Complement

Complement: History



Discovered in 1894 by Bordet

Paul Ehrlich coined the term "complement

It represents lytic activity of fresh serum

Its lytic activity destroyed when heated at 56C for 30 min

1. Fresh serum (ایمونیزه شده) + Vibrio cholera → lysis
2. Fresh serum (56 C for 30 min) + Vibrio cholera → No lysis

آنتی بادی ها در ۶۵ درجه سانتی گراد دناتوره می شوند بنابراین اصطلاح کمپلمان به معنای تقویت کننده عمل آنتی بادی ها است.

Complement Components

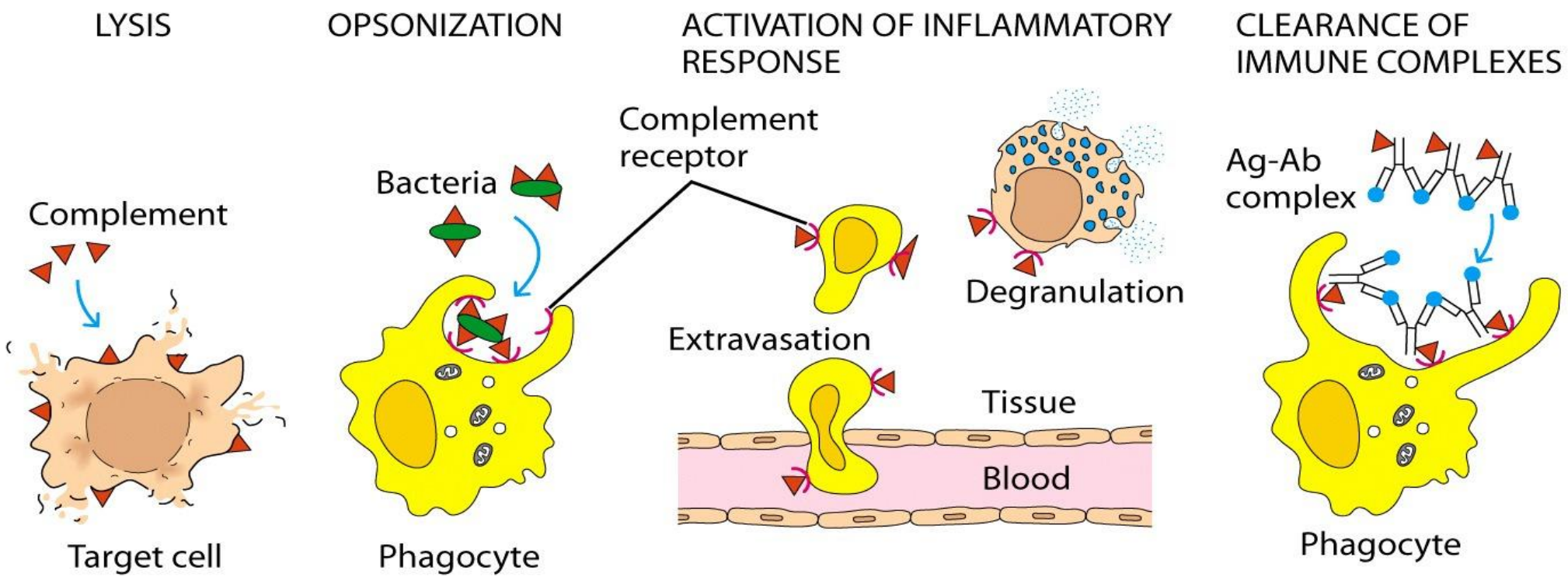
“Set of serum proteins that act in a cascade fashion to increase the immune response”

- Over 20 serum proteins (soluble) and 5 cell-bound (30 proteins)
- Cascade fashion
- Components designated: C1 – C9
- Proteolysis results in: Large fragments “b” and smaller fragments “a” C3a, C5b
- The **exception** is C2, where C2a is the large fragment and C2b is the smaller fragment and diffuses away

The Functions of Complement

- opsonization to enhance phagocytosis
- phagocyte attraction and activation
- lysis of bacteria and infected cells
- regulation of antibody responses
- clearance of immune complexes
- clearance of apoptotic cells
- Inflammation, anaphylaxis

