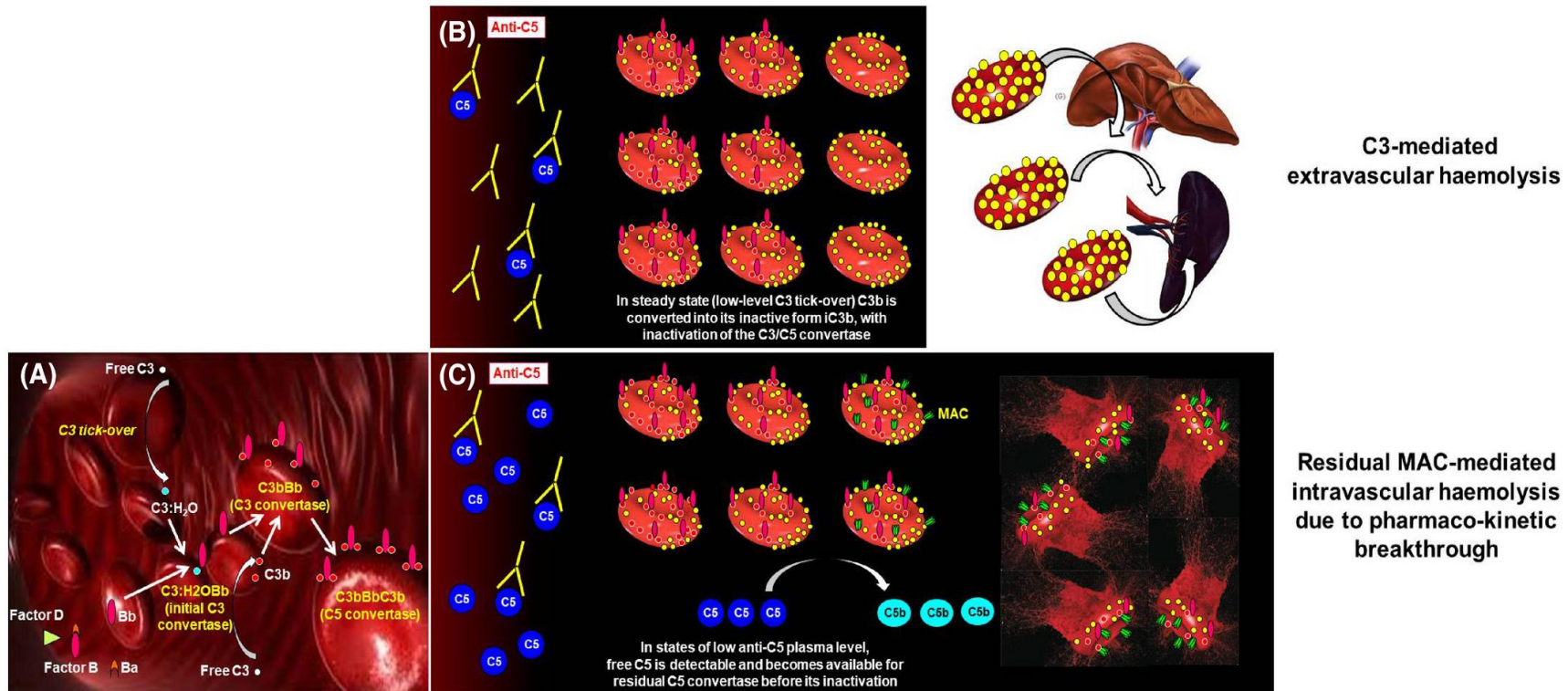
# Pathogenesis of PNH

# Treatment of Paroxysmal Nocturnal Hemoglobinuria

