Humoral immunity

Complement system

Complement system

- Humoral component of non-specific immune response
- Discovered by Border in 1894

- Represented by ability of serum to kill bacteria
- This lytic activity is destroyed by heating the serum at 56˚ C for 30 min

Main functions of Complement

- Opsonization
- Phagocyte attraction and activation
- Lysis of bacteria and infected cells
- Regulation of antibody response
- Clearance of immune complexes
- Clearance of apoptotic cell

- Too much activity is not good

Components of Complement

- C1 (qrs), C2, C3, C4, C5, C6, C7, C8, C9
- Factors – B, D, H, I and Properdin (P)
- Mannonse binding lectin (MBL), and MBL associated serine proteases (MASP1, MASP2)
- C1 inhibitor (C1-INH), C4-binding protein (C4-BP), Decay accelerating factor (DAF), Complement receptor 1 (CR1),…..

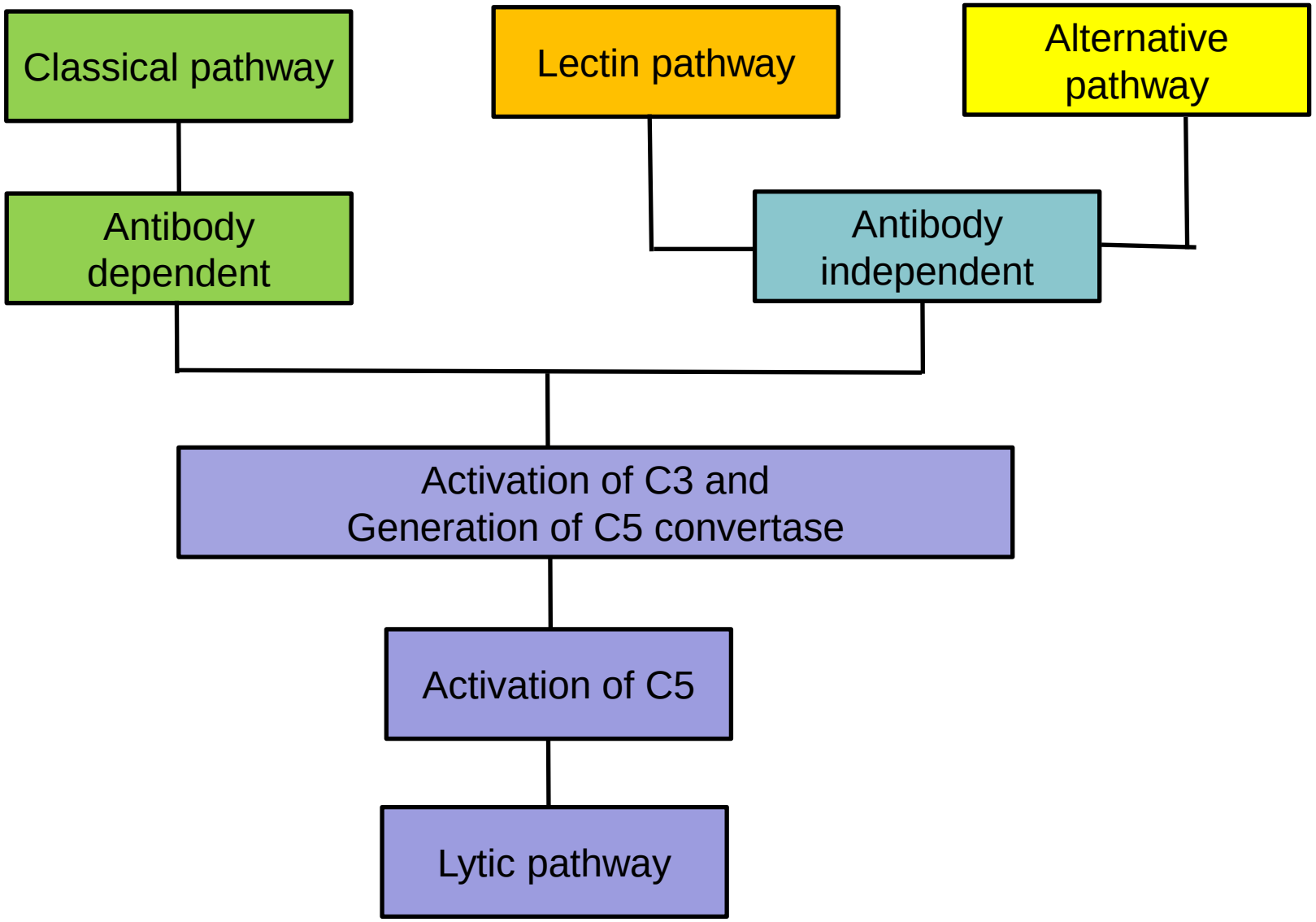
Definitions

- C-activation – alteration of C protein in such a way that it interacts with next component
- C-fixation – utilization of C by Ag-Ab complex
- Hemolytic units (CH50) – dilution of serum which can lyse 50% of standard suspension of Ab-coated RBC
- C-inactivation – denaturation (by heat generally) of an early component resulting in loss of hemolytic activity
- Convertase – altered C-protien that can act as proteolytic enzyme for another component
    - Ex : C3 convertase, C5 convertase

Nomenclature

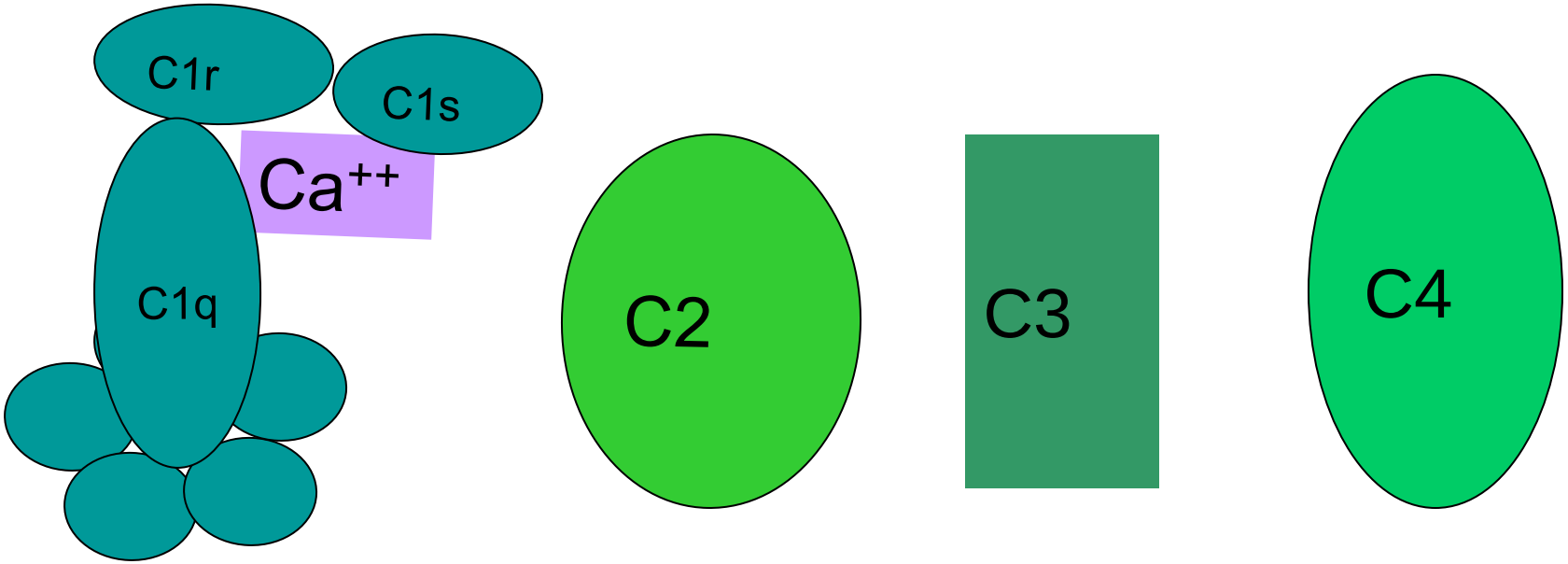
- Activated components are generally over-lined
  - $C1\overline{qrs}$
- When activated C proteins are generally cleaved. The larger moiety binds to the activation complex and the smaller component is released in to environment around it
- Letter “b” is usually added to the larger component and letter “a” is added to the small component
  - $C3 \longrightarrow$ C3b and C3a
- Except C2 – the larger component is “a” and smaller is “a”

