Day in Complement 2025

McMaster University | Health Sciences Continuing Professional Development

THE CANADIAN HEMATOLOGY SOCIETY
SOCIÉTÉ CANADIENNE D'HÉMATOLOGIE

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Canadian Institute for the Transfer of KnowledgE

# Complement-101

## *Introduction to that other cascade.*


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# Disclosures

- **Consultancy/advisory board honoraria**
  - Alexion, Amgen, BioCryst, Novartis, Regeneron, Roche, Sanofi, Sobi, Takeda

- **Speaking honoraria**
  - Alexion, Amgen, Novartis, Sobi

# Objectives

- Provide an overview of complement in health & disease
- Review key components of activation and regulation
- Review the basics of therapeutic complement inhibition

"Many immunologists hold that complement is baffling or irrelevant or, most conveniently, both…

*~ Hobart, 1984 (Trends in Immunology)*

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"Many immunologists hold that complement is baffling or irrelevant or, most conveniently, both… but a recent meeting emphasized that complement is *interesting* and that it *may be important*…"

*~ Hobart, 1984 (Trends in Immunology)*

# A “New” Circulating Protector

# The History of Complement

- Hans Buchner
  - Heat-labile factor in blood, “alexins”
  - Killed bacteria until heated

Nesargikar PN *et al.* (2012) *Eur J Mic Immunol*

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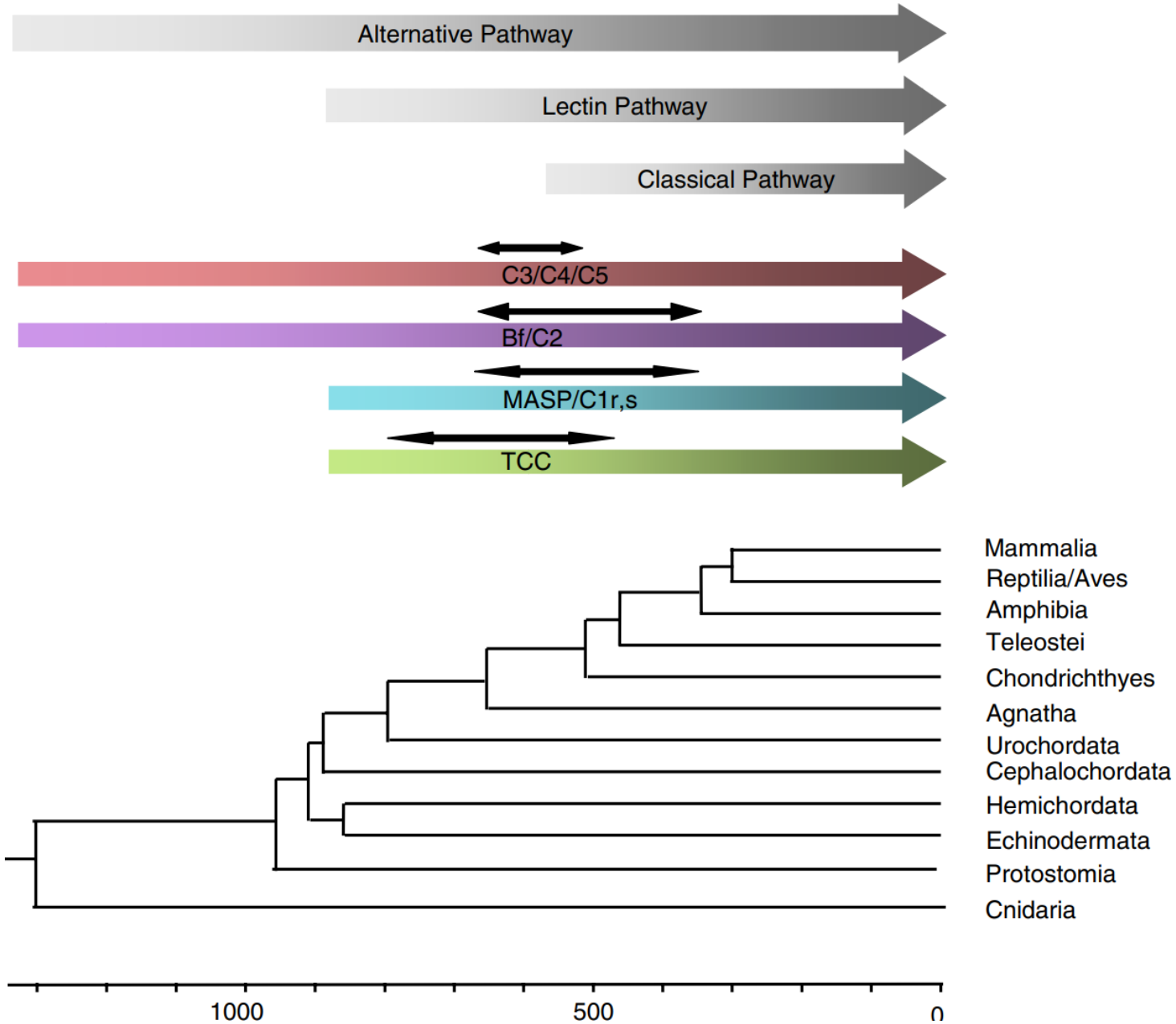
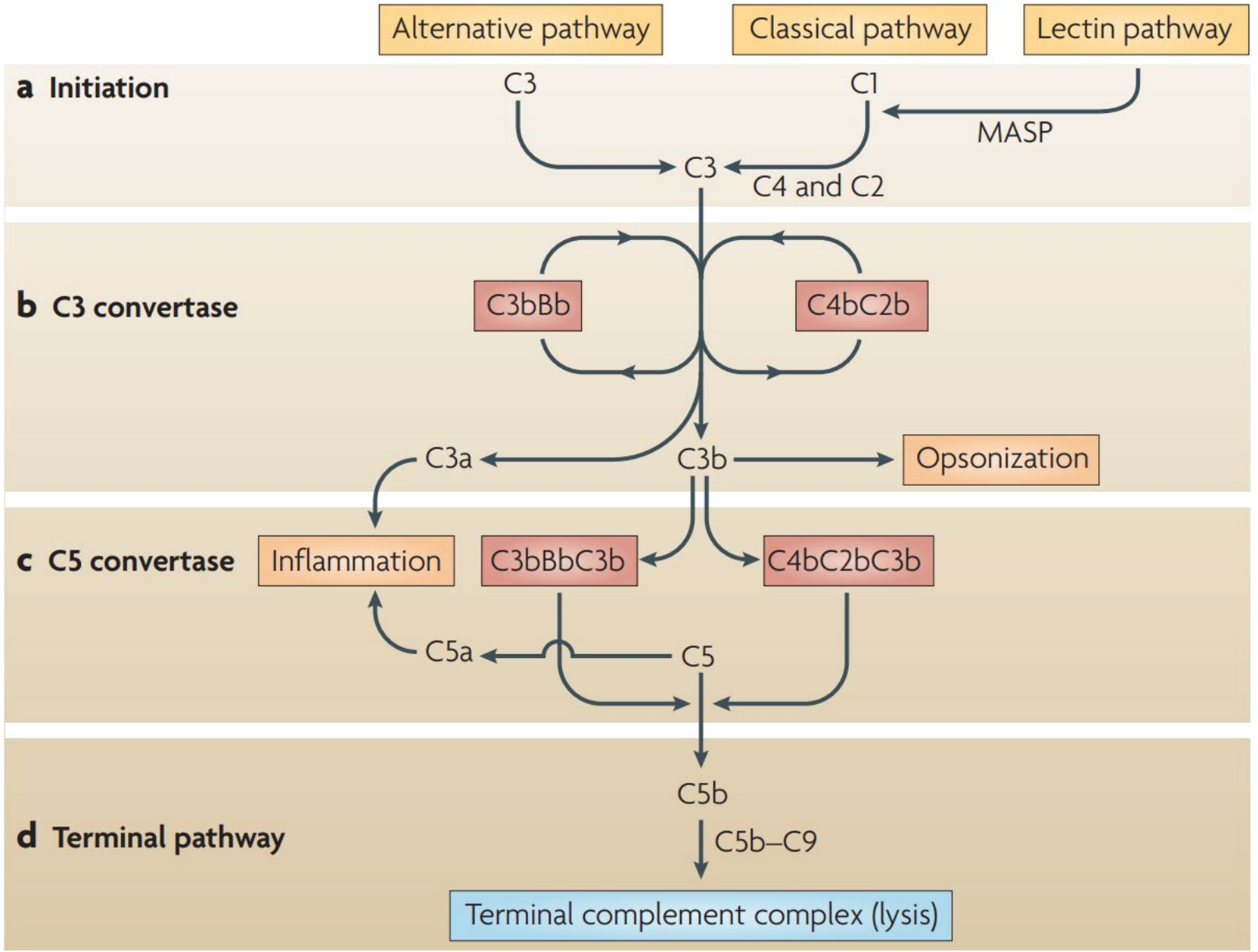
- Paul Ehrlich (Nobel Prize 1908)
  - Focused on “amboceptors” and heat-labile helper molecules which *complement* their activity