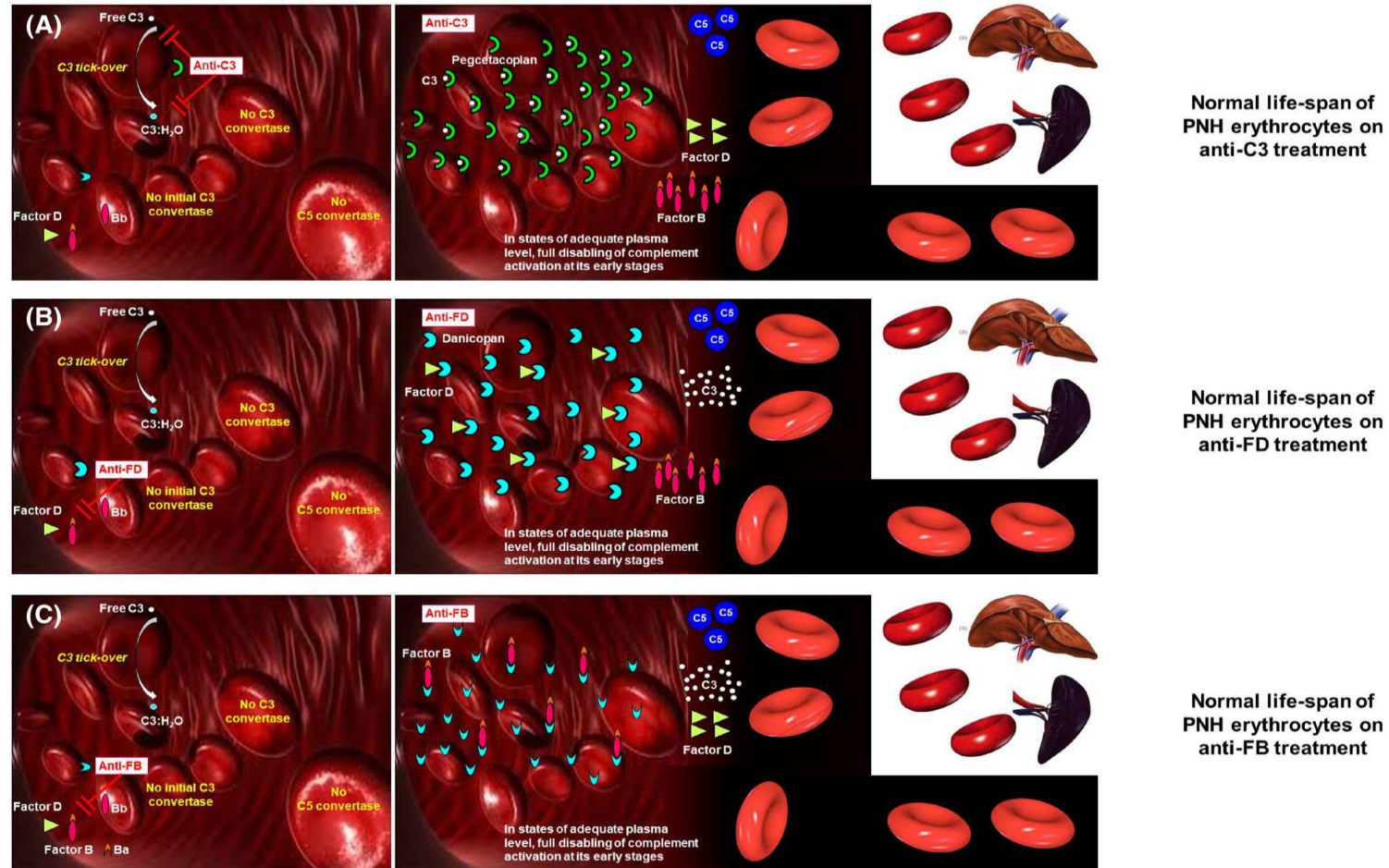
- Transfus Med Hemother. 2024;51(5):310-320. doi:10.1159/000540474