Pathways of complement



Classical pathway

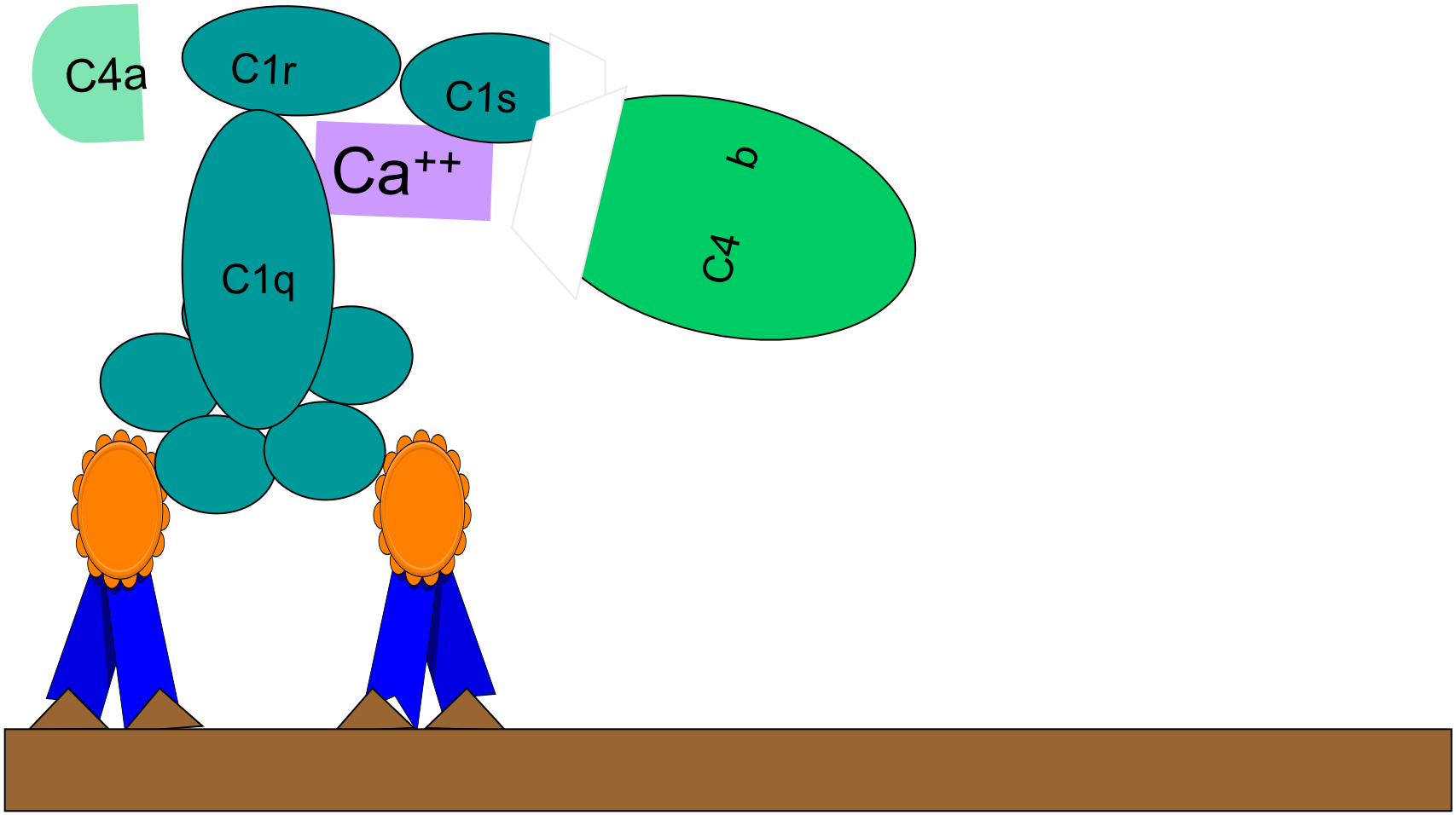
- Components of classical pathway



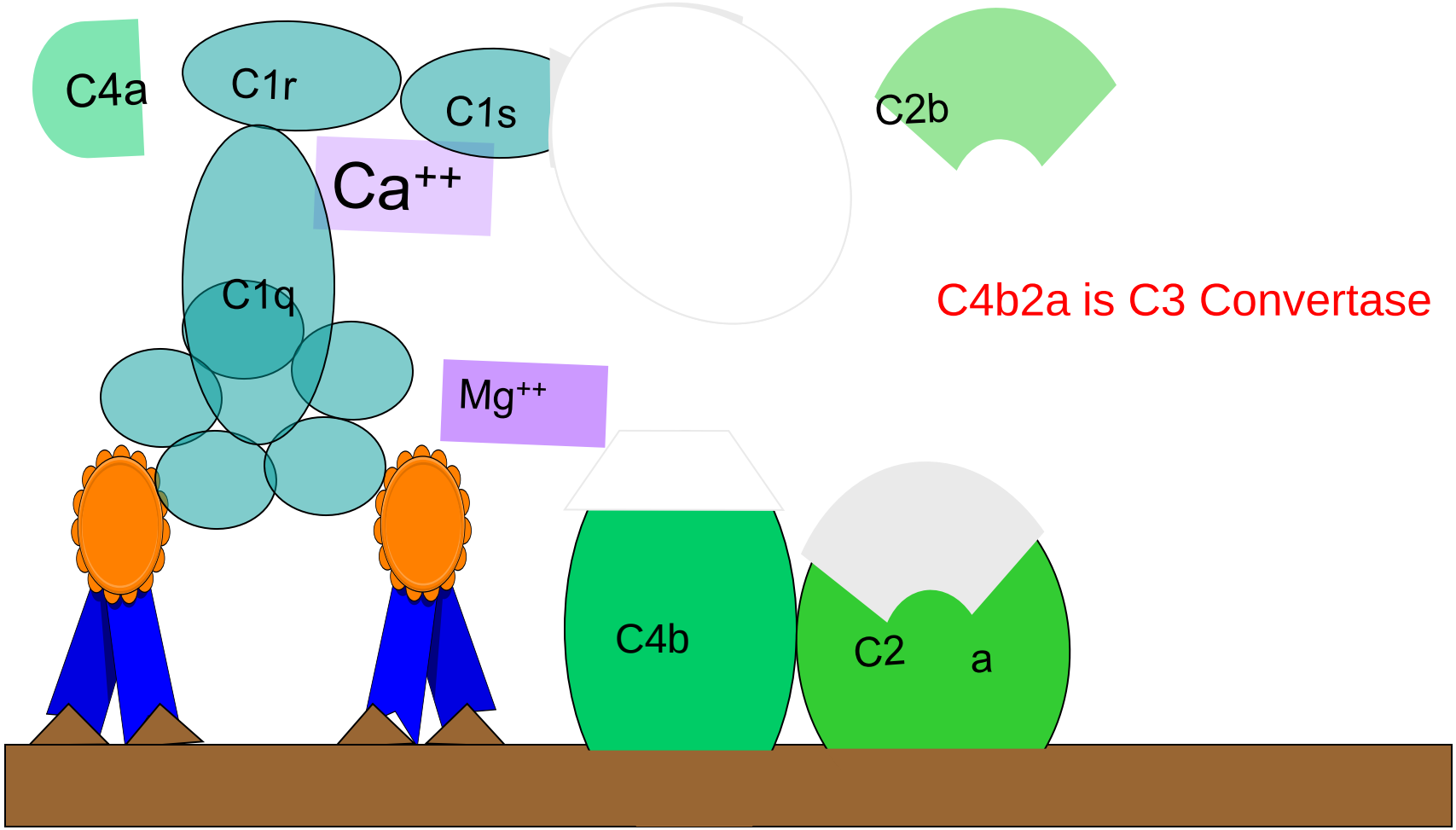
Classical pathway

- Starts with Ag-Ab complex
- Ag-Ab complex binds to C1qrs which is Ca^{++} dependent
- This results in proteolytic activity of C1r and cuts C1s
- Now this is $C1\overline{qrs}$
- $C1\overline{qrs}$ cleaves C4 in to C4a and C4b
- C4b binds to bacterial surface
- $C1\overline{qrs}$ also cuts C2 in to C2a and C2b
- C2a associates with C4b
- C4b2a is C3 convertase, this will act on C3
- C3 will be converted in to C3a and C3b
- C3b binds to bacteria
- Now this complex C4b2a3b is C5 convertase of classical pathway