The Functions of Complement



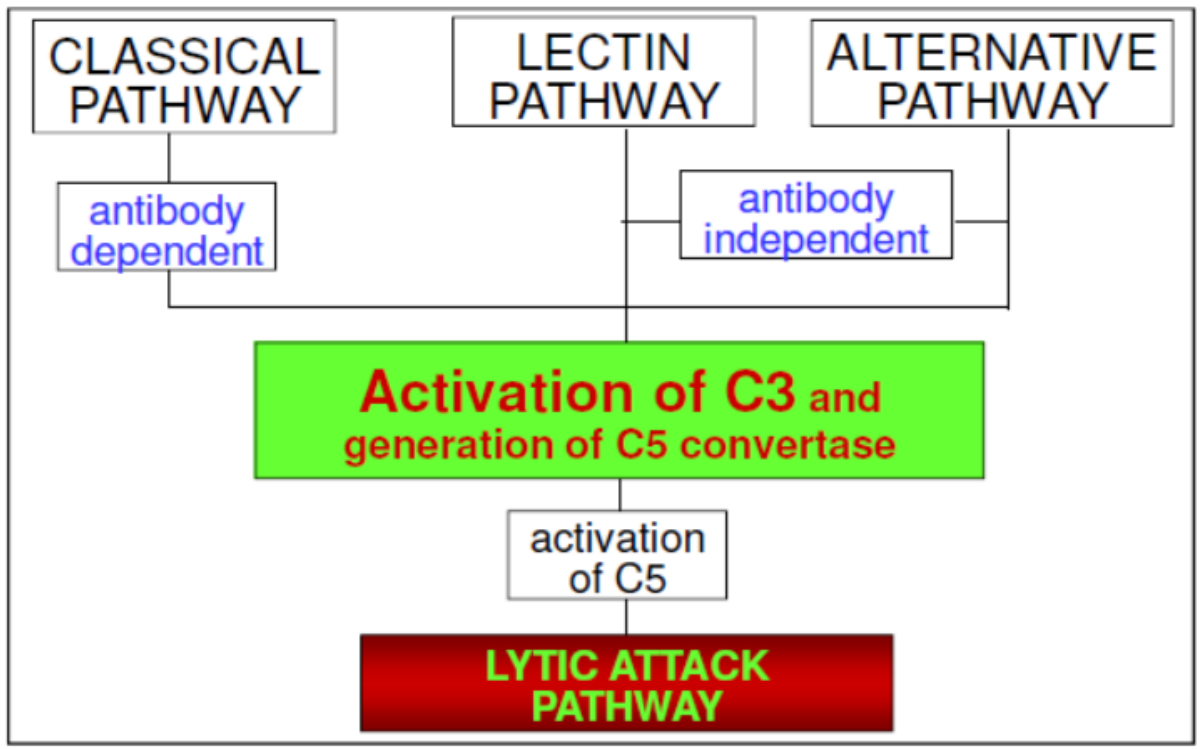
Pathways of complement activation

- 1) Classical Pathway – activated by antigen-antibody interaction. Best Ab for complement activation: IgM, IgG1, IgG2

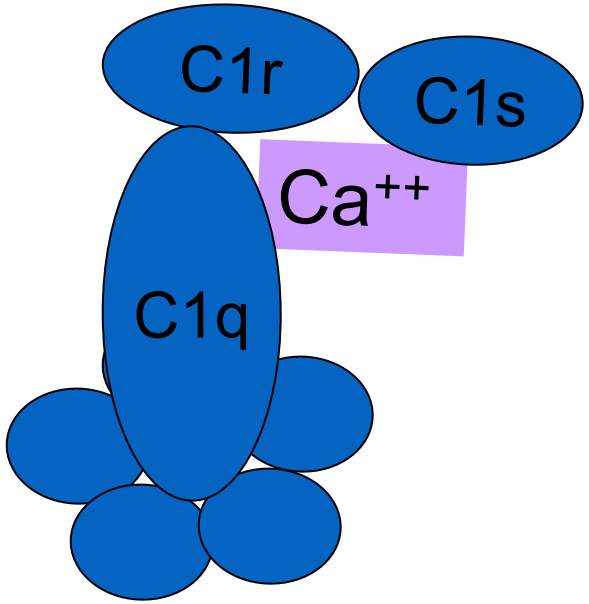
- 2) Alternative pathway – activated by C3b binding to microbial cell surfaces

- 3) Lectin pathway – binding of the mannose-binding lectin (MBL) to the surface of pathogens.