# Breakthrough hemolysis



# Breakthrough hemolysis



Drug	Phase	NCT ID	Study Design	Population	Intervention	Comparator	Outcome
Terminal inhibitors	Ravulizumab	C5	NCT02598583	Phase I/II, open-label	Untreated PNH	Intra-patient DE by IV infusions	Yes <sup>95</sup>
			NCT02605993	Phase I/II, open-label	Untreated PNH	MAD; IV infusions	
			NCT02946463	Phase III, randomized <i>versus</i> Ecu	Untreated PNH	IV infusions (every eight weeks)	Yes <sup>47,48,96</sup>
			NCT03056040	Phase III, randomized <i>versus</i> Ecu	Stable responders PNH	IV infusions (every eight weeks)	Yes <sup>47,48,79</sup>
	Crovalimab	C5	NCT03157635	Phase I/II, multi-part study	Untreated PNH and stable responders PNH	Intra-patient DE by IV infusions, followed by SC injections	Yes <sup>83</sup>
	LFG316 (tesidolumab)	C5	NCT02534909	Phase II, open-label	Untreated PNH	IV infusions	Pending
	REGN3918 (pozelimab)	C5	NCT03946748	Phase II, open-label, POC	Untreated PNH	IV and SC infusions	Pending
			NCT04162470	Phase II, open-label, extension	Pozelimab-treated PNH	IV and SC infusions	Ongoing
	ABP959	C5	NCT03818607	Phase III, randomized <i>versus</i> Ecu	Stable responders PNH	IV infusions	Ongoing
Proximal inhibitors	Pegcetacoplan	C3	NCT02264639	Phase Ib, open label, MAD, POC	Poor responders PNH	Daily, SC infusions	Yes <sup>86</sup>
			NCT02588833	Phase Ib, open label, MAD, POC	Untreated PNH	Daily, SC infusions	
			NCT03531255	Phase III, open label, extension	PNH exposed to APL-2	Daily, SC infusions	
			NCT03500549	Phase III, randomized <i>versus</i> Ecu	Poor responders PNH	SC infusions, BIH	Yes <sup>87</sup>
	Danicopan	FD	NCT03053102	Phase Ib, open label, MD, POC	Untreated PNH	Orally, TID	Yes <sup>89</sup>
			NCT03181633	Phase II, open-label, extension	PNH exposed to ACH-4471	Orally, TID	Ongoing
			NCT03472885	Phase II, open label, MD, POC	Poor responders PNH	Orally, TID	Yes <sup>90</sup>
			NCT04469465	Phase III, randomized <i>versus</i> Ecu	Phase III, randomized vs Ecu	Orally, TID	Ongoing
	ACH5020	FD	NCT04170023	Phase II, open label, POC	Danicopan-treated PNH, poor-responders to anti-C5 and untreated PNH	Orally, BID	Ongoing
	BCX9930	FD	NCT04330534	Phase I–II	PNH untreated	Orally, BID	Pending
			NCT04702568	Phase II, open label, extension	PNH, BCX9930-treated	Orally, BID	Ongoing
	Iptacopan	FB	NCT03439839	Phase II, open label, POC	Poor responders PNH	Orally, BID	Yes <sup>93</sup>
			NCT03896152	Phase II, open label, POC	Untreated PNH	Orally, BID	Pending
			NCT04558918	Phase III, randomized <i>versus</i> Ecu	Poor responders PNH	Orally, BID	Ongoing