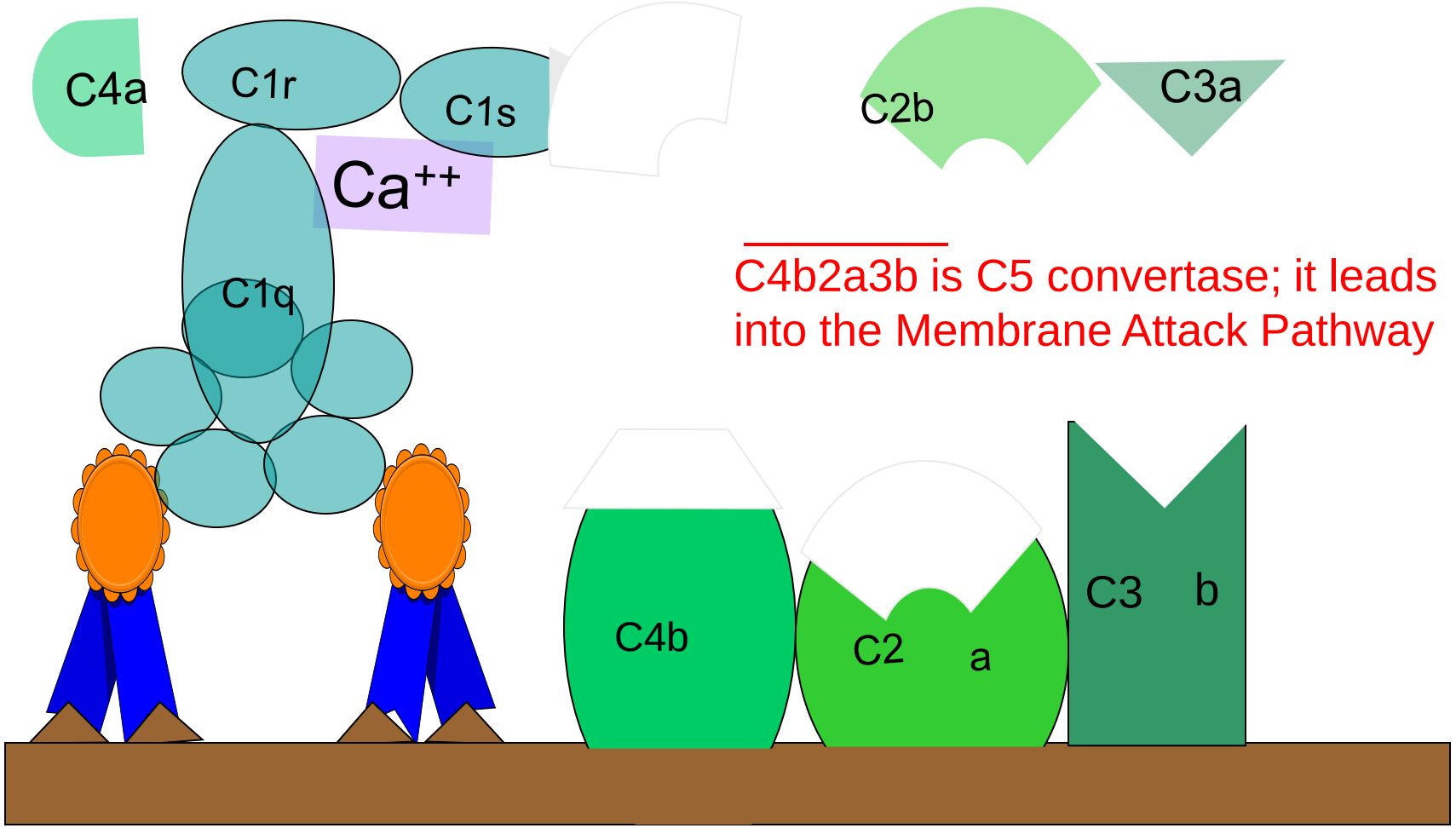
Classical pathway



Classical pathway



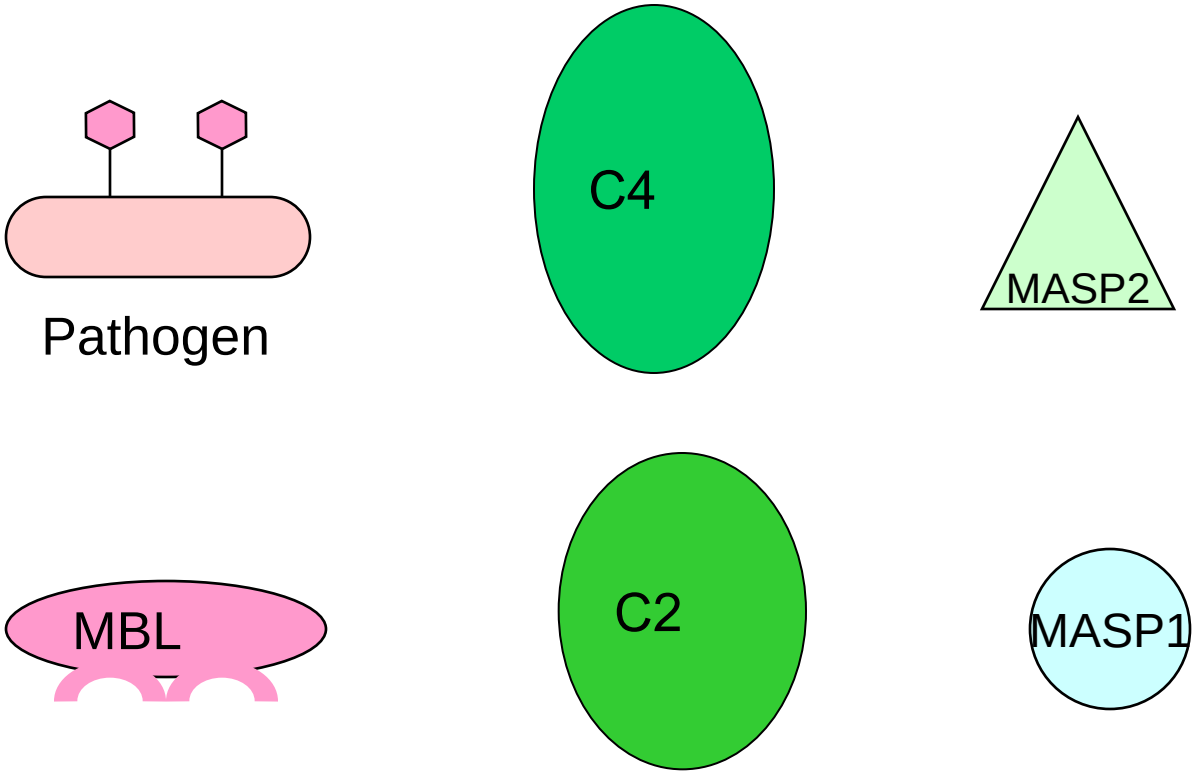
Classical pathway



$\overline{C4b2a3b}$ is C5 convertase; it leads into the Membrane Attack Pathway

Lectin pathway

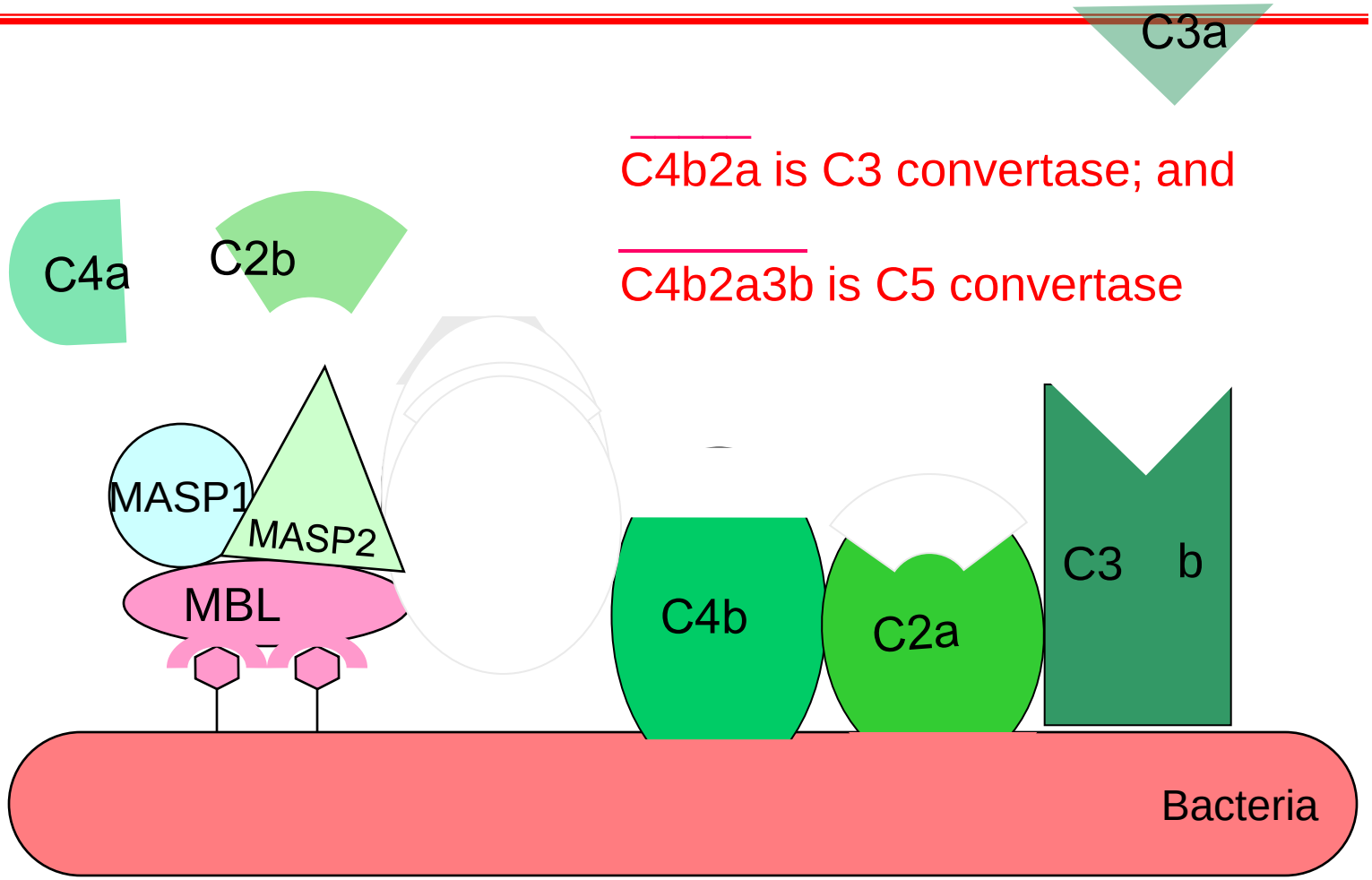
- Components of lectin pathway



Lectin pathway

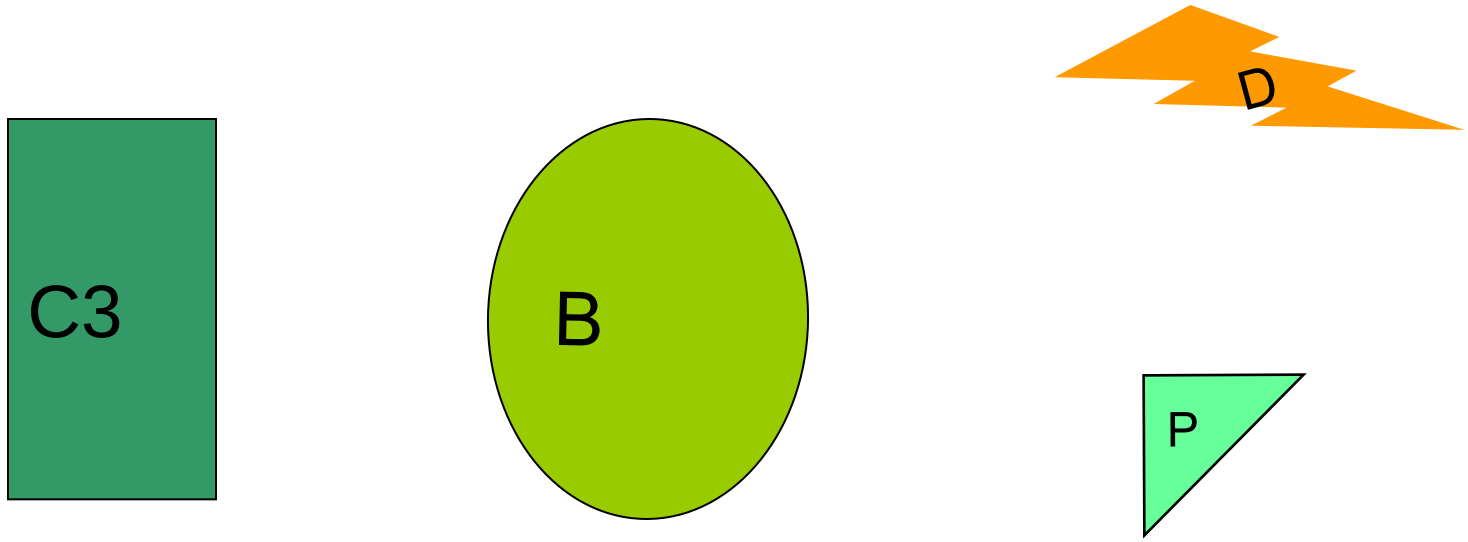
- Starts with bacteria containing mannose
- MBL binds to mannose
- This will recruit MASP1 and MASP2 to MBL
- This results in activation of MASP2
- This is analogous to C1qrs of classical pathway
- Rest of the sequences are similar to classical pathway

Lectin pathway



Alternative pathway

- Components of Alternative pathway



Alternative pathway

- Starts with C3
- C3 is susceptible to spontaneous hydrolysis and will be converted in to C3i
- C3i binds factor B
- This makes factor B susceptible to factor D and cleaves factor B. This forms C3iBb complex
- C3iBb can bind free C3 and cleaves it to form C3b