Nesargikar PN *et al.* (2012) *Eur J Mic Immunol*

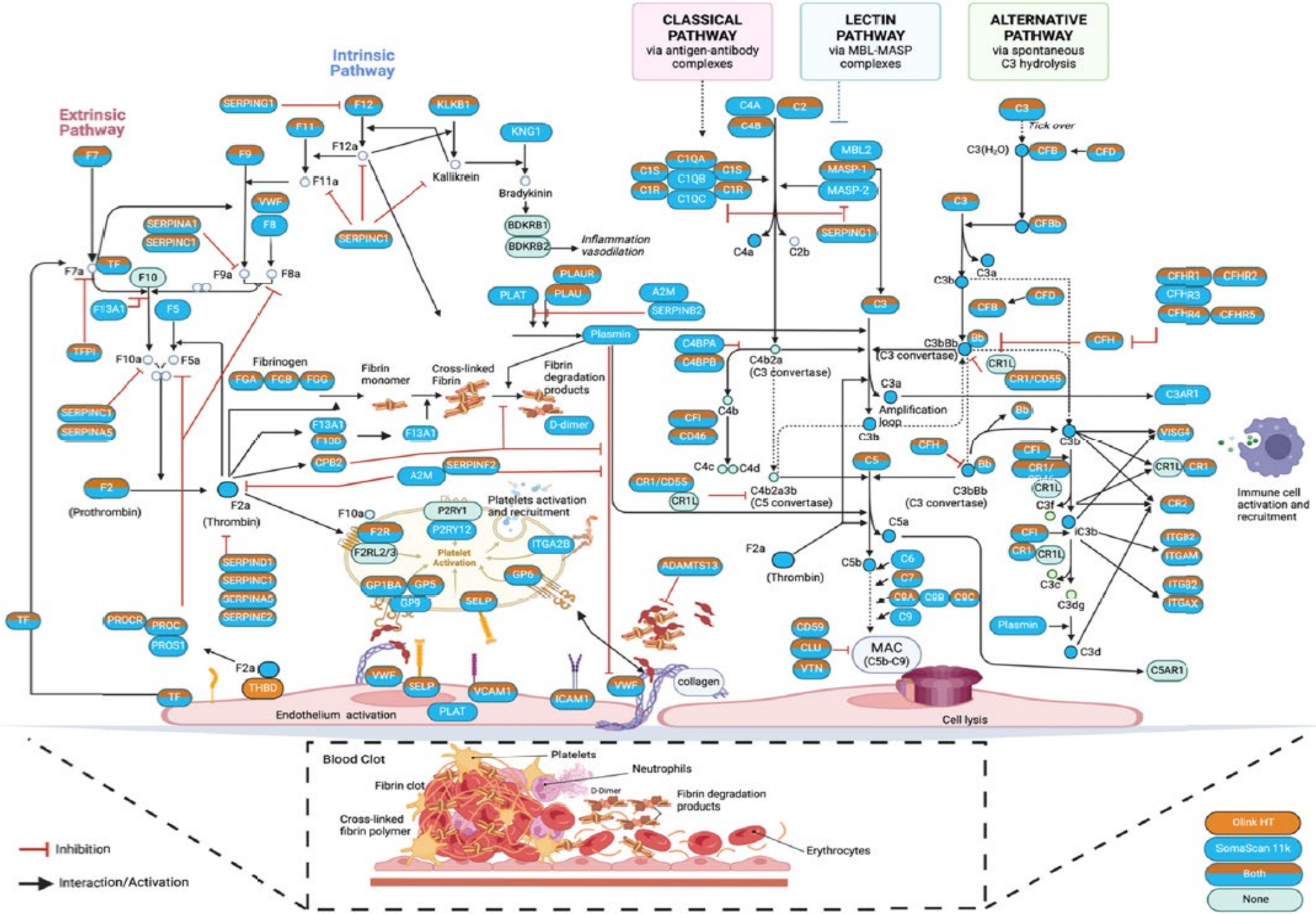



Nonaka & Kimura (2006) *Immunogenetics*

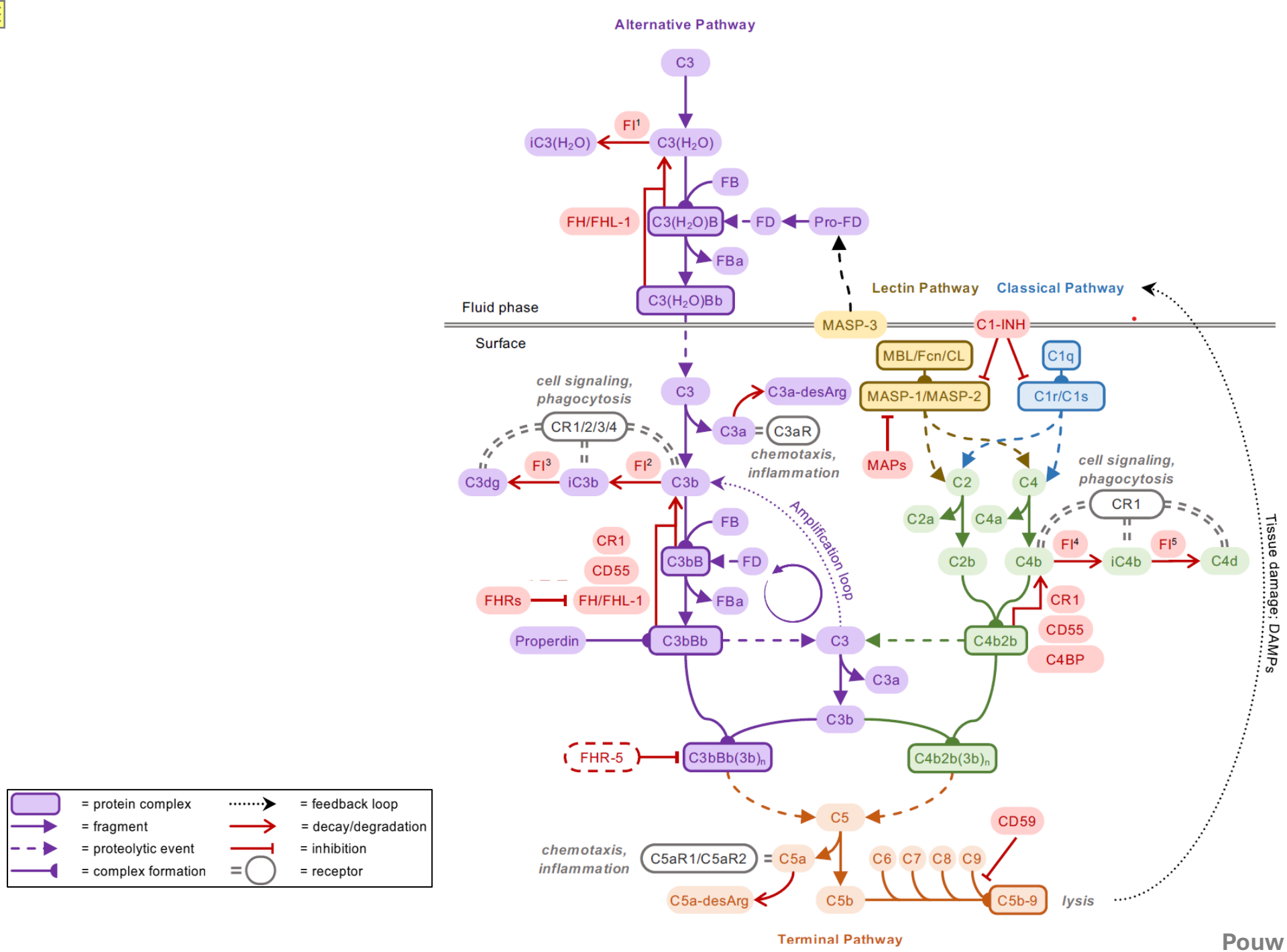
# Drivers of Activation & Regulation

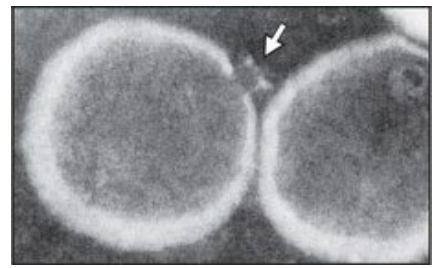


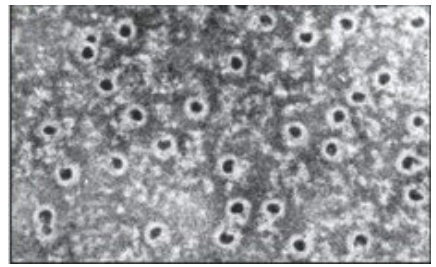

Zipfel & Skerka (2009) *Nature Reviews Immunology*




Johansson E *et al.* (2025) *Expert Review of Proteomics*

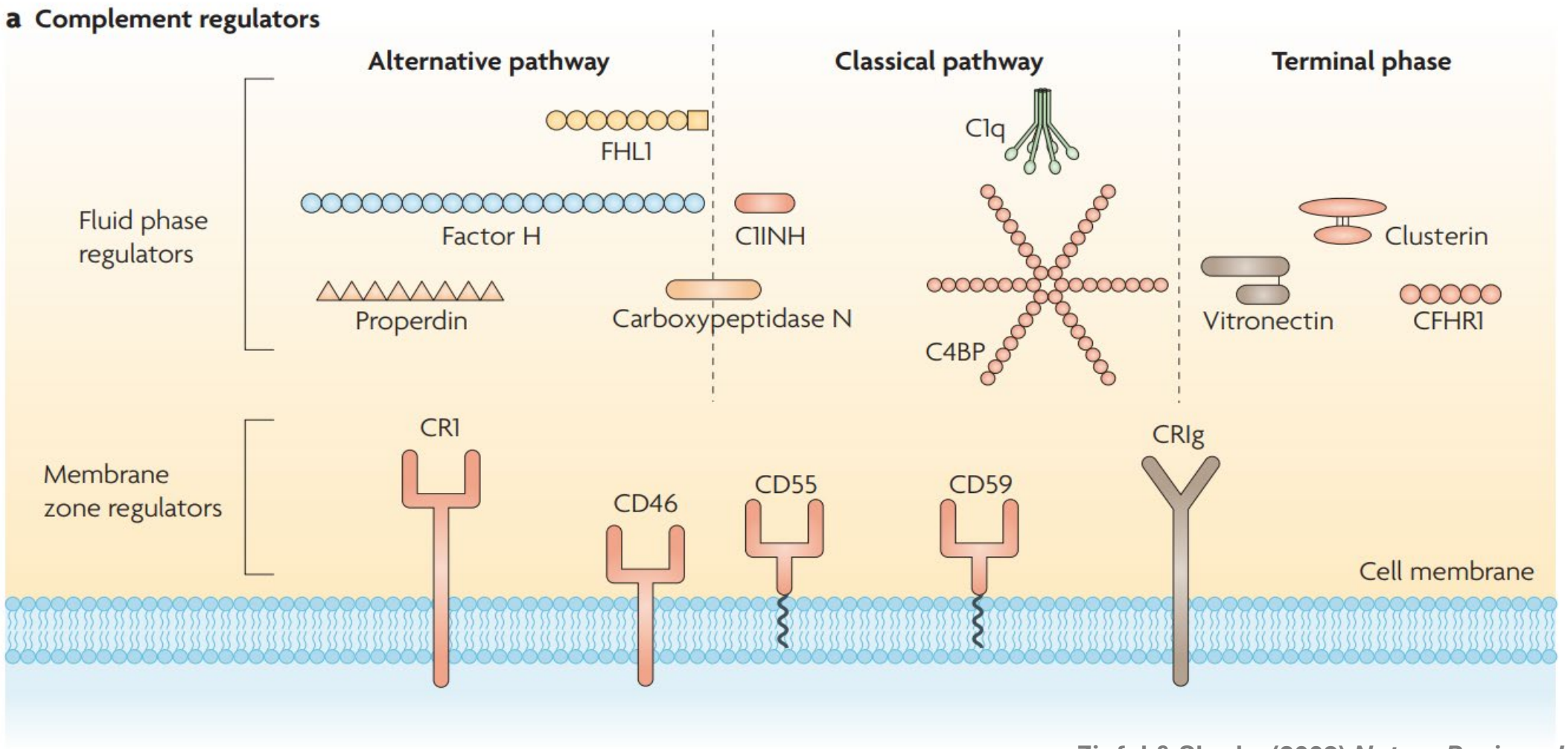




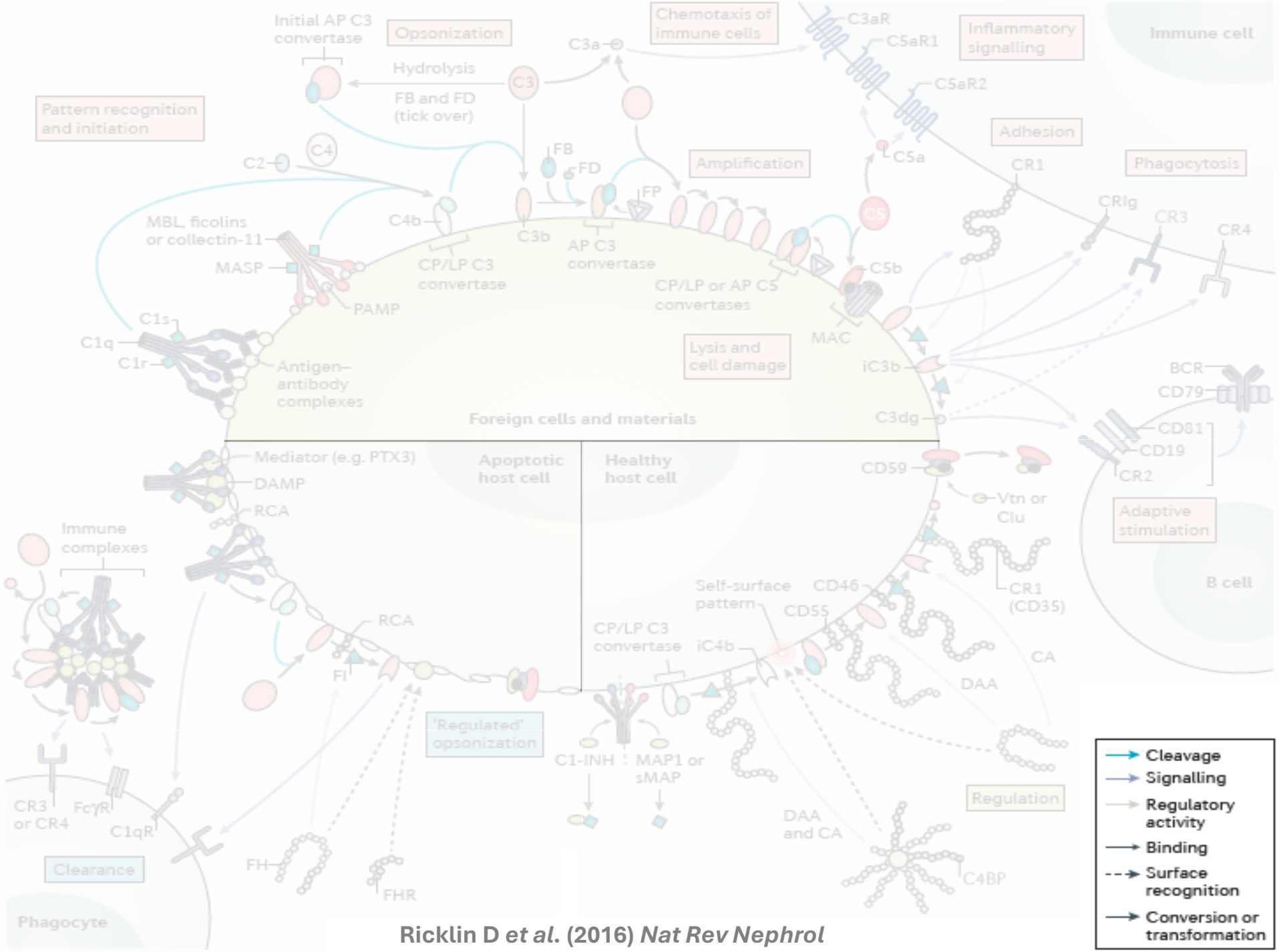
Pouw & Ricklin (2021) *Sem Immunopath*

# Regulators of Complement Activity



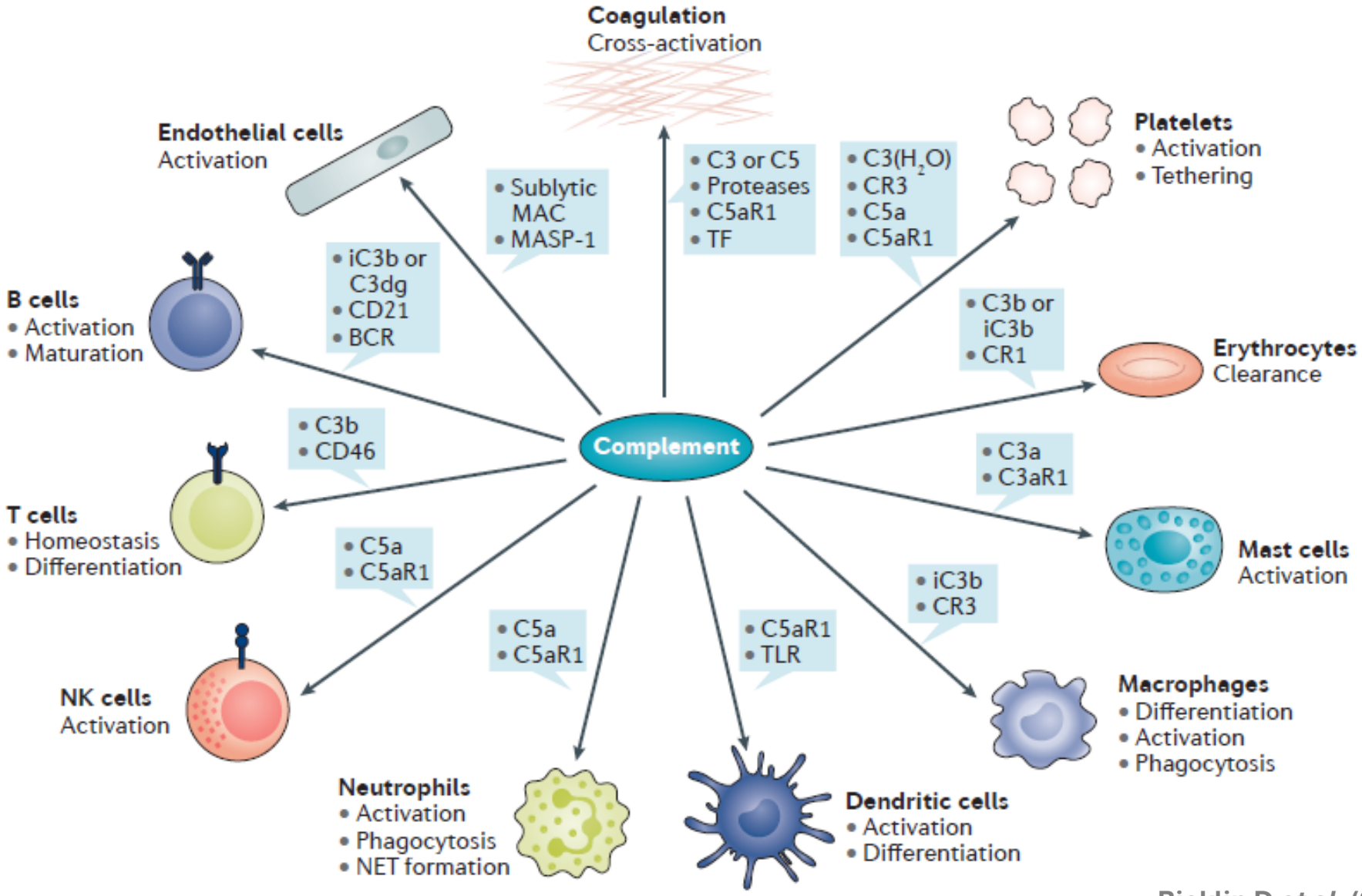

Zipfel & Skerka (2009) *Nature Reviews Immunology*