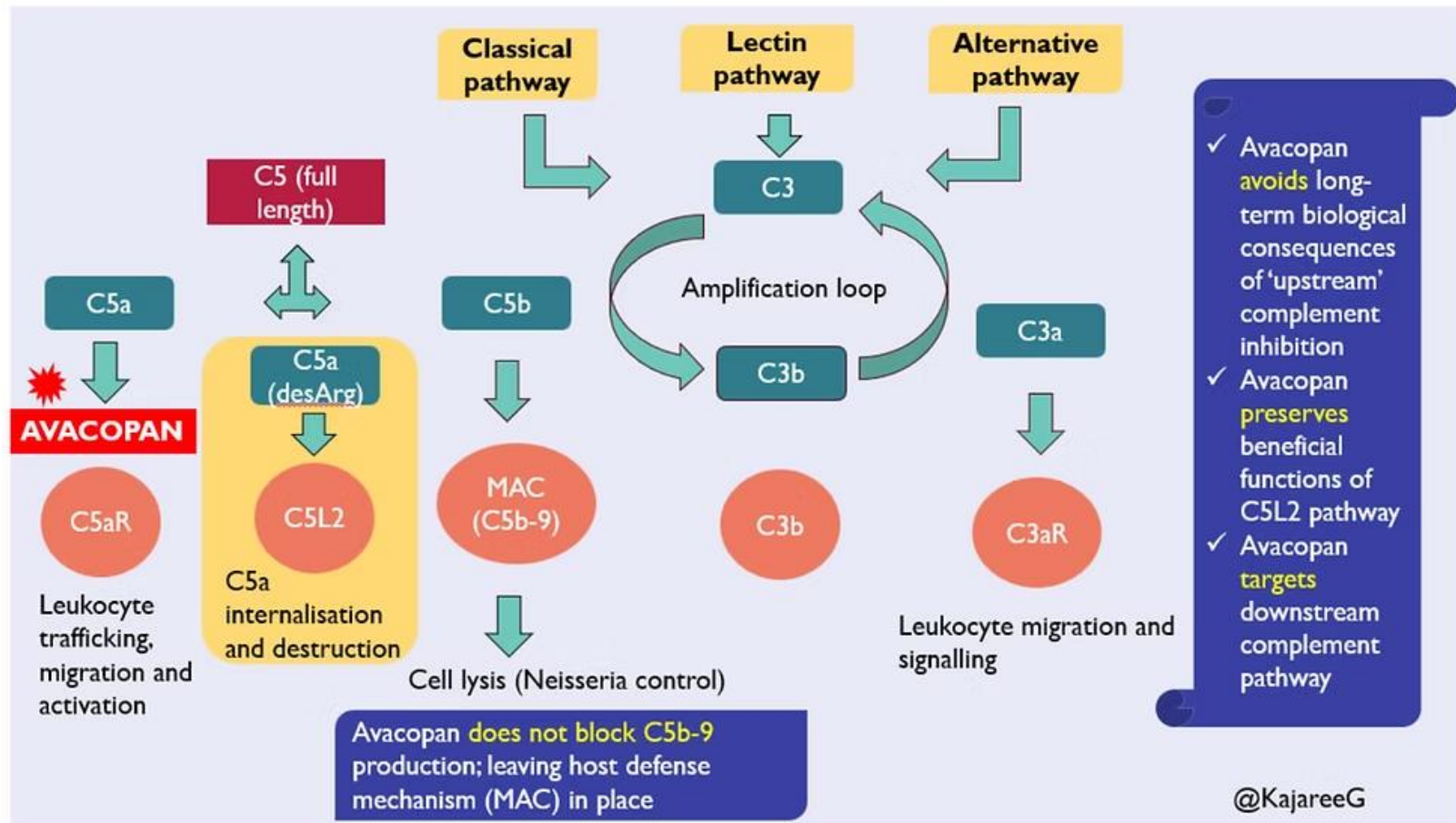
BID, *bis in die* (twice a day); BIH, *bis in hebdomade* (twice a week); DE, dose escalation; Ecu, eculizumab; IV, intravenous; LDH, lactate dehydrogenase; MAD, multiple ascending doses; MD, multiple daily; PNH, paroxysmal nocturnal hemoglobinuria; POC, proof of concept; SC, subcutaneous; TID, three times daily; FD, full dose; FB, full body; PNH, paroxysmal nocturnal hemoglobinuria; POC, proof of concept; SC, subcutaneous; TID, three times daily; FD, full dose; FB, full body.