- C3b binds factor B which makes it susceptible to factor D and factor B gets cleaved forming C3bBb
- C3bBb can bind more C3 to produce C3b
- This can form loop which can go continuously
- This can lead to usage of all C3 present

Alternative pathway

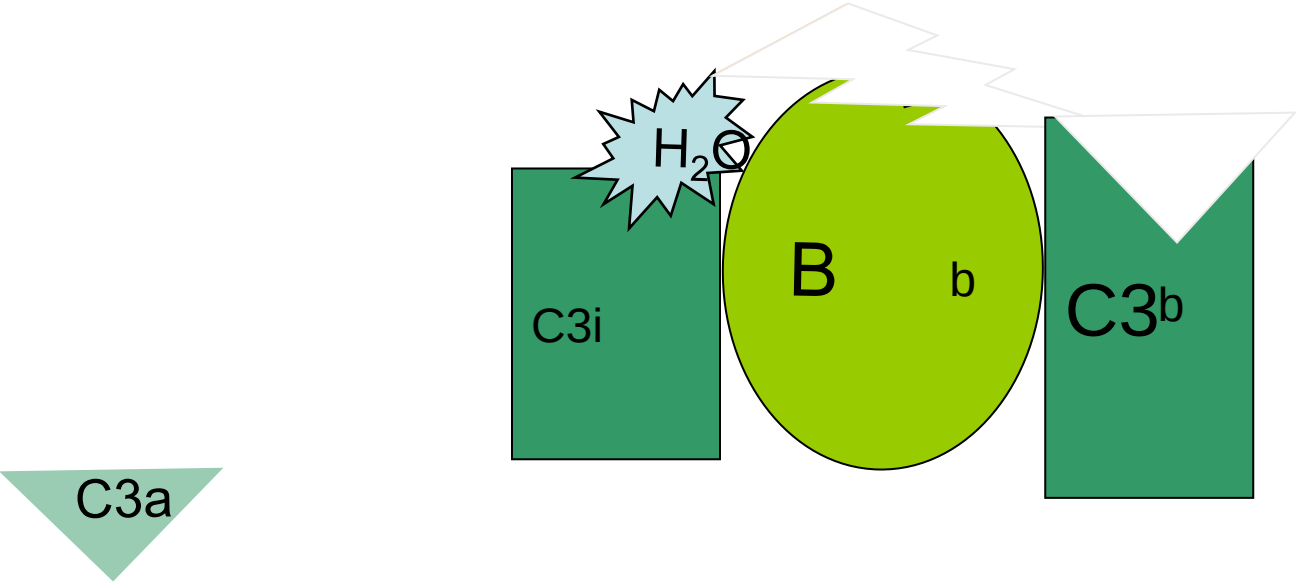
- This loop is controlled by Decay Accelerating Factor (DAF) which prevents binding of factor Bb to C3b. DAF also disassociates already formed complex also
- In addition factor I can also degrade C3b
- Also factor H can dissociate C3bBb complex making C3b more susceptible to factor I
- Stabilization of C3b…..
  - There is a special factor which binds to C3bBb complex.
  - This factor is called Properdin factor (factor P)
  - Alternative pathway can also be called properdin pathway

Alternative pathway

- Properdin bound C3bBb and recruit free C3 and converts it in to C3b resulting in the formation of C3bBbC3b. This is C5 convertase of alternative pathway