# Not Just For Antimicrobial Defense




Ricklin D *et al.* (2016) *Nat Rev Nephrol*

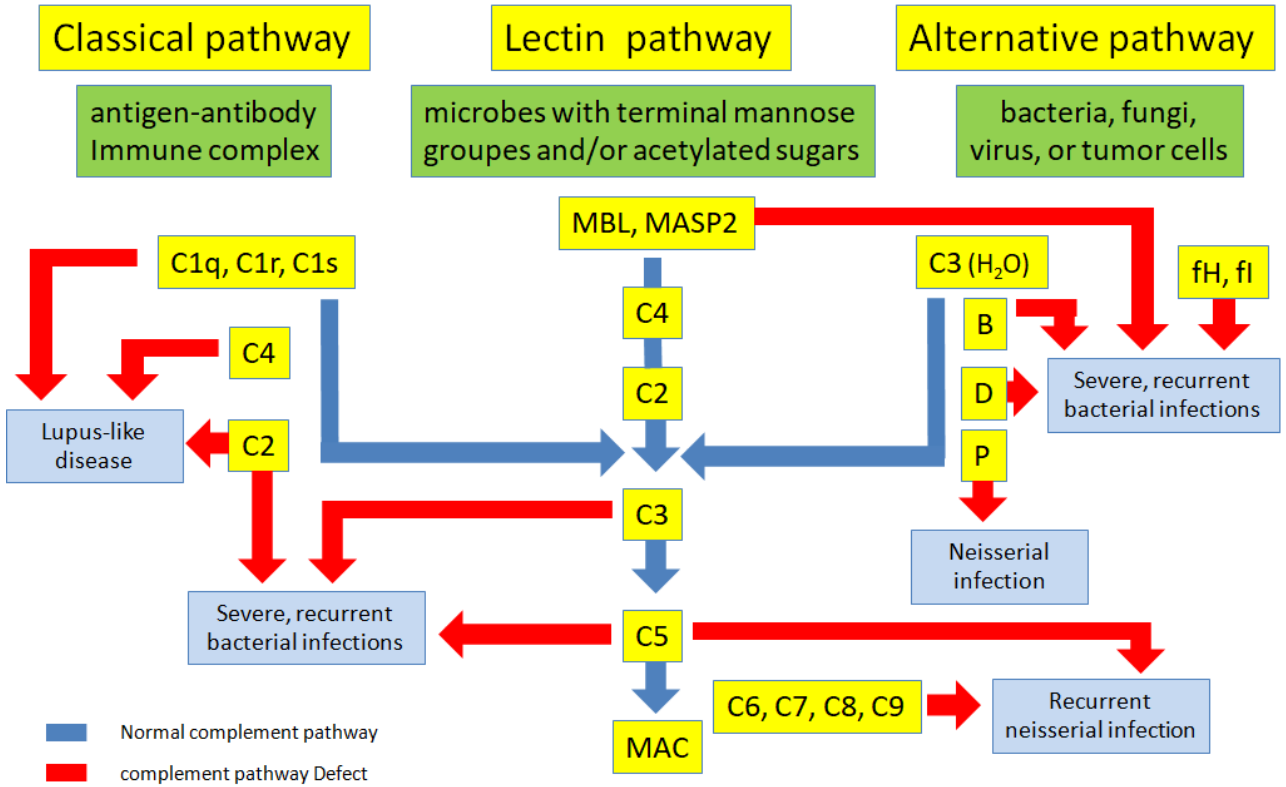
**“In life, the devices through which the body protects itself form a seamless web, unwrinkled by our artificialities.” ~ *Ratnoff, 1969***




Ricklin D *et al.* (2016) *Nat Rev Nephrol*

| Complement protein | Comments | Effects reported |
|---|---|---|
| C1q, C1r, C1s | autosomal recessive | increase in immune complex disorders, e.g. SLE; vasculitis*<br>increase in pyogenic infections (Gram positive) |
| C4 | autosomal recessive | increase in immune complex disorders, e.g. SLE; vasculitis *<br>increase in pyogenic infections (Gram positive) |
| C2 | autosomal recessive | increase in immune complex disorders, e.g. SLE; vasculitis *<br>increase in pyogenic infections (Gram positive) |
| C3 | autosomal recessive | frequent and severe bacterial infections resulting in pneumonia, septicemia and meningitis<br>increase in immune complex disorders |
| C5, C6, C7, C8 | autosomal recessive | recurrent neisserial infections (meningitis, gonorrhea) |
| C9 | | asymptomatic |
| Factor D, P | | recurrent neisserial infections (meningitis; gonorrhea) |
| C1INH | autosomal dominant | hereditary angioedema |
| MBL | autosomal dominant or recessive | increased susceptibility to a variety of extracellular pathogens |
| Factor H | autosomal dominant | leads to depletion of C3 and symptoms similar to C3 deficiency |