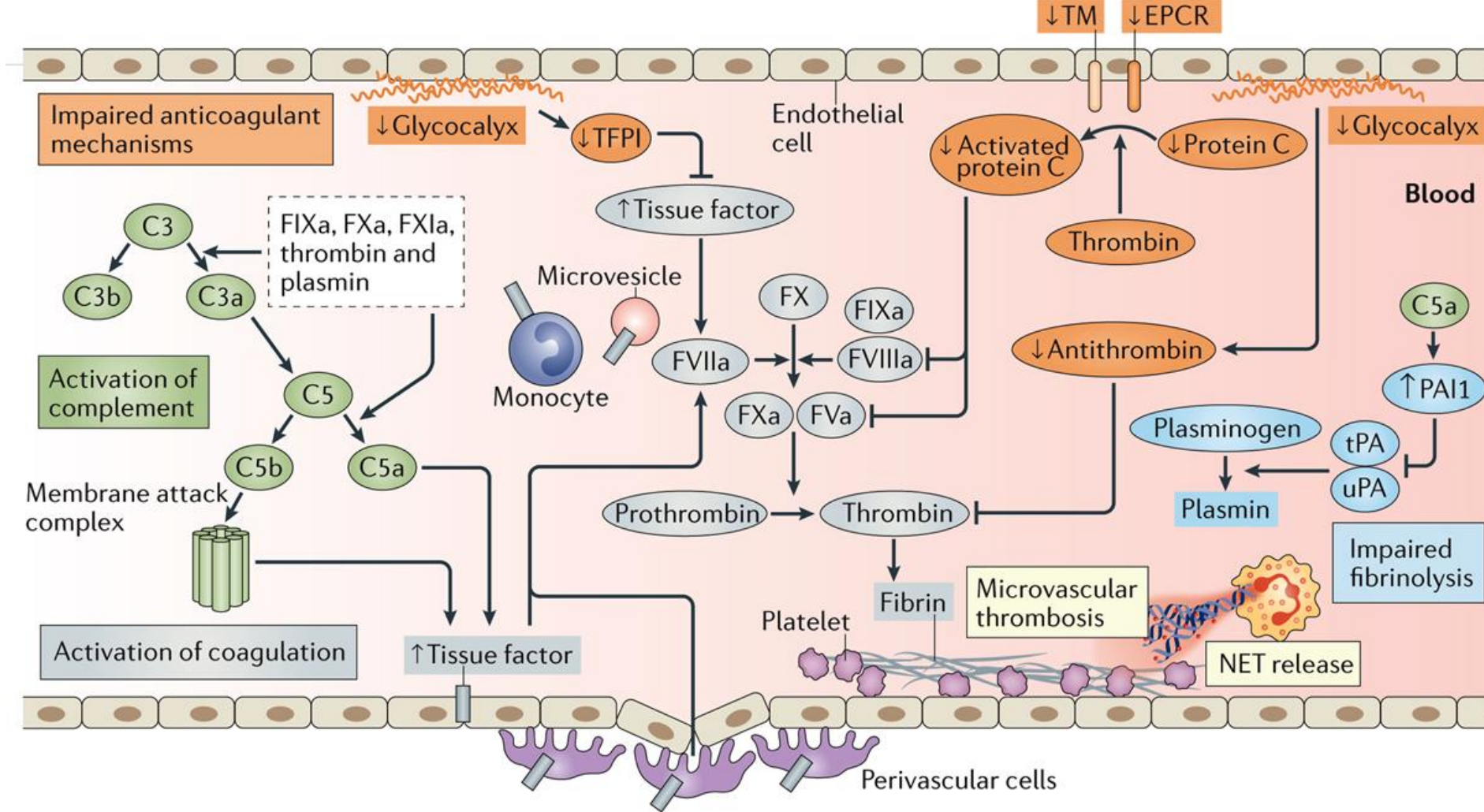


## Complement inhibitors in the treatment of treatment of glomerular disorders

DRUG	TARGET	INDICATIONS
Eculizumab, Ravulizumab	C5	aHUS
Pegcetacoplan	C3	C3 glomerulopathy, IgA nephropathy, Membranous nephropathy
Iptacopan	Factor B	aHUS, C3 glomerulopathy, Membranous nephropathy, IgA nephropathy
Danicopan	Factor D	C3 glomerulopathy
Narsoplimab	MASP 2	IgA nephropathy
Avacopan	C5a receptor	ANCA associated vasculitis