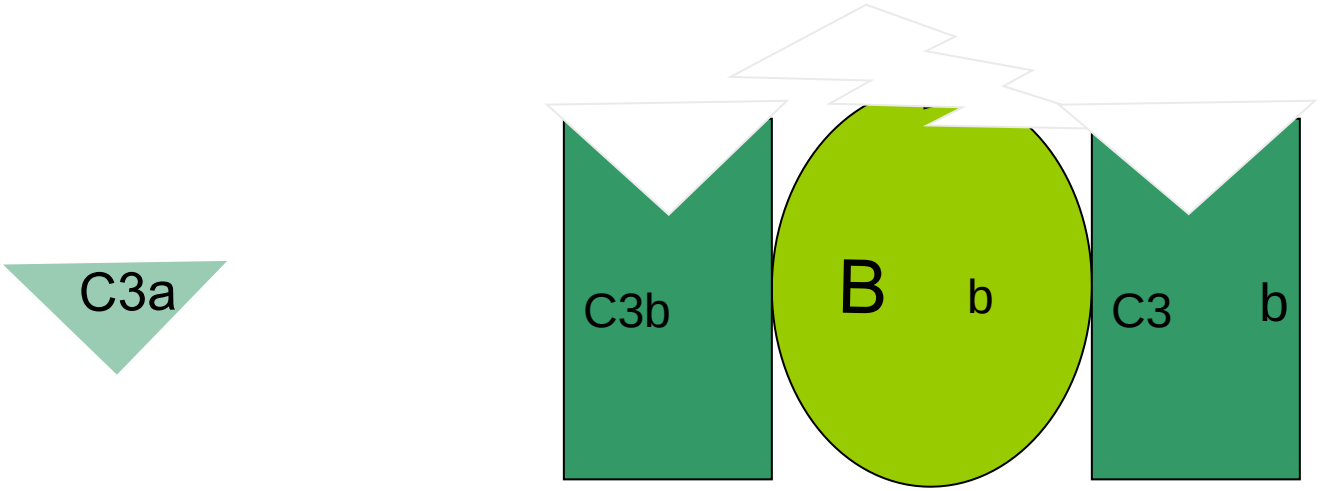
Alternative pathway

- Spontaneous C3 activation



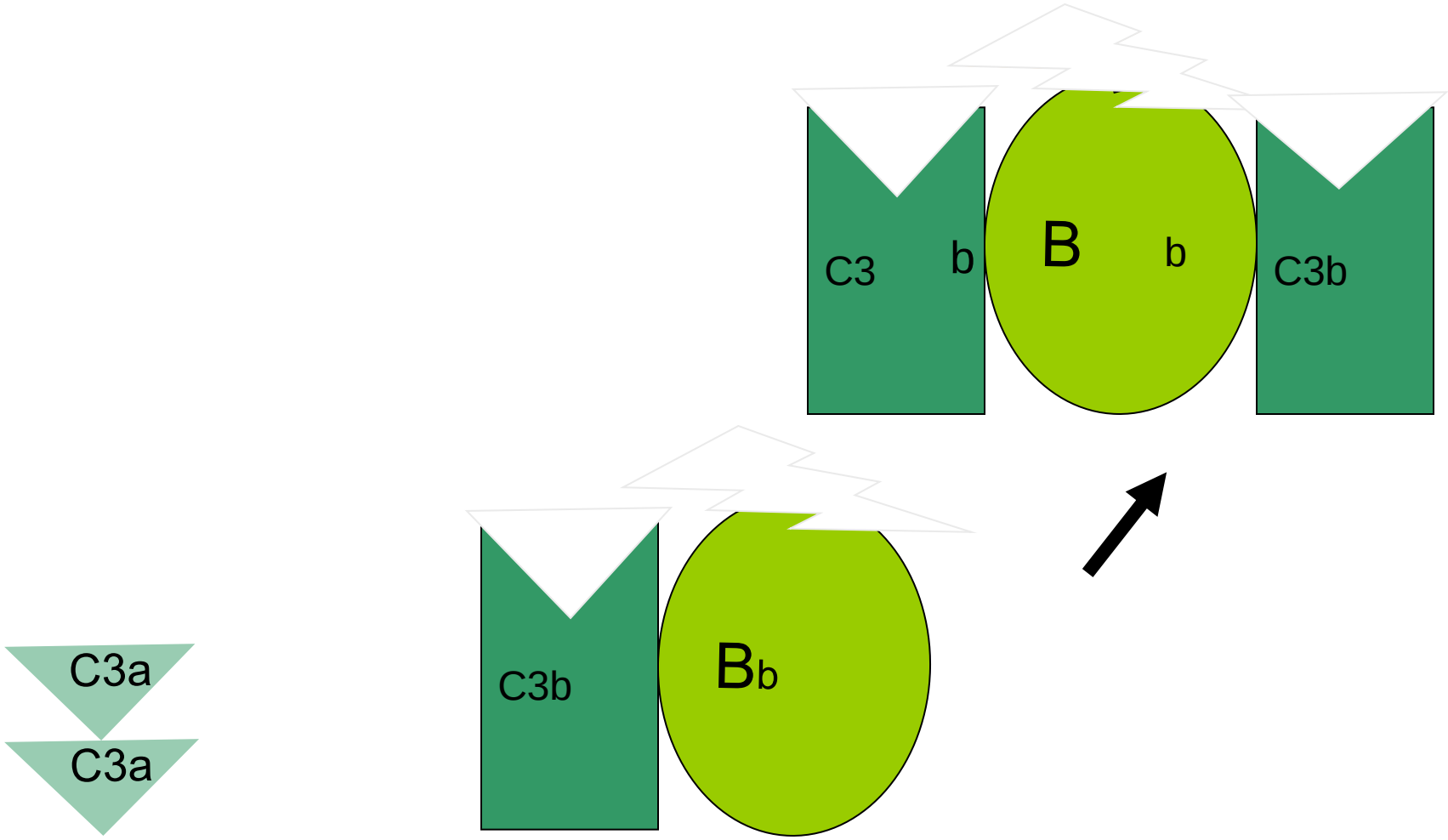
Alternative pathway

- Spontaneous C3 activation



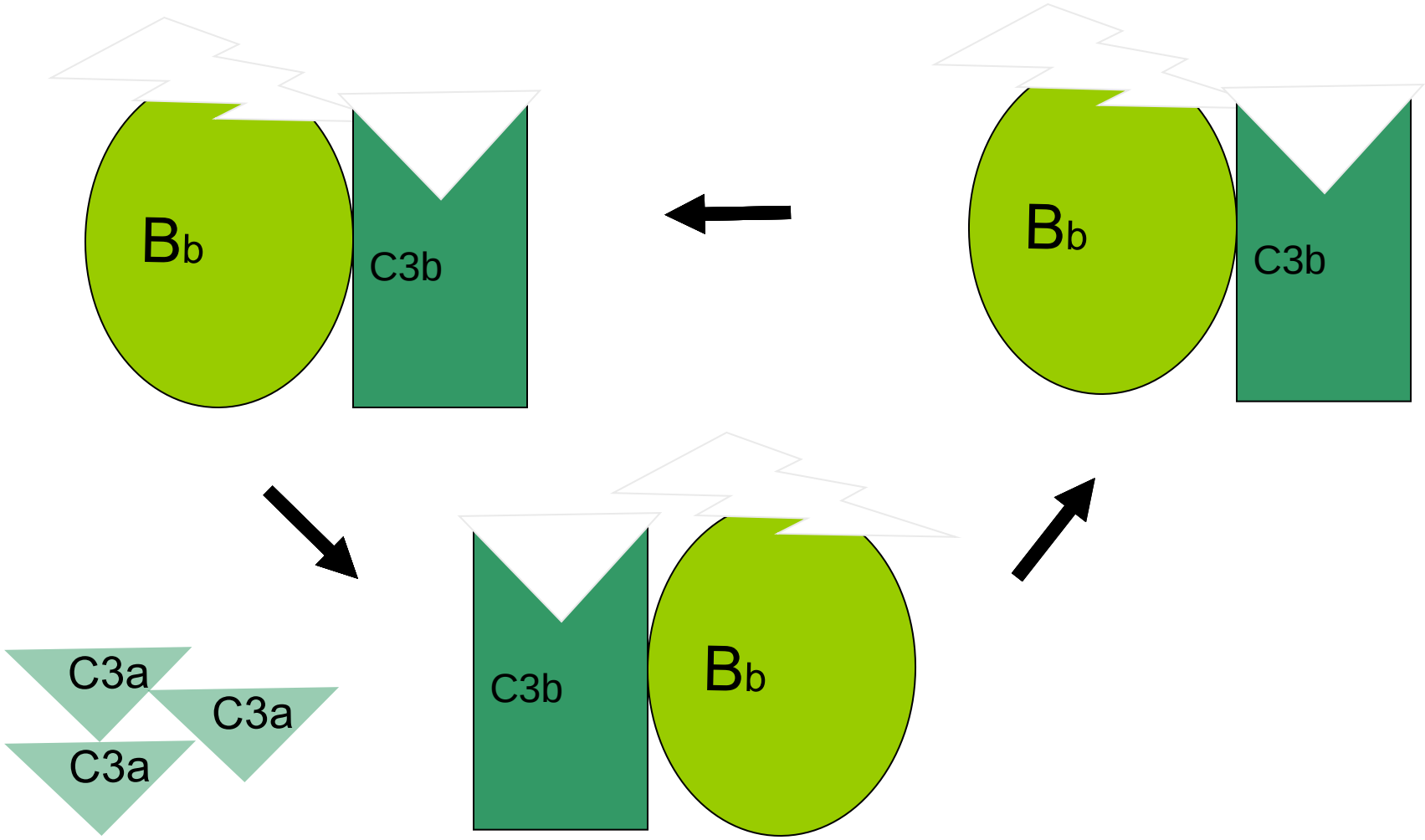
Alternative pathway

- C3 activation amplification loop



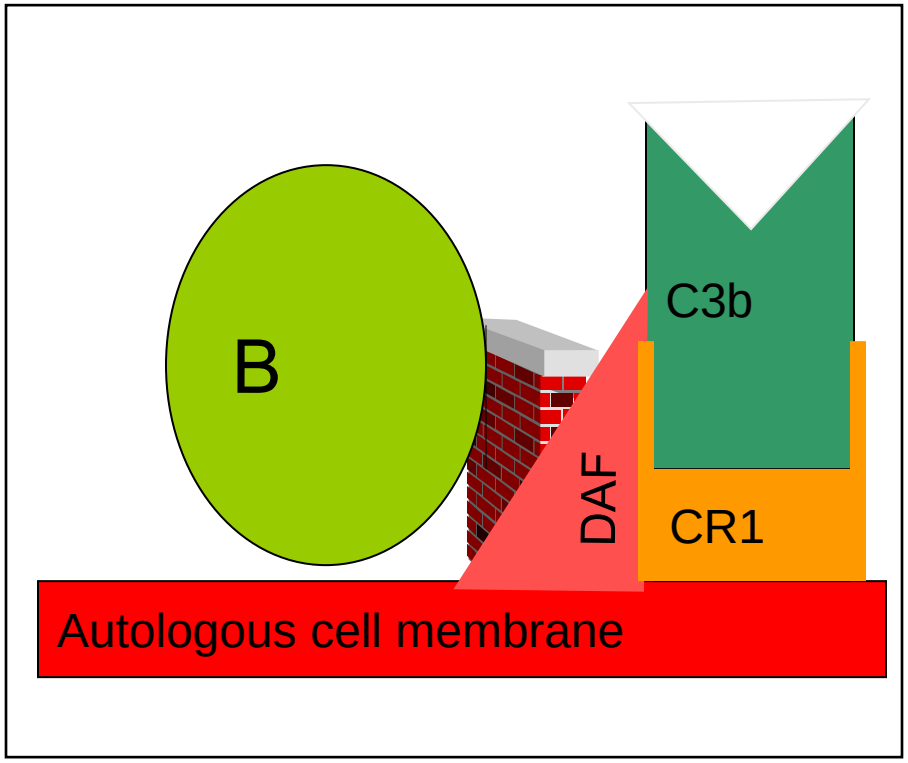
Alternative pathway

- C3 activation amplification loop



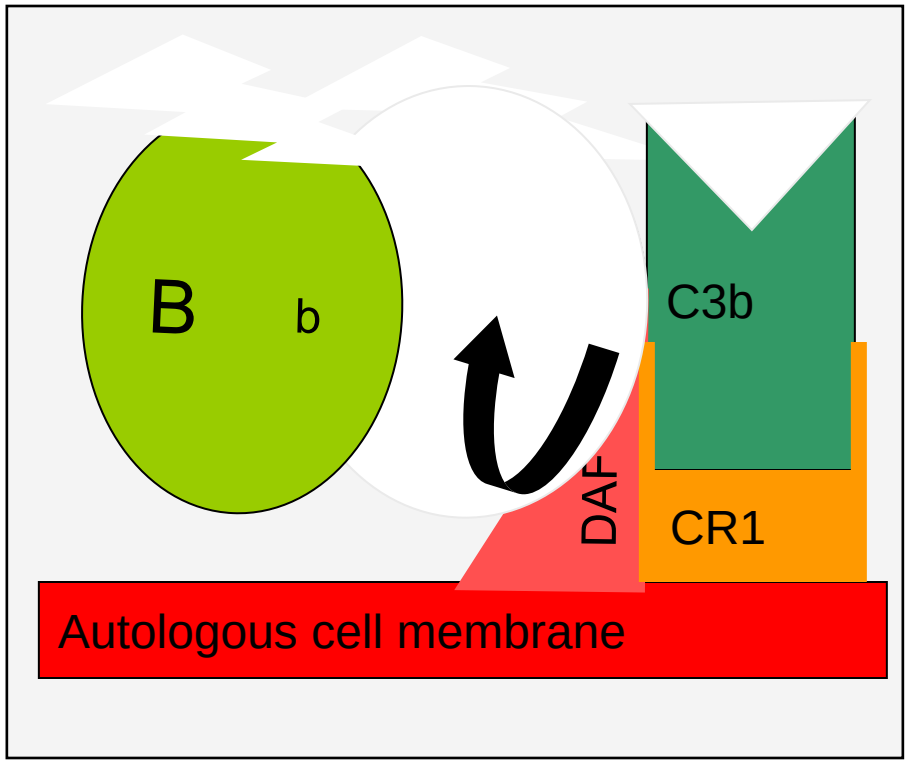
Alternative pathway

- Control of C3 activation amplification loop
- DAF prevents the binding of factor B to C3b