# Complement system pathways and defects



# Available Complement Testing

| | Characteristics | First-Tier Assays | Second-Tier Assays | Genetic Testing | Considerations |
|---|---|---|---|---|---|
| Complement deficiencies | Individual components or control proteins are low or absent. Gene mutations are usually involved | CH50 and AH50 | If only CH50 is low: test for C1, C4, C2 (function and antigen concentrations).<br>If only AH50 is low: test for FD, FB, properdin.[a]<br>Both CH50 and AH50 low: test for C3, C5, C6, C7, C8, and C9 (function and antigen concentrations).<br>Both CH50 and AH50 normal: test for MBL pathway function[b] | Sequence genes coding for low serological results is recommended, but not mandatory, once the phenotypical presentation is characterized | If more than one component is measured as low, it is important to look for technical errors, or states of chronic activation. A possible complement autoantibody, deficiency in a control protein, malnutrition, protein-losing states, or age (newborn state) should be considered |
| SLE, RA, other autoimmune diseases<br>Monoclonal gammopathies and HCV infections | Increased immunoglobulin production (with or without cryoglobulinemia) or immune complex formation will lead to classical pathway overactivation. Deposits of immune complexes in the kidneys are common | CH50, C3, C4. Common results in the setting of hypocomplementemia are low CH50 and low C4, with normal or low C3 | C1q function and antigen concentration. Autoantibodies to C1q are associated with lupus nephritis [120]. Activation products of C3 and C4 can provide estimates of disease activity in SLE [121] | Not usually required | Hypocomplementemia may be associated with these conditions. Complement in vitro activation will generate the same findings, therefore sample collection and transportation should be performed carefully to prevent activation and consumption |

Frazer-Abel F *et al.* (2016) *Advances in Clinical Chemistry*

| | Characteristics | First-Tier Assays | Second-Tier Assays | Genetic Testing | Considerations |
|---|---|---|---|---|---|
| Immune complex-mediated MPGN and complement-mediated MPGN | Rare kidney diseases with deposits on the glomerular basement membrane. Immune complex-mediated MPGN results from infectious processes, autoimmune diseases, or monoclonal gammopathies, whereas complement-mediated MPGN subcategories (DDD and C3GN) differ by electron microscopy findings. Complement mediated MPGN has the dysfunction of AP as its defining pathophysiology | CH50, AH50, C3, C4, FB, FH, sMAC | Immune complex-mediated MPGN: classical pathway involvement may be evident when activation products (C4d) are tested. C4 nephritic factors have been reported [48,122]. C3 glomerulopathies: strong involvement and dysfunction of AP. Activations products such as Bb and sMAC as well as C3 nephritic factors and antibodies to FH are recommended tests | Genetic causes of C3G include mutations of *C3* complement gene and regulatory proteins (*CFH*, *CFI*, *MCP*, *CFHR5*, *CFHR3-1*) [123–128]. Allele variants for *CFH* and copy number variation for the *CFHR* cluster have also been reported [126,129] | Diagnosis should be made prior to initiation of therapy. The acute phases of diseases will be critical to determine complement involvement |
| Atypical hemolytic uremic syndrome (aHUS) | This heterogeneous, rare disorder with presentations of nonimmune hemolytic anemia, thrombocytopenia, and renal impairment has strong AP involvement | A panel of assays including CH50, AH50, C3, C4, C4d, factor B, Bb, factor H, and sMAC will provide enough information to discern between CP or AP involvement | FI and autoantibodies to FH may provide additional information | Sequencing *CFH* and copy number variation for *CFHR1, CFHR3, CFHR4,* sequencing *CFB, CFI, C3, CD46,* and *THBD* | Complement function and activation markers are usually measured; sample handling is critical for accurate results |

Frazer-Abel F *et al.* (2016) *Advances in Clinical Chemistry*

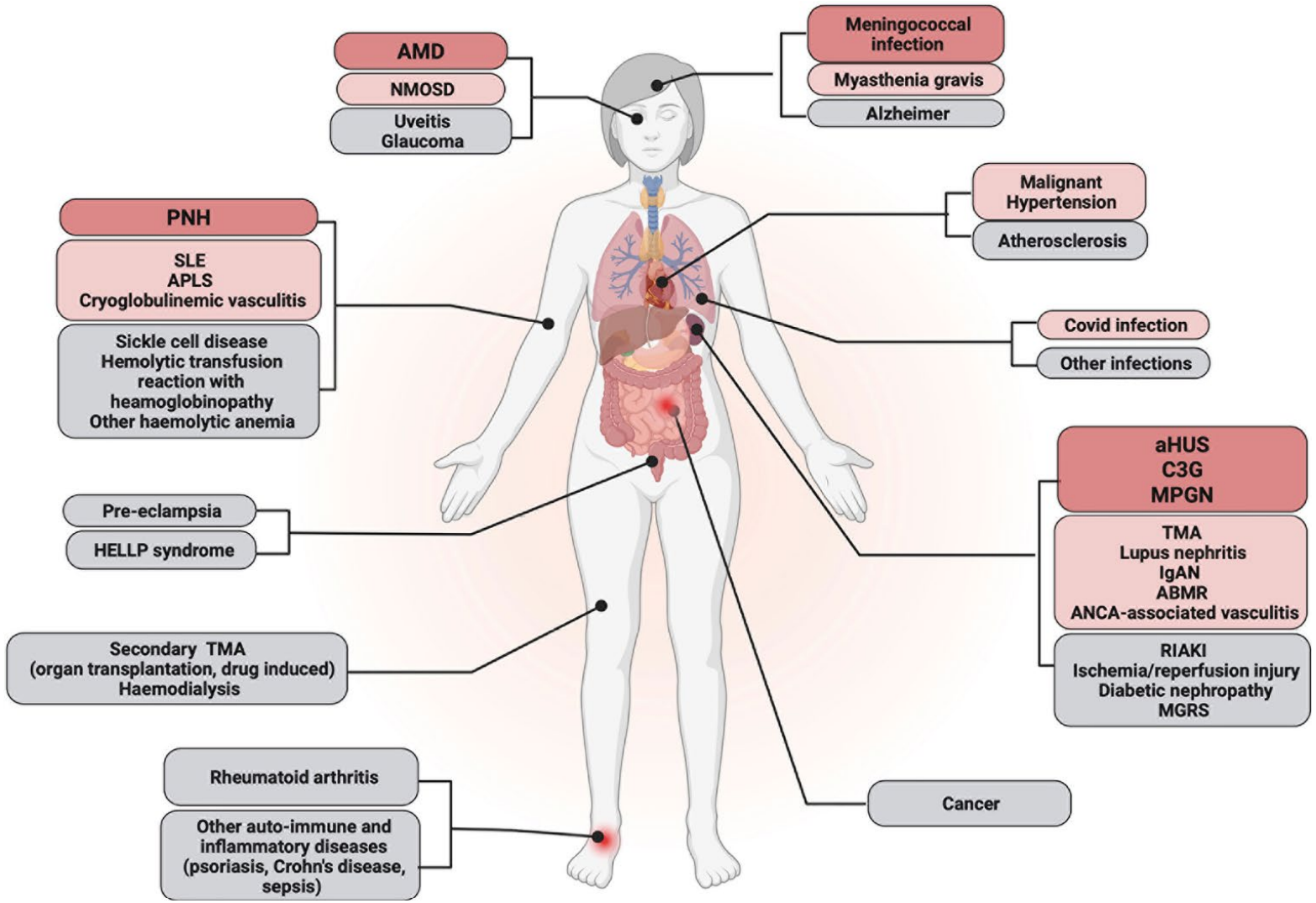
| | Characteristics | First-Tier Assays | Second-Tier Assays | Genetic Testing | Considerations |
|---|---|---|---|---|---|
| Paroxysmal nocturnal hemoglobinuria (PNH) | PNH is an acquired hematologic disorder characterized by nocturnal hemoglobinuria, chronic hemolytic anemia, thrombosis, pancytopenia, and, in some patients, acute or chronic myeloid malignancies | CH50, the Ham's test or flow-cytometry panel | Flow cytometry can detect the presence or absence of GPI-linked proteins in granulocytes, monocytes, erythrocytes, and/or lymphocytes. A partial list of known GPI-linked proteins include CD14, CD16, CD24, CD55, CD56, CD58, CD59, C8-binding protein, alkaline phosphatase, acetylcholine esterase, and a variety of high frequency human blood antigens. In addition, fluorescent aerolysin (FLAER) binds directly to the GPI anchor and can be used to evaluate the expression of the GPI linkage | Mutations in the phosphatidylinositol glycan A gene, *PIGA*, have been identified consistently in patients with PNH, thus confirming the biological defect in this disorder | PNH affects erythroid, granulocytic, and megakaryocytic cell lines. The abnormal cells in PNH have been shown to lack GPI-linked proteins in erythroid, granulocytic, megakaryocytic, and, in some instances, lymphoid cells |