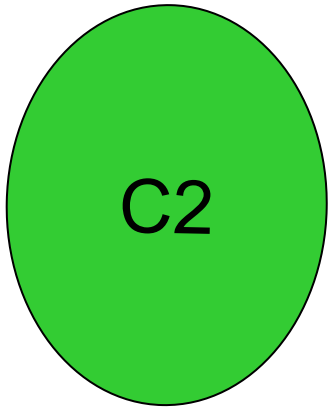
Pathways of complement activation

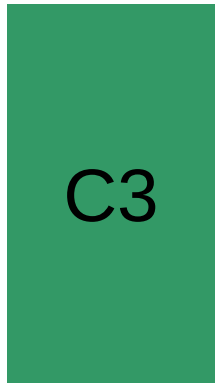


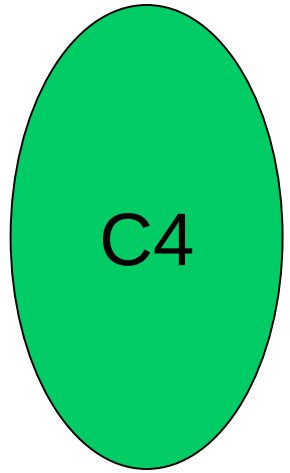
Components of the Classical Pathway

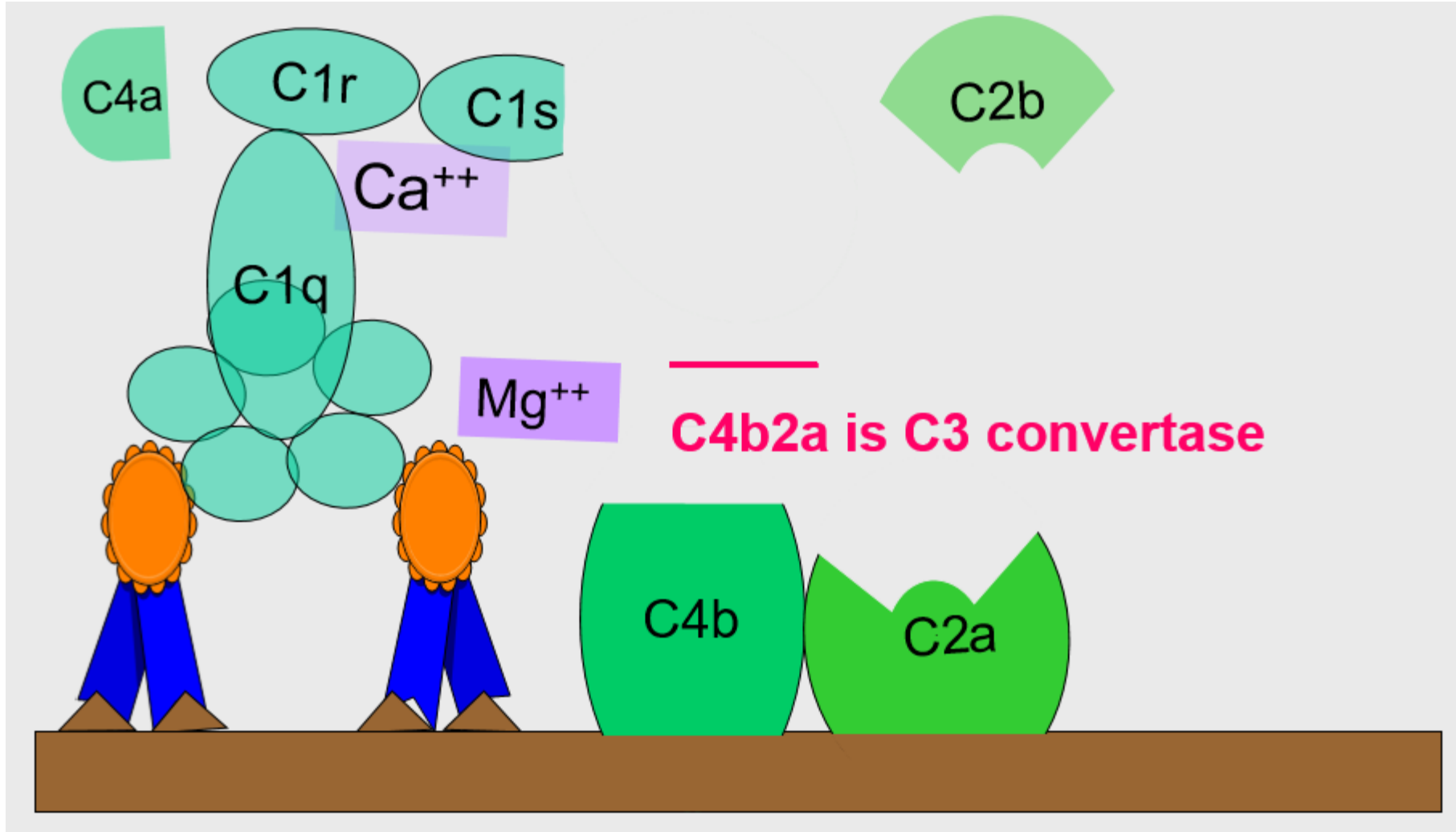


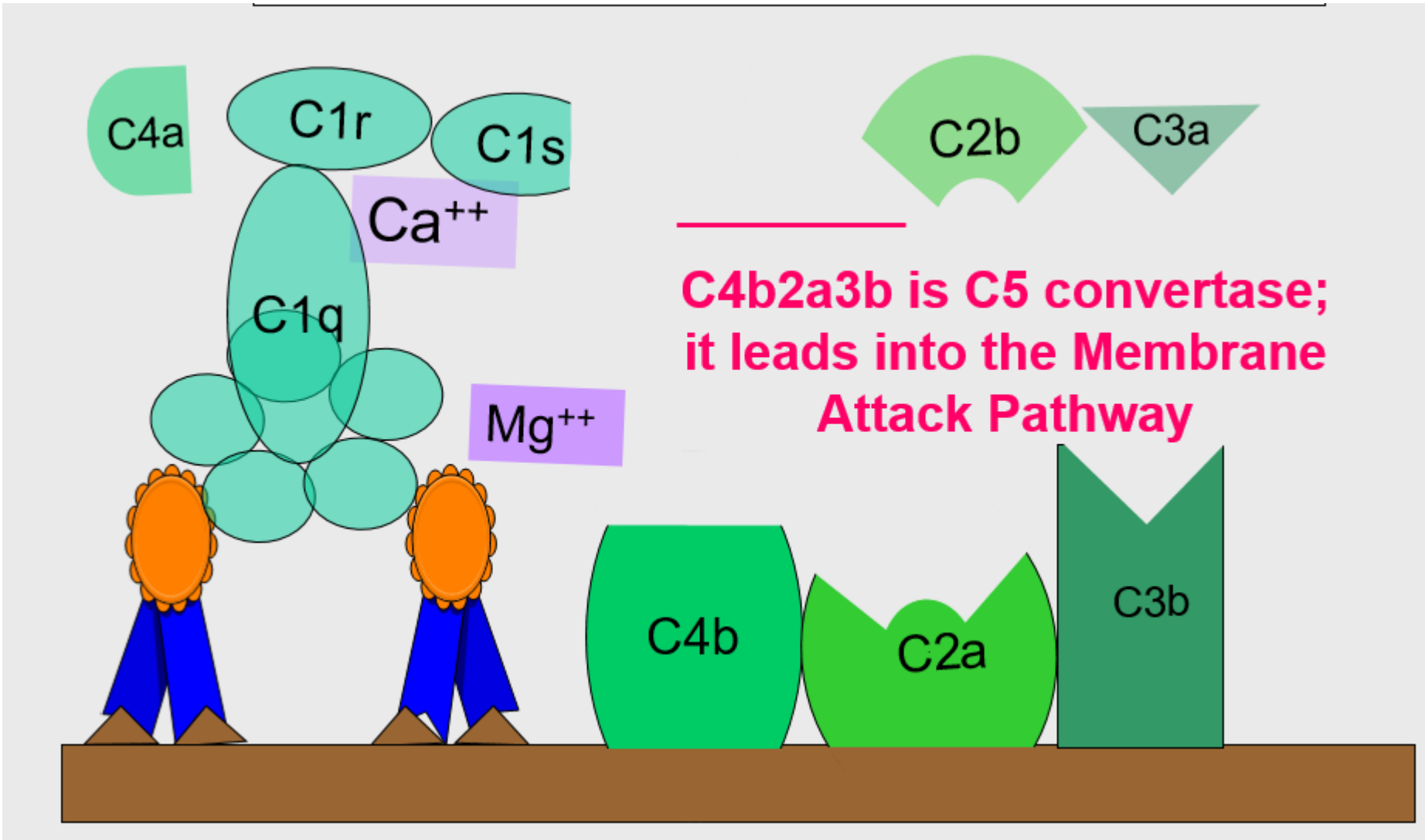