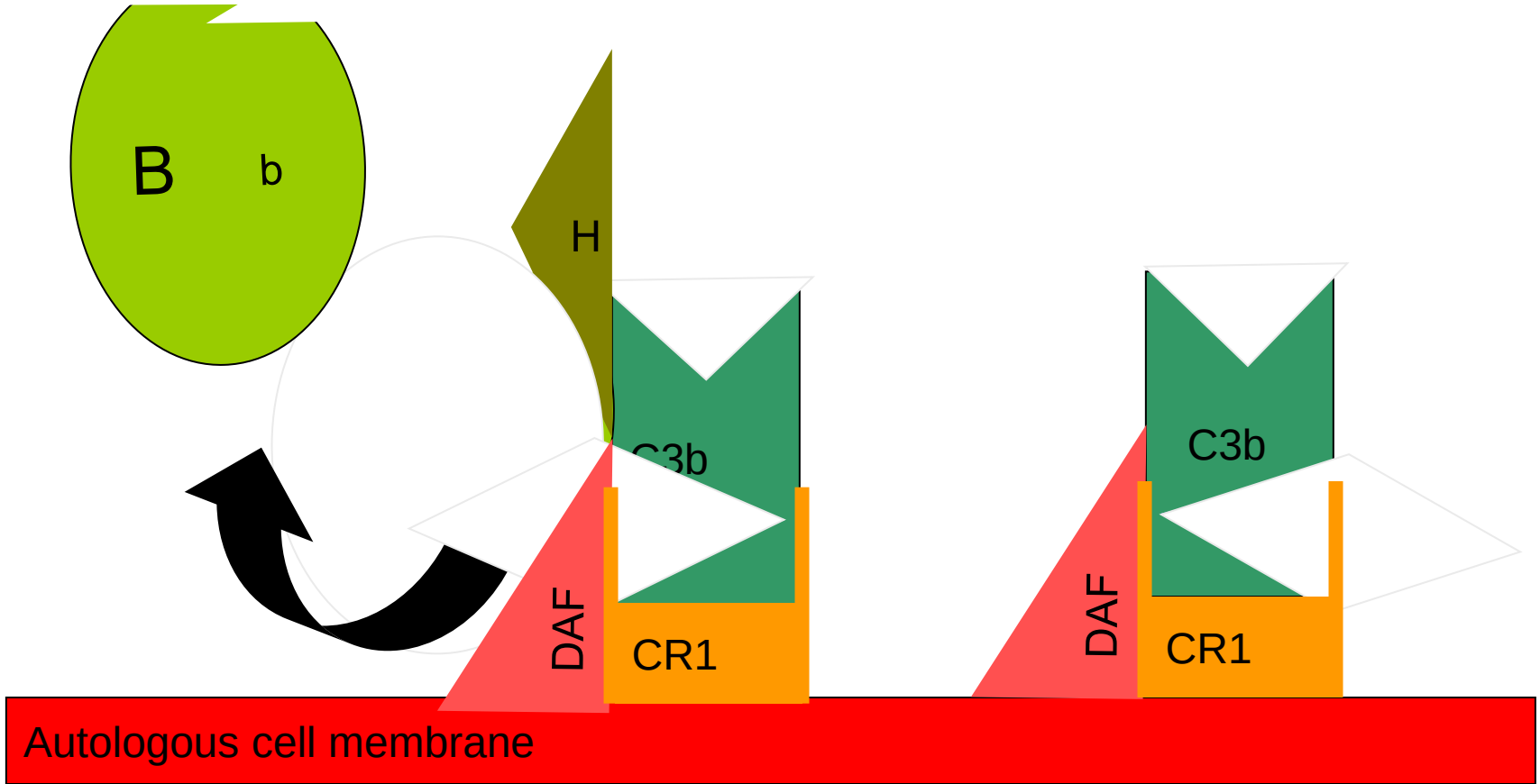
Alternative pathway

- Control of C3 activation amplification loop
- DAF also dissociates C3b bound factor Bb