**We remain limited in terms of other complement testing and biomarkers in Canada.**
***Available in some labs include sC5b9, anti-CFH, ex vivo deposition, CH50, AH50, complement component panels, and C3d erythrocyte flow cytometry.***

Frazer-Abel F *et al.* (2016) *Advances in Clinical Chemistry*

# Therapeutic Complement Inhibition

# Complementopathy in Many Different Diseases




Meuleman MS *et al.* (2022) *Frontiers in Immunology*

# Is The Complement System Druggable?

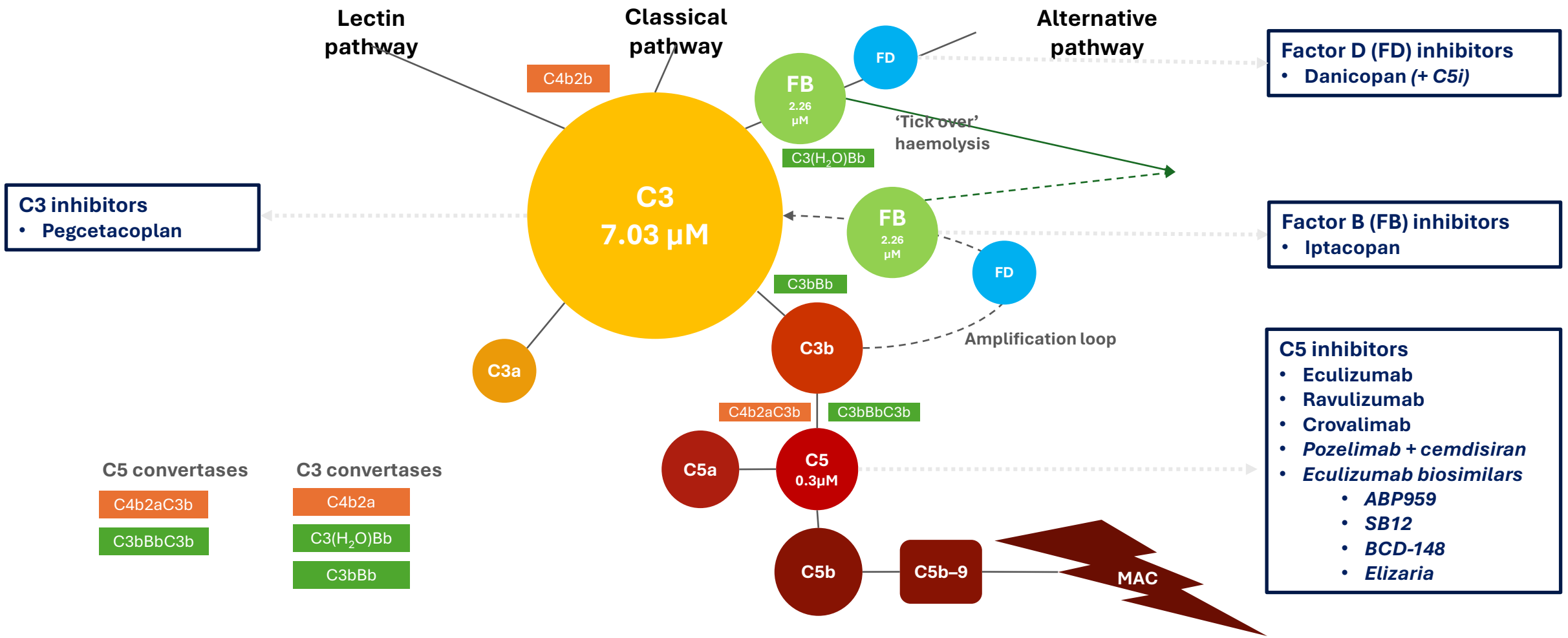



Image modified from: Kulasekararaj AG & Lazana I (2023) *Am J Hematol*

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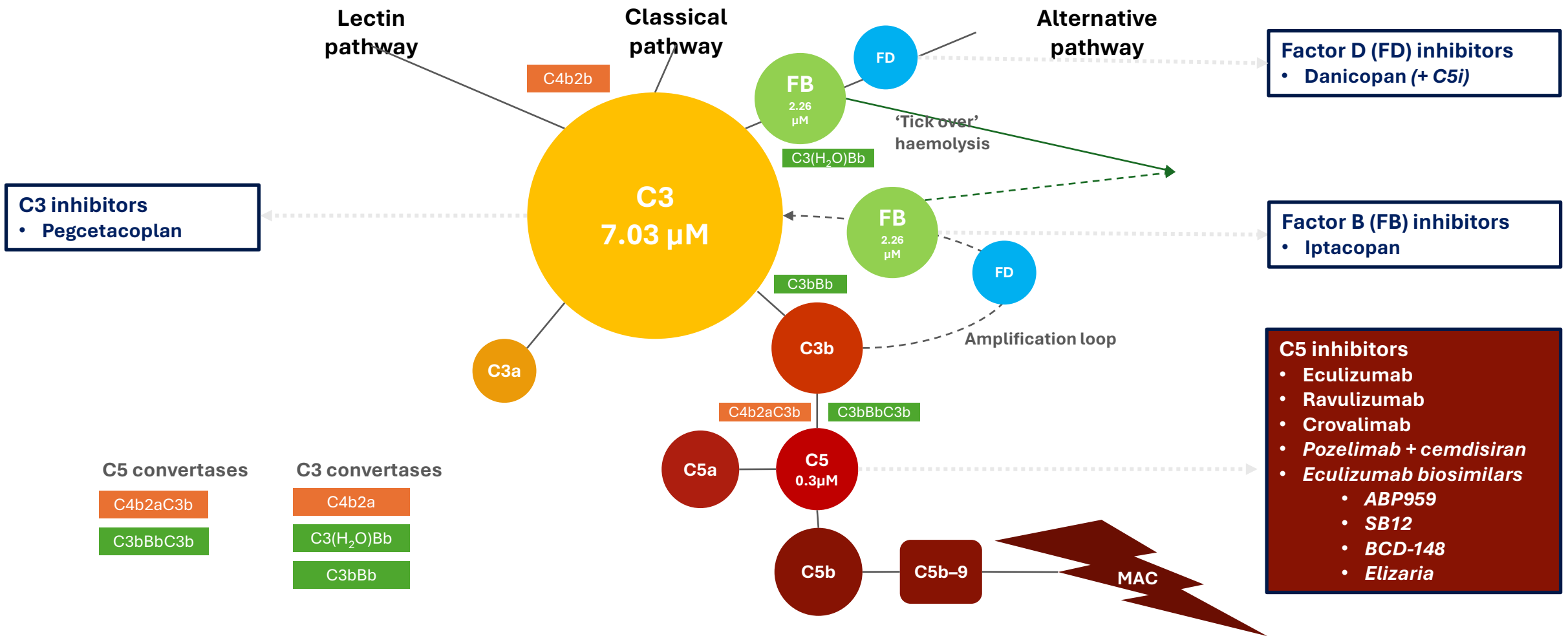


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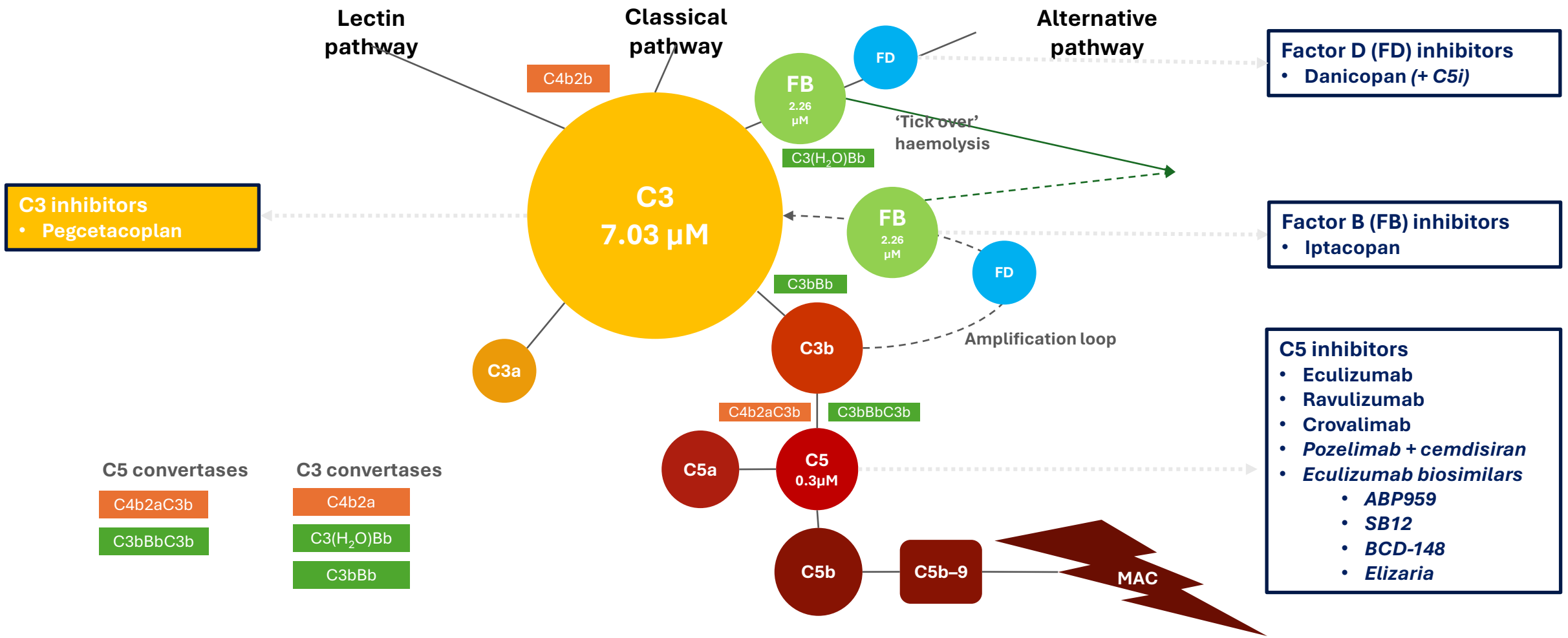