C1 complex



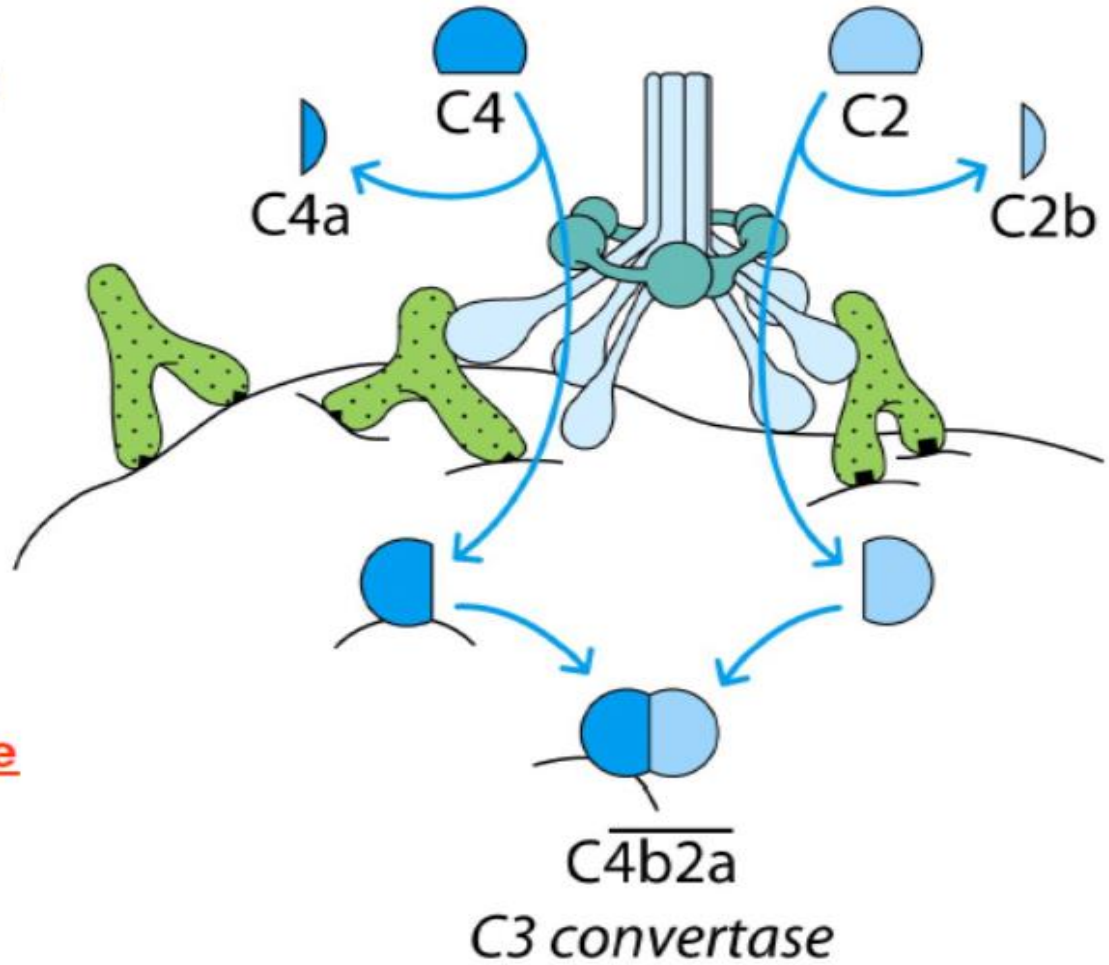




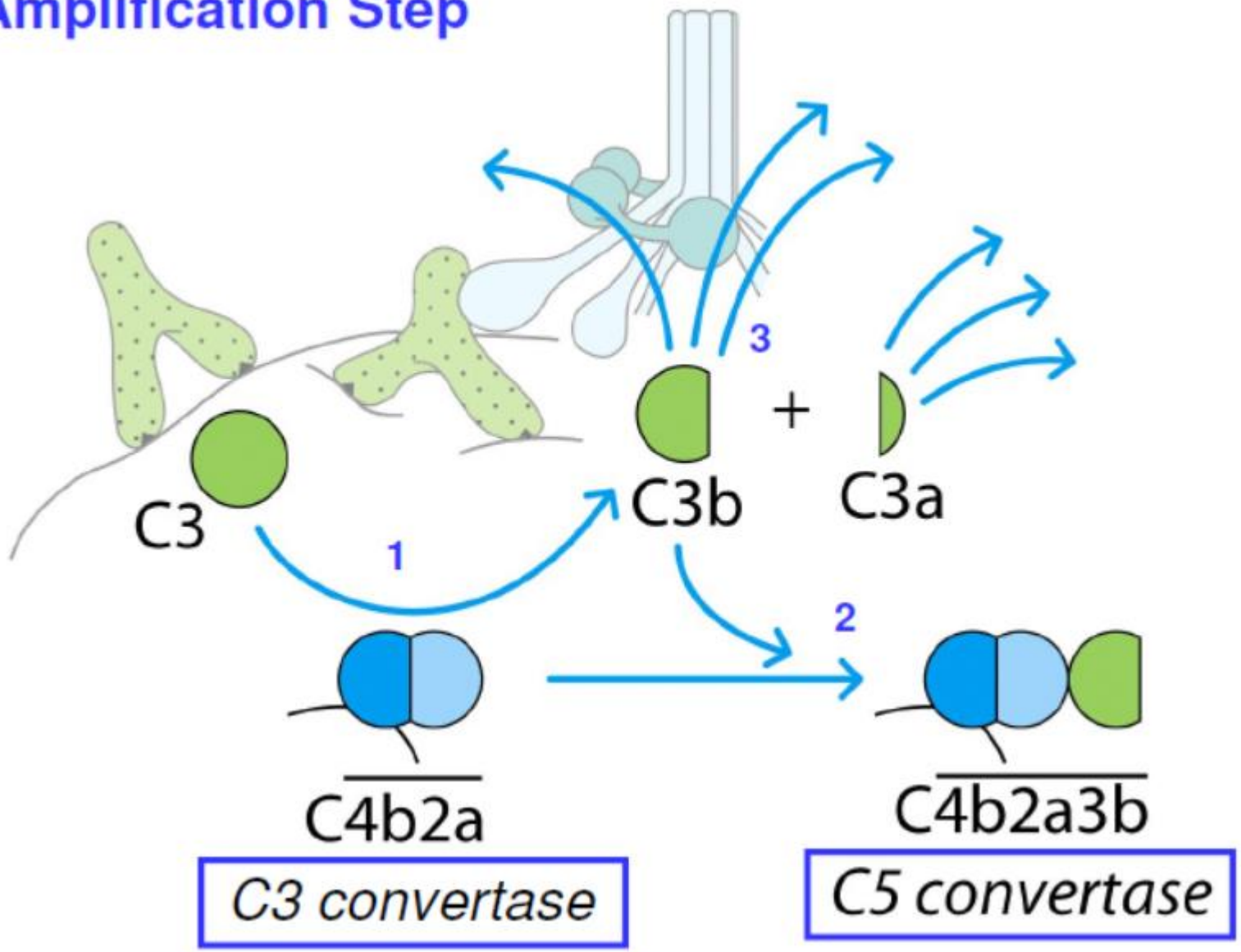

C4a
C1r
C1s
C2b
Ca++
C1q
Mg++
C4b2a is C3 convertase
C4b
C2a

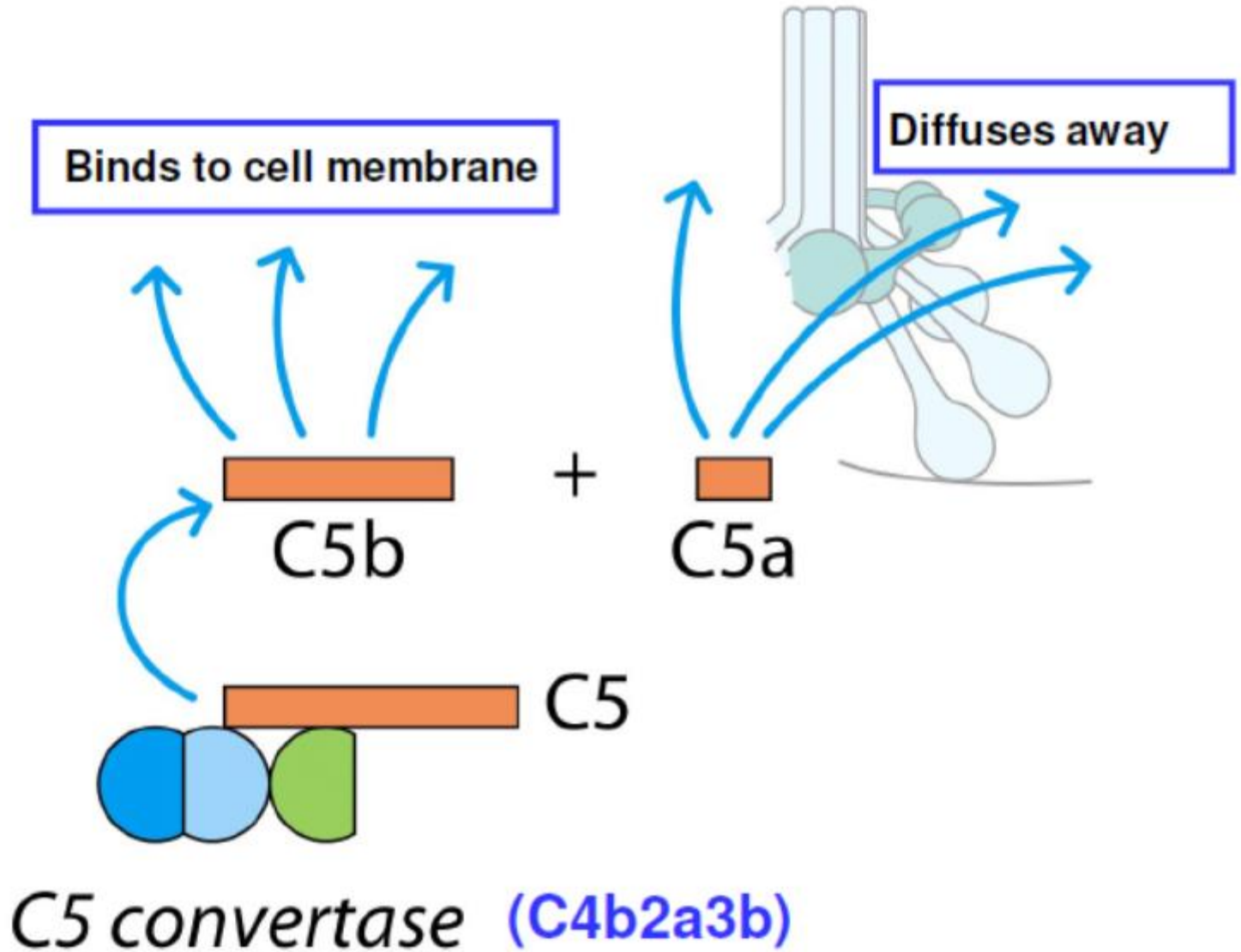

C4a
C1r
C1s
Ca++
C1q
Mg++
C2b
C3a
C4b2a3b is C5 convertase;
it leads into the Membrane
Attack Pathway
C4b
C2a
C3b

- C1complex (C1s) hydrolysis C4, resulting in C4a (small) and C4b. C4b binds to the cell surface
- C1 complex (C1s) hydrolysis C2 resulting in C2b (small) and C2a which binds to C4b to form the C3 convertase