@DrNikhiU1



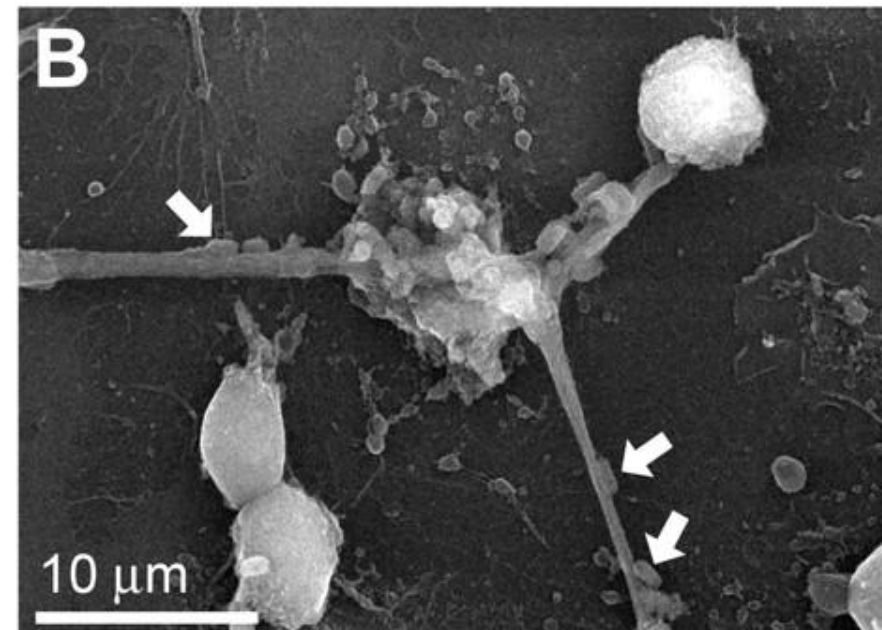
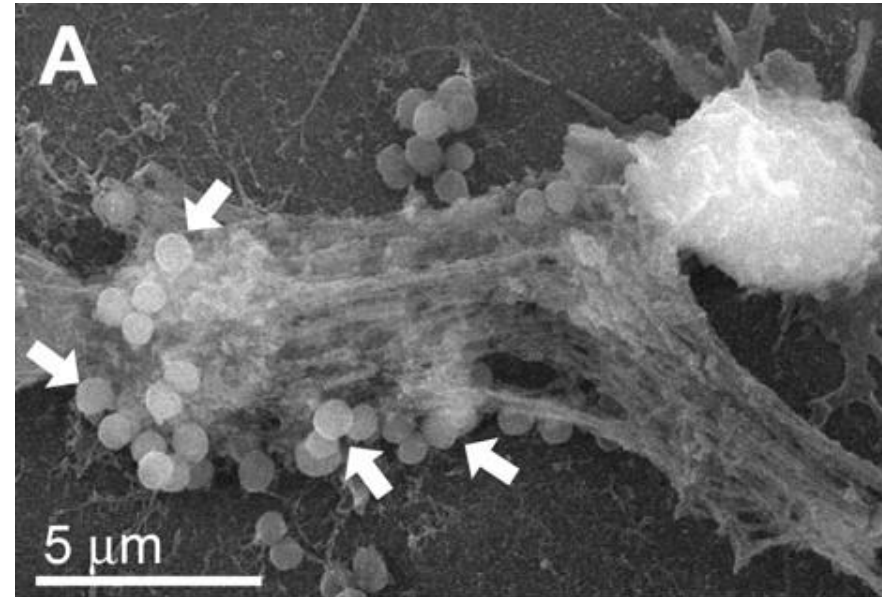