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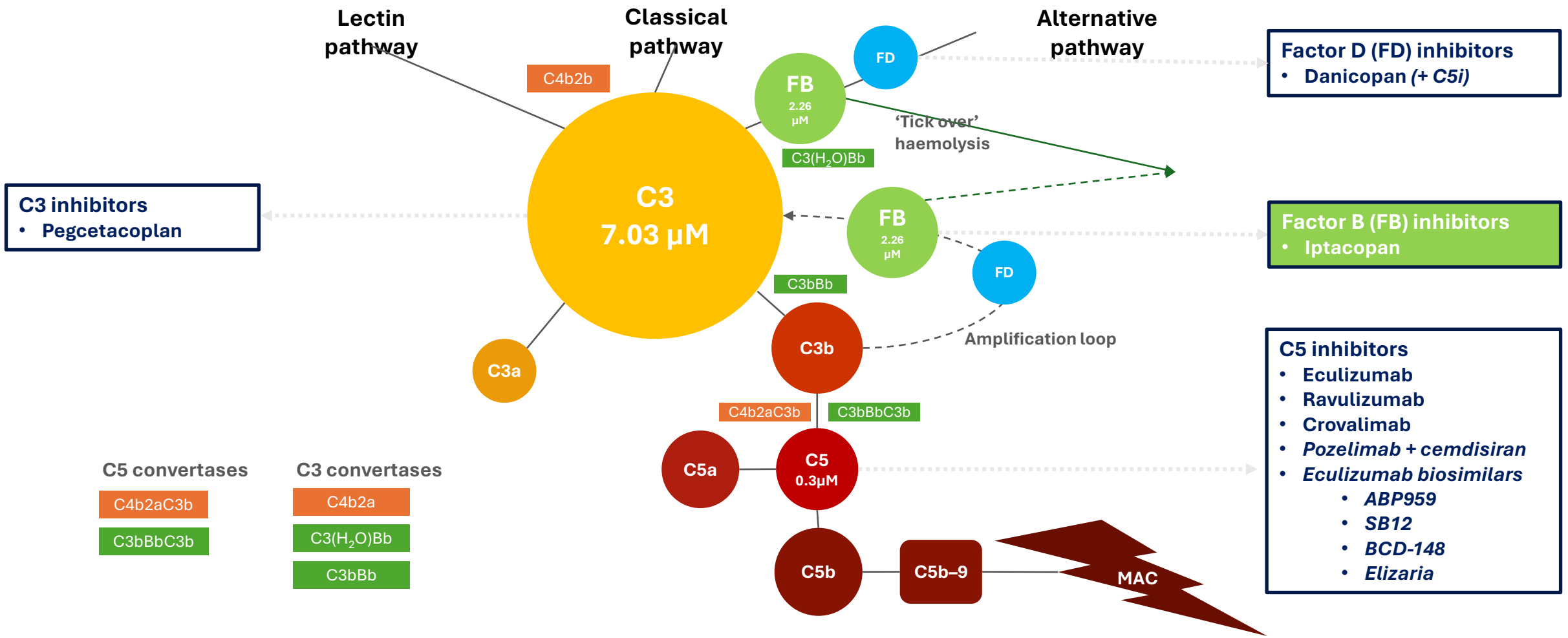


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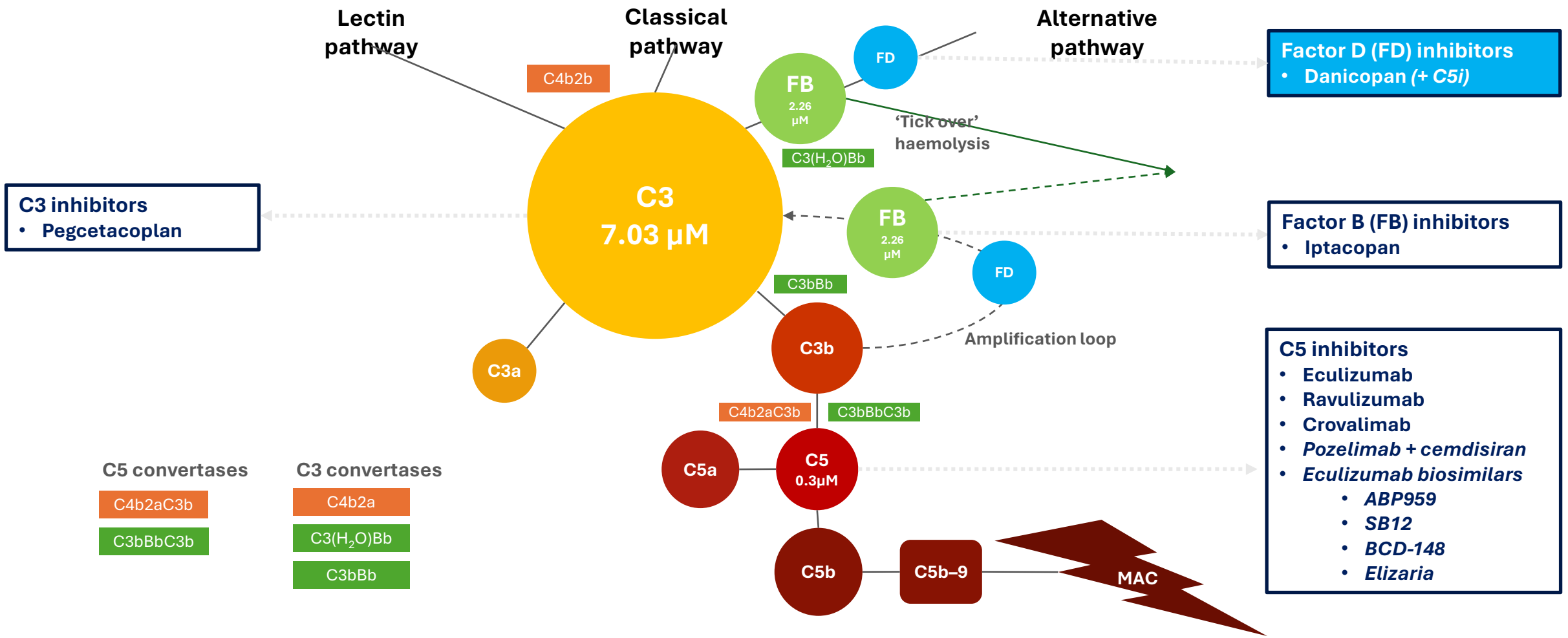