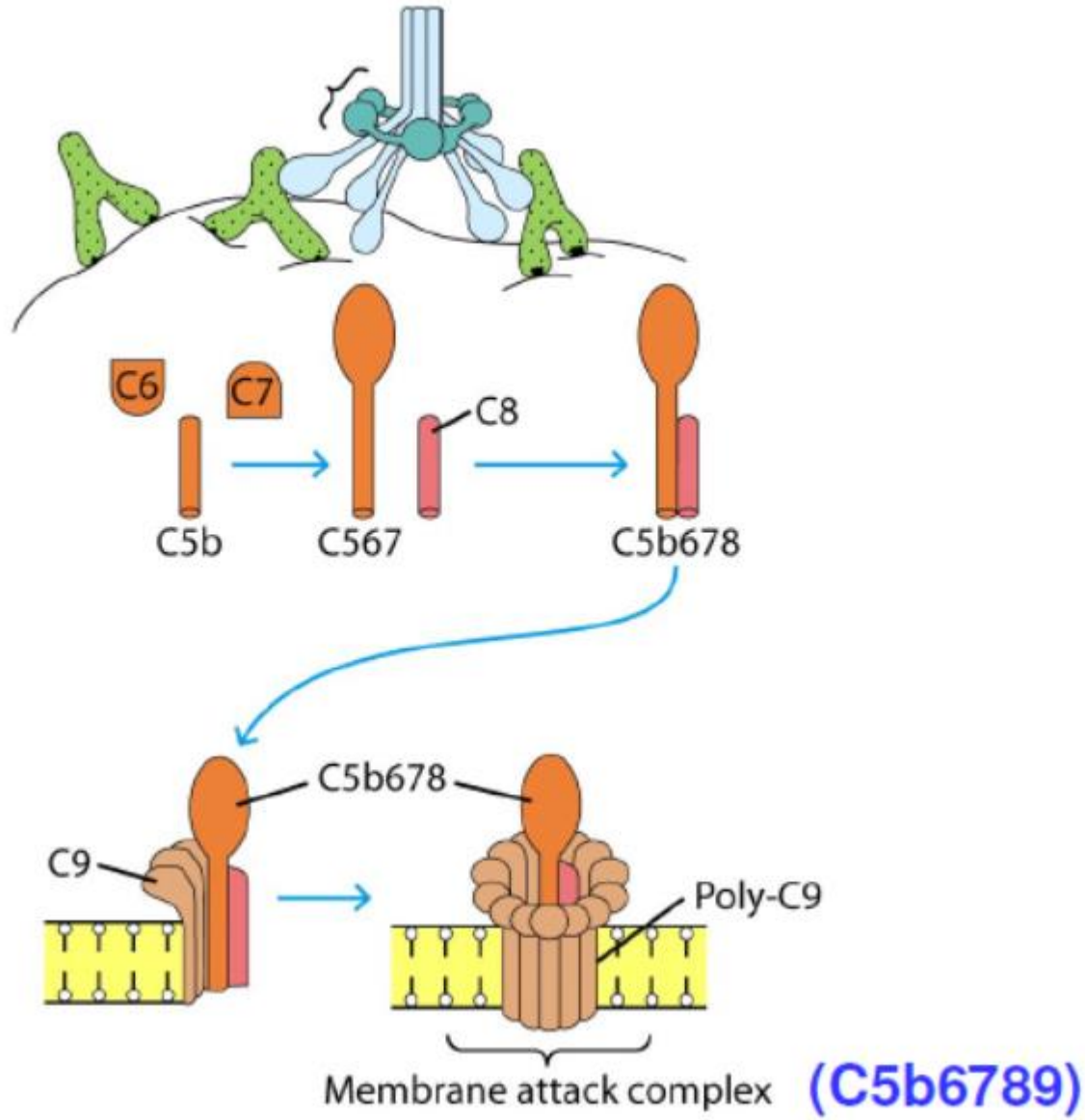


Amplification Step





C5 convertase **(C4b2a3b)**


C6
C7
C8
C5b
C567
C5b678
C5b678
C9
Poly-C9
Membrane attack complex
(C5b6789)

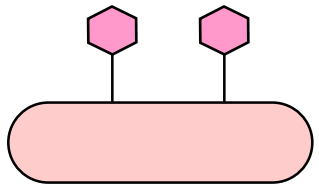
Biological Activities of Classical Pathway Components

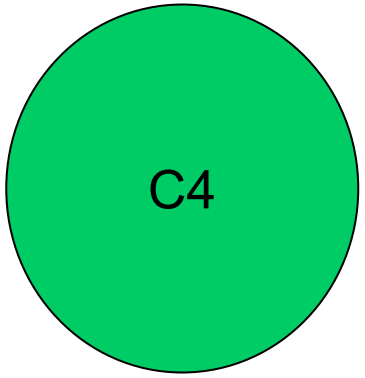
Component	Biological Activity
C2b	Prokinin; cleaved by plasmin to yield kinin, which results in edema
C3a	Anaphylotoxin; can activate basophils and mast cells to degranulate resulting in increased vascular permeability and contraction of smooth muscle cells, which may lead to anaphylaxis
C3b	Opsonin Activation of phagocytic cells
C4a	Anaphylaotoxin
C4b	Opsonin

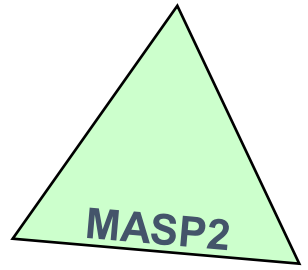
Control of Classical Pathway Components

Component	Regulation
All	C1-inhibitor (C1-INH); dissociates C1r and C1s from C1q
C3a	C3a-inactivator (C3a-INA; Carboxypeptidase B)
C3b	Factors H and I; Factor H facilitates the degradation of C3b by Factor I
C4a	C3a-INH
C4b	C4 binding protein (C4-BP) and Factor I; C4-BP facilitates degradation of C4b by Factor I; C4-BP also prevents the association of C2a with C4b thus blocking formation of C3 convertase

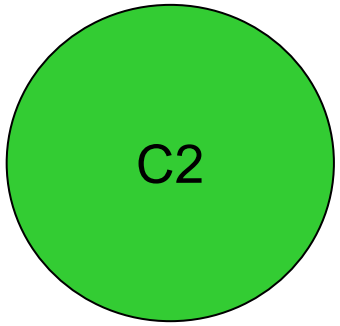
Components of mannose-binding lectin pathway