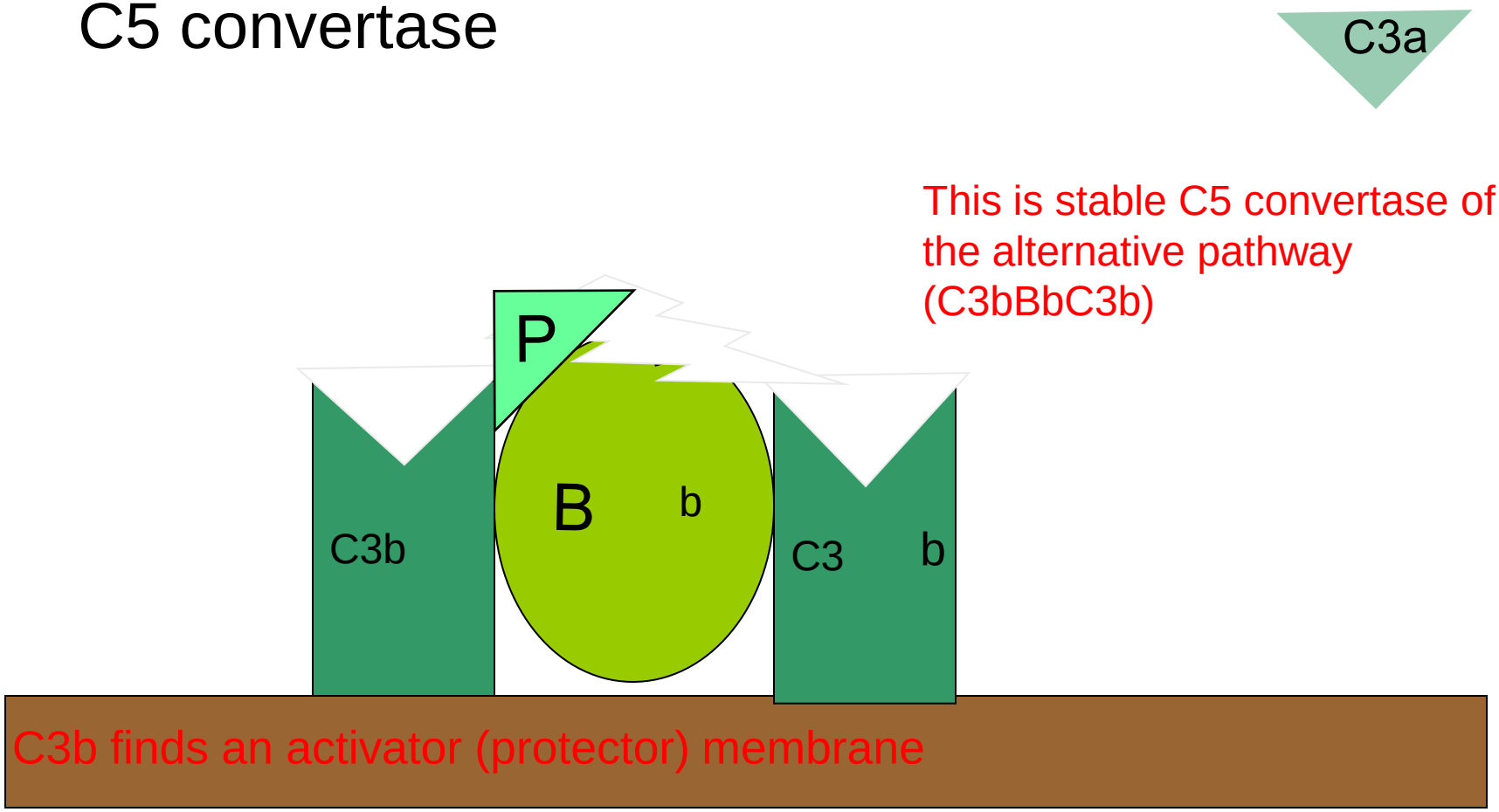
Alternative pathway

- Control of C3 activation amplification loop
- Role of factor I and factor H



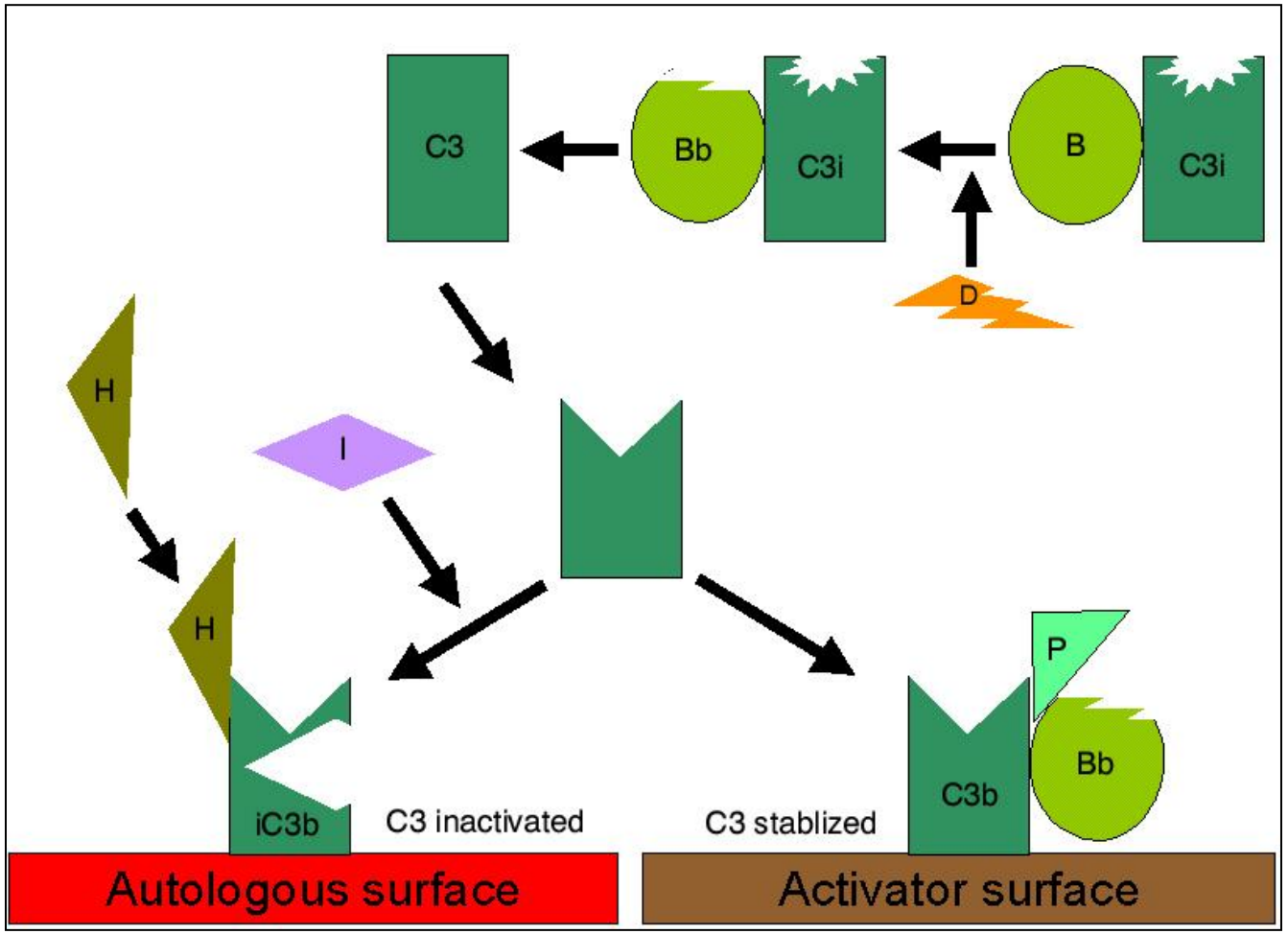
Alternative pathway

- C3 stabilization and activation and generation of C5 convertase



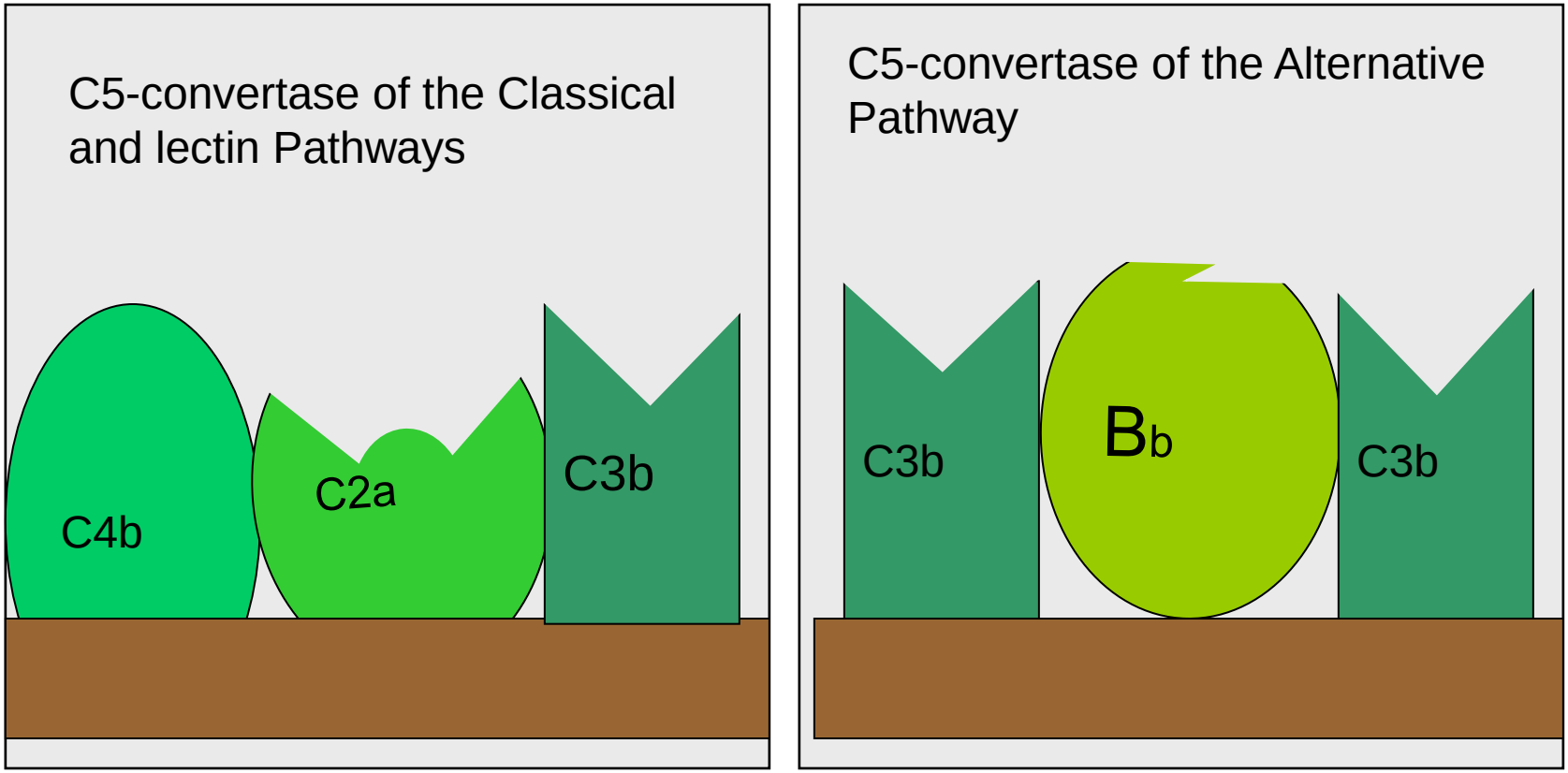
Alternative pathway

- C3b regulation on self and activator surfaces

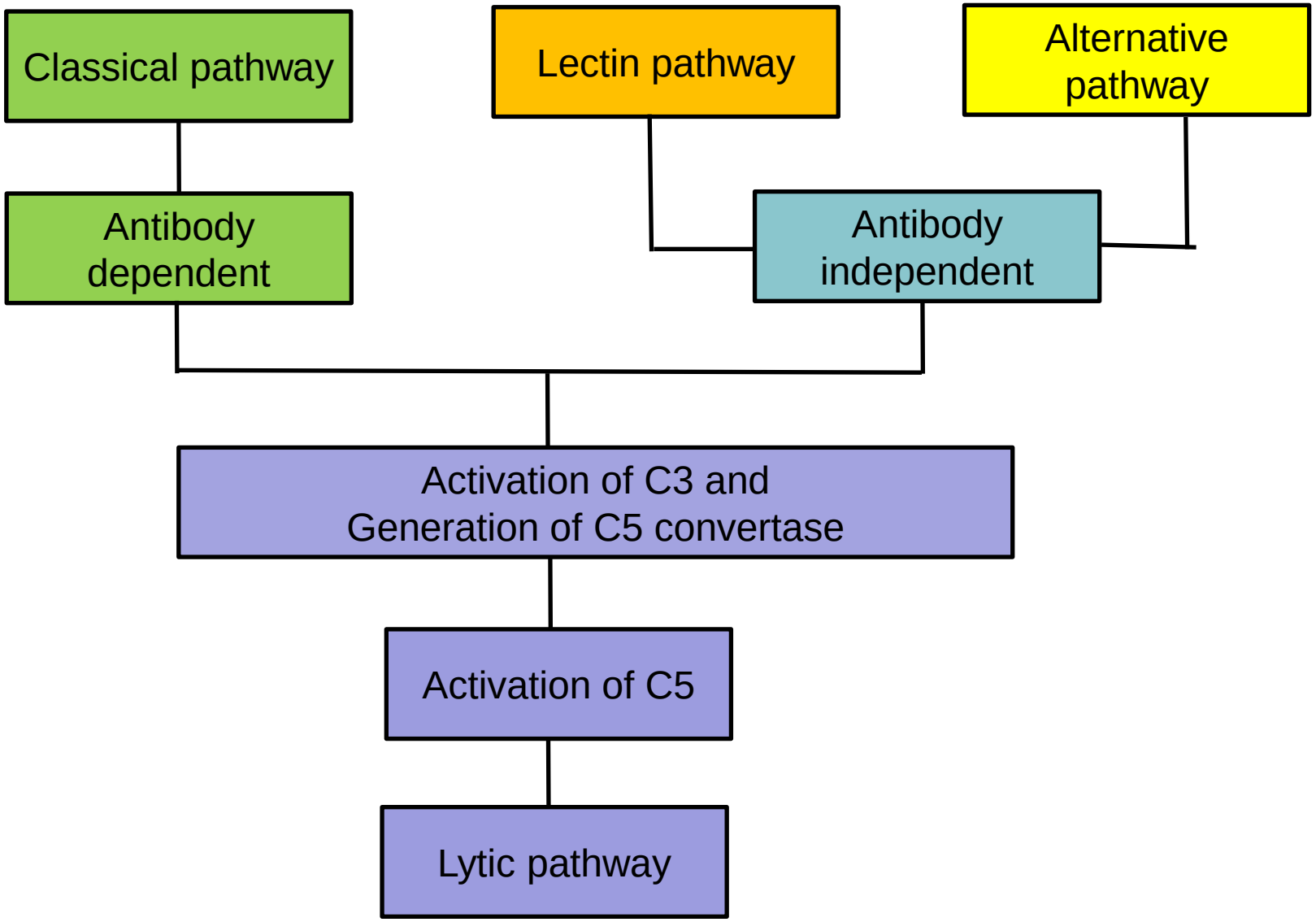


Complement pathways

- C5 convertases of classical, lectin and alternative pathways

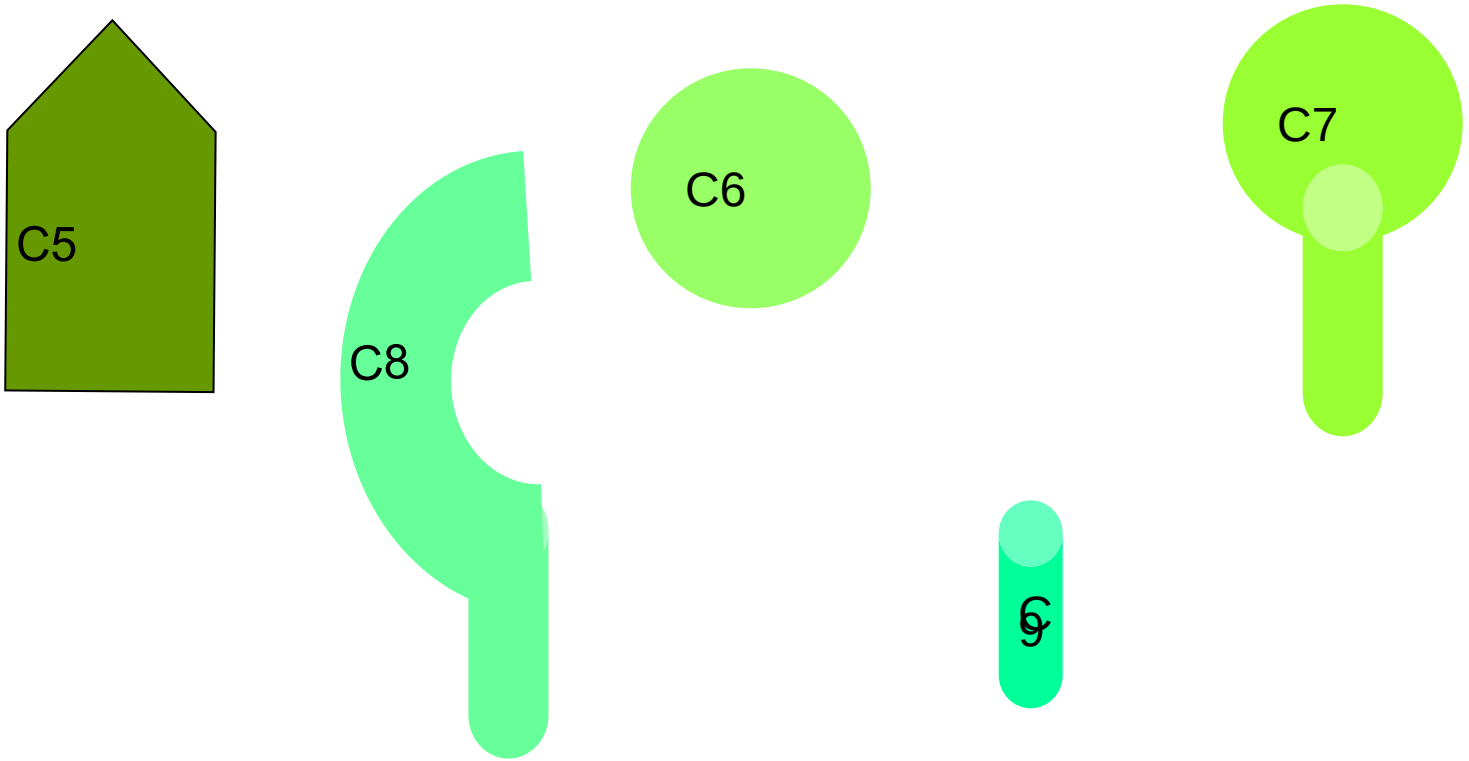