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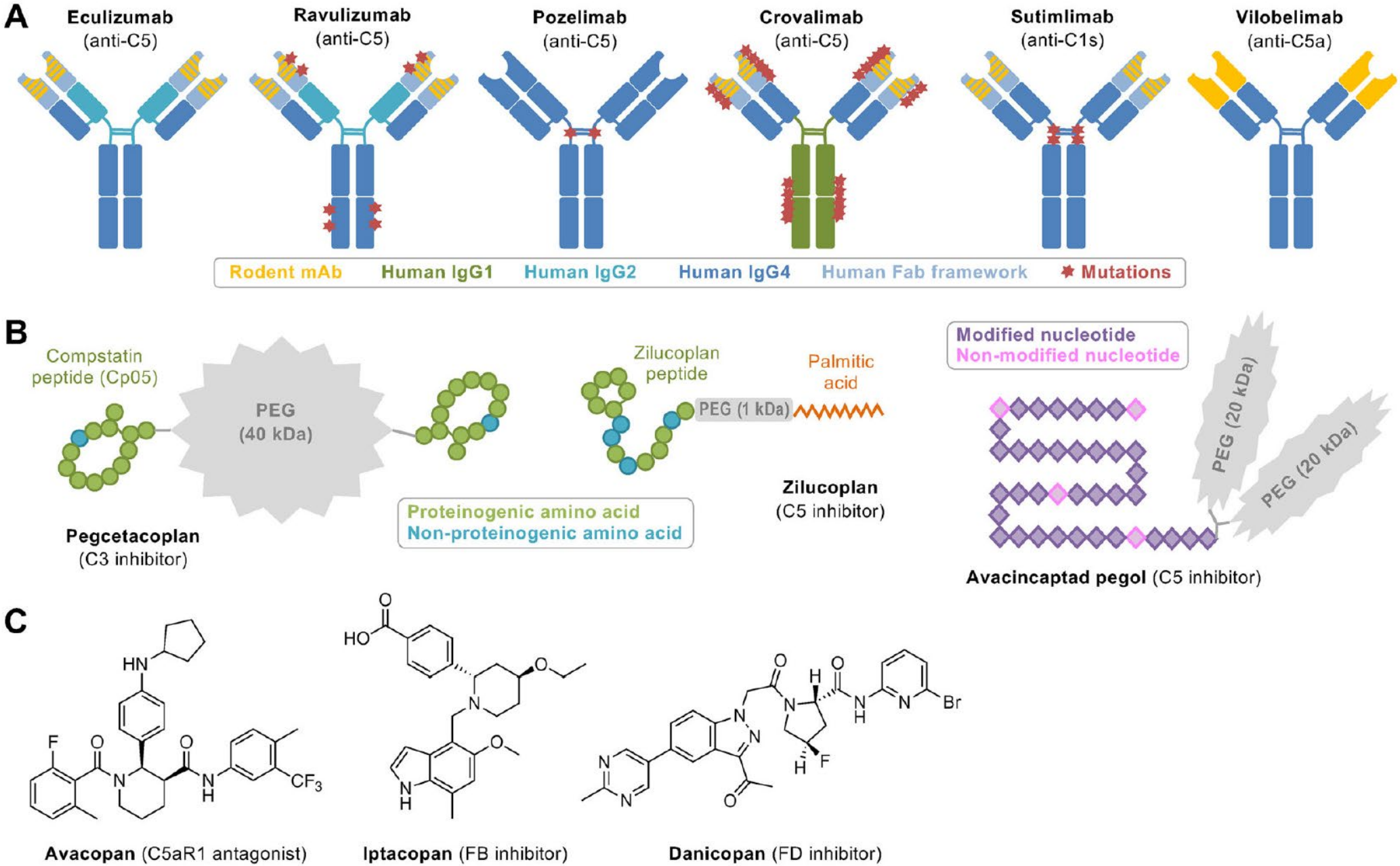
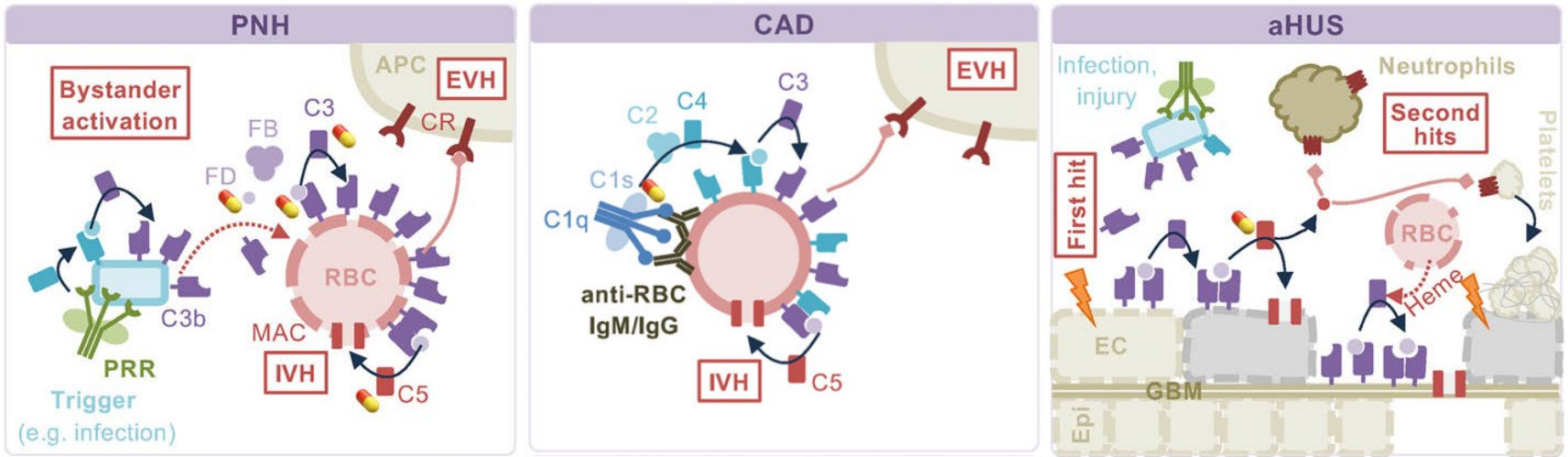
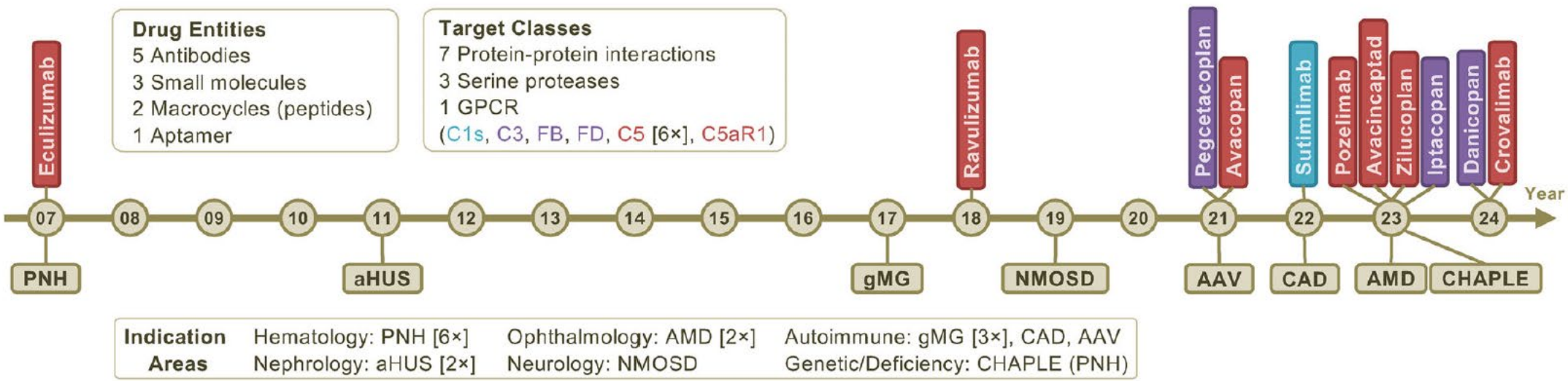



Ricklin D (2024) *Eur J Immunol*




***Not shown – wAIHA, APS, TA-TMA.***




Ricklin D (2024) *Eur J Immunol*

# Is *Everything* a Complement-Mediated Disease?!?

# Questions to Consider

1. Is complement dysfunction **central** to the pathophysiology?

**PNH *vs.* wAIHA**

2. Is the complementopathic process easily **druggable**?

**PNH *vs.* AMD**

3. Does therapeutic complement manipulation **improve outcomes**?

**PNH *vs.* CAD**

Modification of McLeod's Criteria

# Wrapping Up

# Complement 101 Conclusions

- Complement is not just for antimicrobial protection, but serves protean homeostatic functions
- Complementopathy contributes variably to many hematologic diseases (and that list is growing…)
- Therapeutic manipulation of complement is possible, generally safe, and effective in various diseases
- It's not *that* baffling, it's clearly not *irrelevant*, and it is important!

# SAVE THE DATE!

# TORONTO COMPLEMENT CONFERENCE SEPT 24-26, 2026

**Friday, September 25 to Saturday, September 26, 2026**
**In-person and hybrid registration available – *opening Spring 2026***
**Toronto, Ontario**

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# TCC Academy!

An exclusive webinar series for complement-curious scientists and clinicians

**First Webinar: Wednesday, December 17, 2025 | 12:00 – 1:30 p.m. (ET)**

Scan for more info and a link to register!

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# Thank you.

Comments? Questions?

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