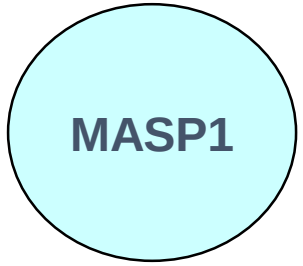




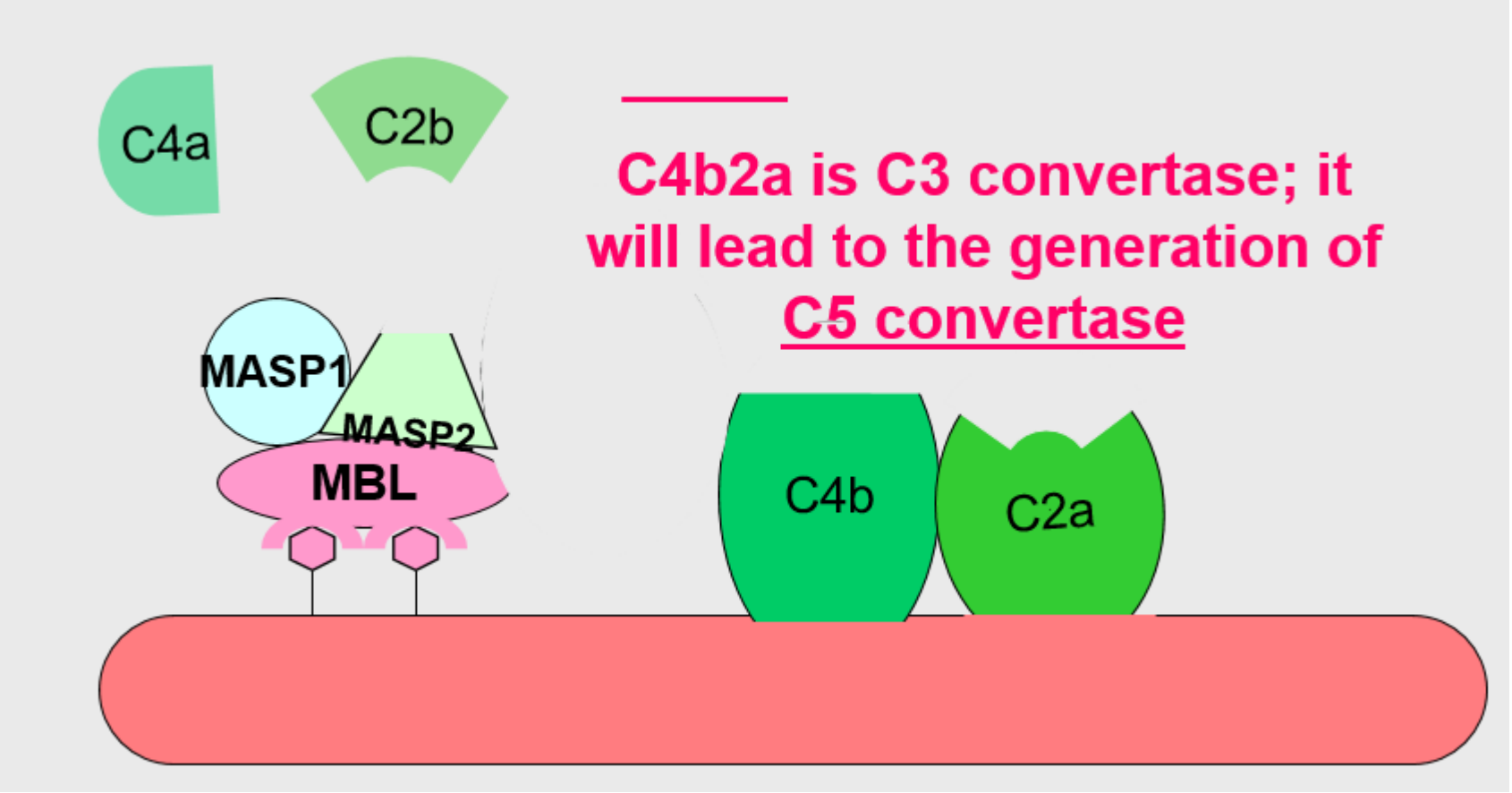








Mannose-binding lectin pathway



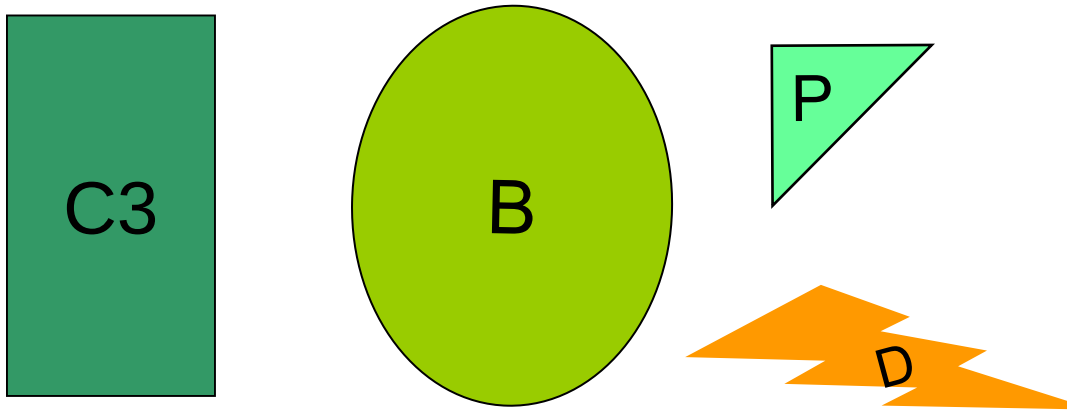
Lectin Pathway

- **Lectins** are carbohydrate-binding proteins
- Does not require antibody
- Recognizes mannose residues on glycoproteins
- The mannose-binding lectin **(MBL)** is an acute phase protein that increases during inflammation
- Plays a similar role to that of C1q
- After binding to mannose-residues on the cell surfaces, associates with MBL-associated serine proteases (**MASP-1** and **MASP-2**).
- This complex activates C4 and C2 just as in the classical pathway
- MASP-1 and MASP-2 very similar to **C1r** and **C1s**

Alternative Pathway

• Activated by microbial cell wall and cell wall components

Components of the alternative pathway

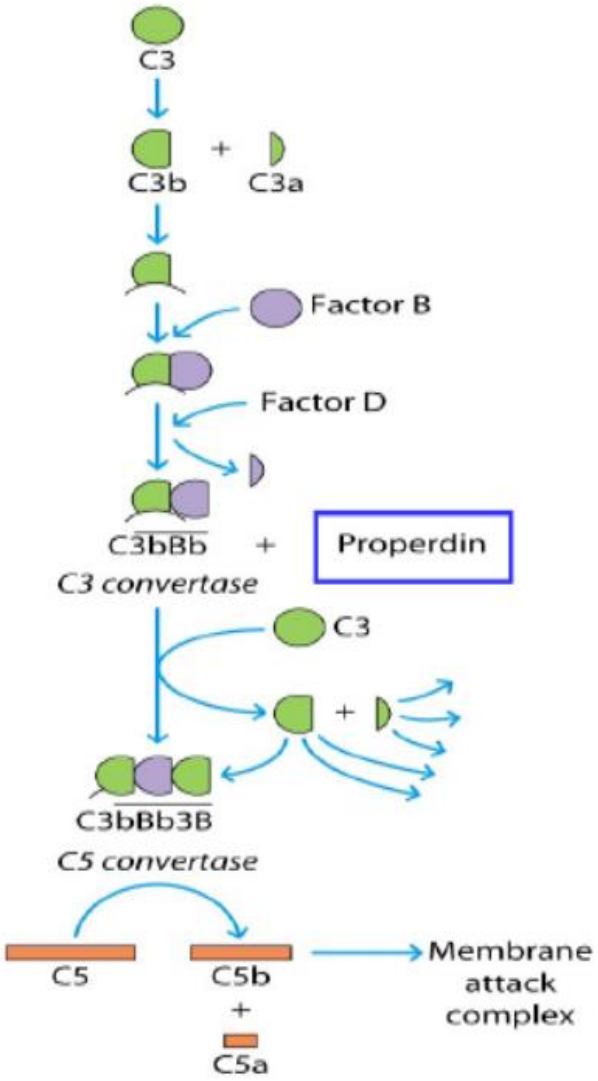


- C3b bound to cell surfaces is stabilized by Factor B

- Factor D is recruited and acts on Factor B to generate a large (Bb) and small fragment (Ba)