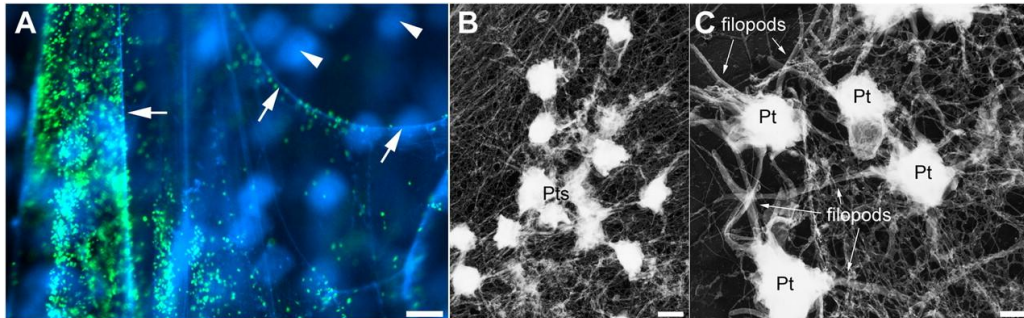
Nature Reviews | Immunology

# Complement and coagulation

Van der Poll, et al, Nat Rev Immunol, 2017

# Neutrophil extracellular traps





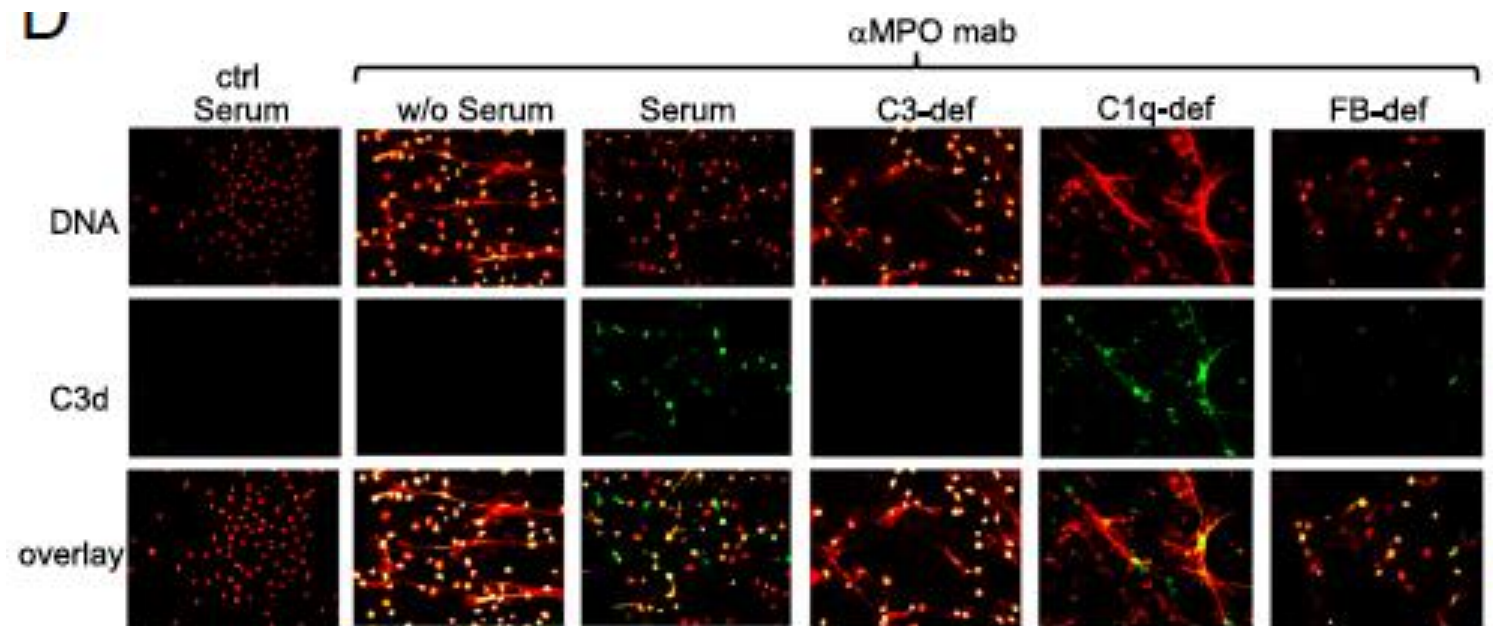
Fuchs et al, PNAS, 2010

NETs provide a  
scaffold for platelet  