- C3bBb is the C3 convertase

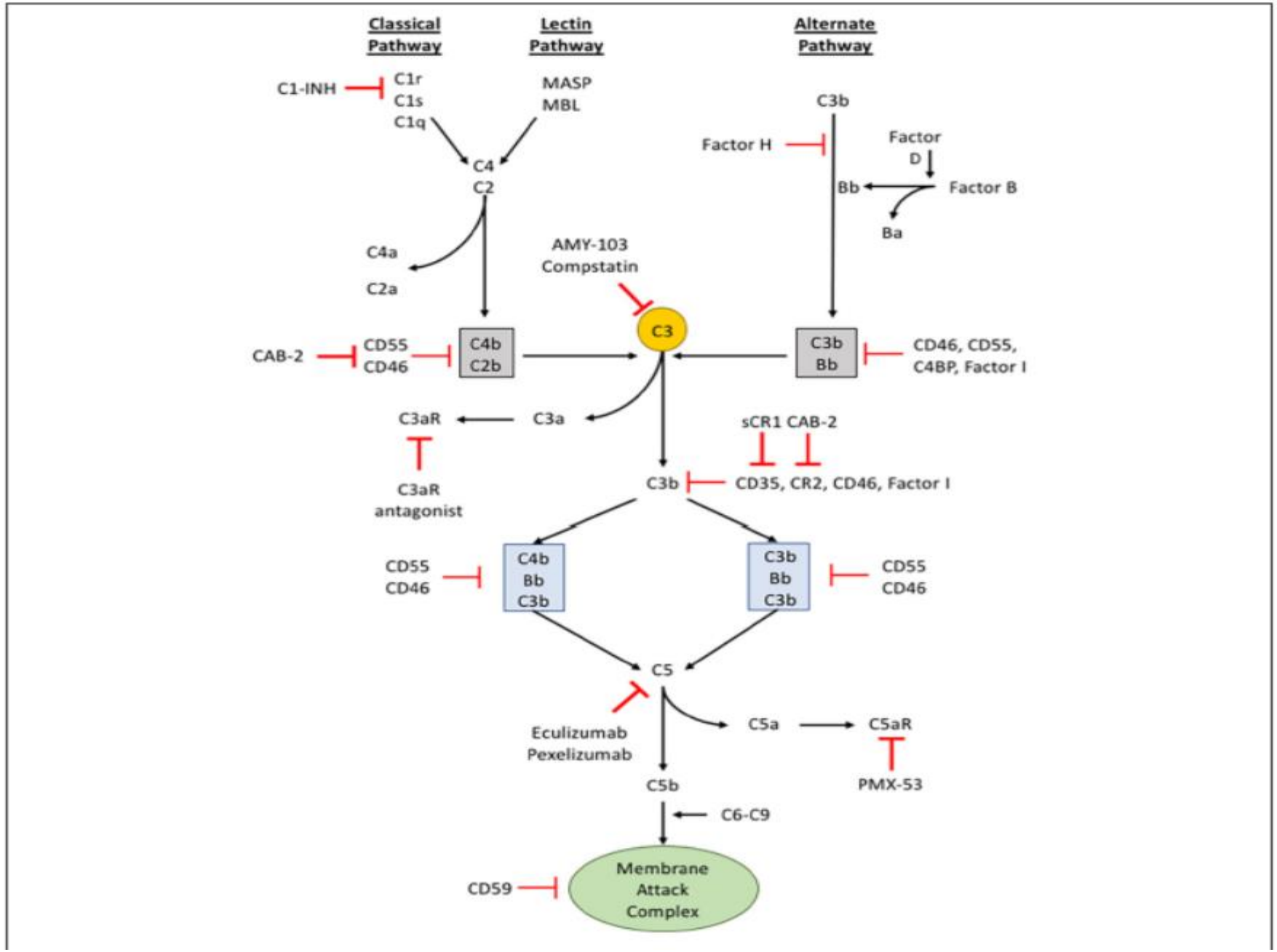
- Properdin (small protein) stabilizes the C3 convertase



Regulation of Complement

TABLE 13-2 Proteins that regulate the complement system

Protein	Type of protein	Pathway affected	Immunologic function
C1 inhibitor (C1Inh)	Soluble	Classical	Serine protease inhibitor: causes $C1r_2s_2$ to dissociate from C1q
C4b-binding protein (C4bBP)*	Soluble	Classical and lectin	Blocks formation of C3 convertase by binding C4b; cofactor for cleavage of C4b by factor I
Factor H*	Soluble	Alternative	Blocks formation of C3 convertase by binding C3b; cofactor for cleavage of C3b by factor I
Complement-receptor type 1 (CR1)*	Membrane bound	Classical, alternative, and lectin	Block formation of C3 convertase by binding C4b or C3b; cofactor for factor I-catalyzed cleavage of C4b or C3b C3bBb
Membrane-cofactor protein (MCP)*			
Decay-accelerating factor (DAE or CD55)*	Membrane bound	Classical, alternative, and lectin	Accelerates dissociation of $C4\overline{b2a}$ and $C3\overline{bBb}$ (classical and alternative C3 convertases)


Classical Pathway
Lectin Pathway
Alternate Pathway
C1-INH
C1r
C1s
C1q
MASP
MBL
C3b
Factor H
Factor D
Bb
Factor B
Ba
C4
C2
C4a
C2a
AMY-103
Compstatin
C3
CAB-2
CD55
CD46
C4b
C2b
C3b
Bb
CD46, CD55, C4BP, Factor I
C3aR
C3a
sCR1
CAB-2
C3aR antagonist
C3b
CD35, CR2, CD46, Factor I
CD55
CD46
C4b
Bb
C3b
C3b
Bb
C3b
CD55
CD46
C5
Eculizumab
Pexelizumab
C5a
C5aR
PMX-53
C5b
C6-C9
CD59
Membrane Attack Complex