adhesion and  
aggregation



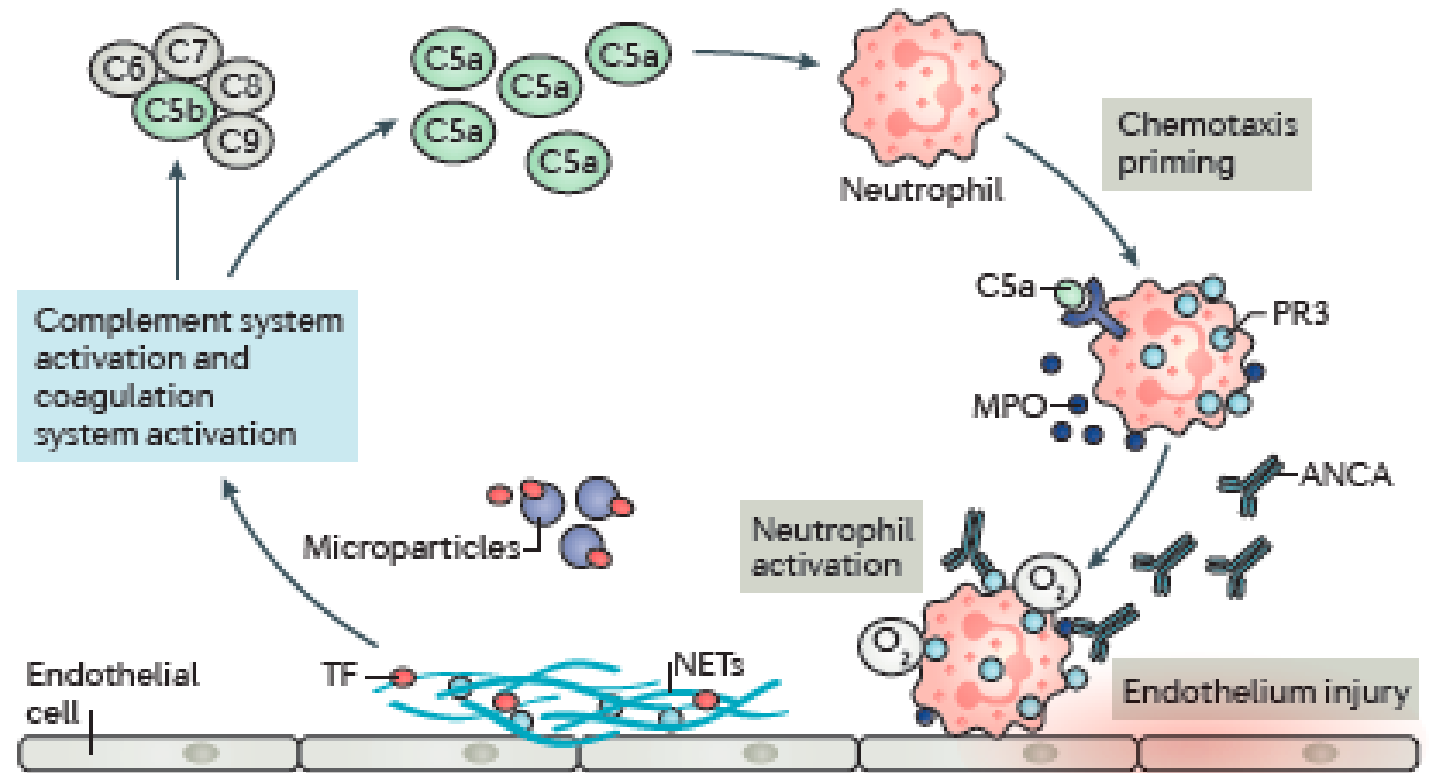
Schreiber et al, PNAS,  
2017

# NETs activate alternative complement pathway



Chen et al, Nat Rev  
Nephrol, 2017

# Complement- NETs-VTE in ANCA vasculitis





Thank you for your  
attention