Pathways of complement



Lytic pathway

- Generation of C5 convertase leads to activation of lytic pathway
- Components of lytic pathway

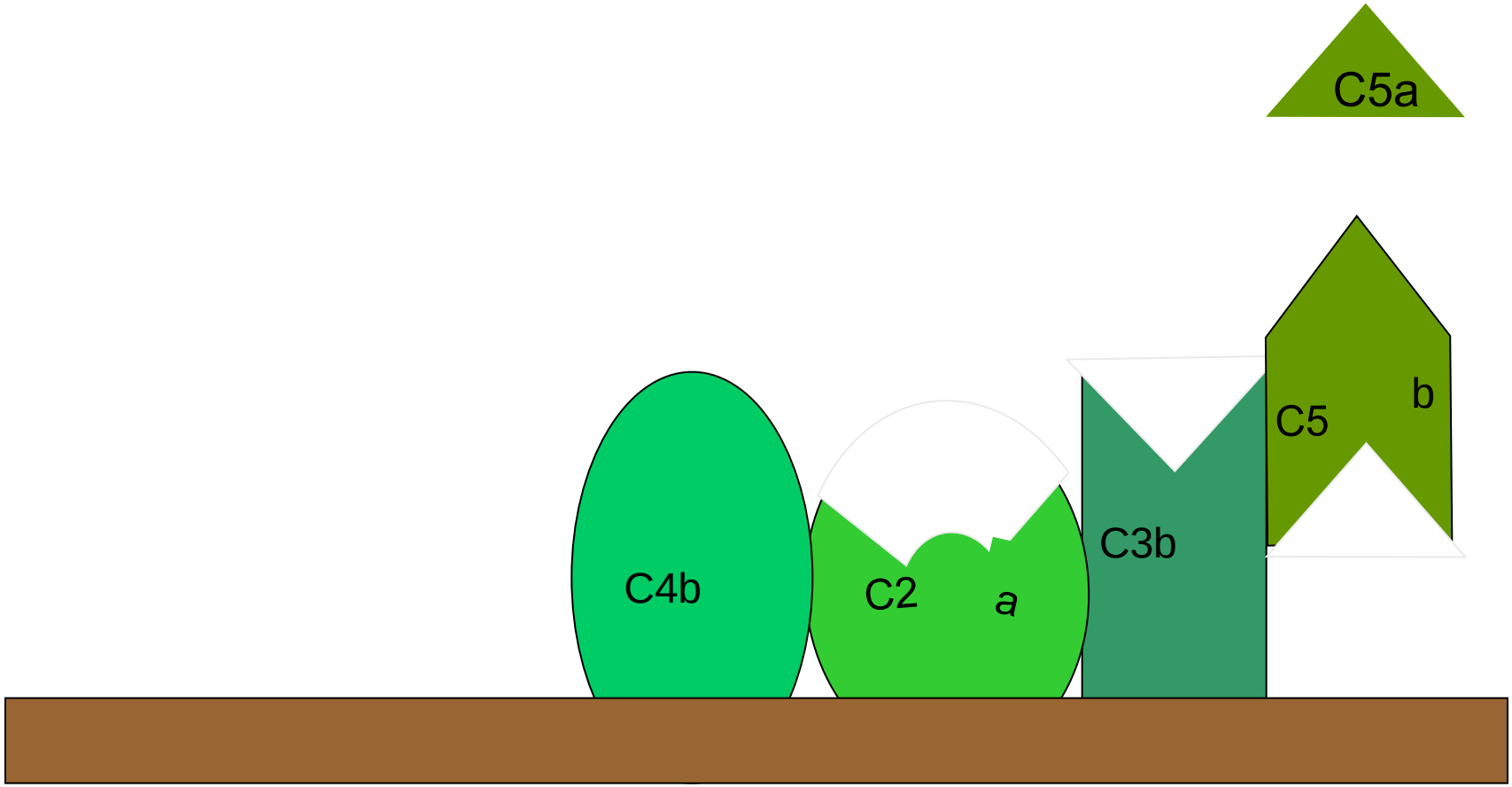


Lytic pathway

- C5 convertase from any of the pathways will act on C5 to generate C5b
- C5b binds to C6 followed by C7
- This complex is C5b67 is called Membrane Attack Complex (MAC). This binds to membrane
- Once bind to membrane MAC recruits C8
- This leads to the recruitment of multiple copies of C9 which is a transmembrane protein
- Multiple copies of C9 forms pores in the membrane

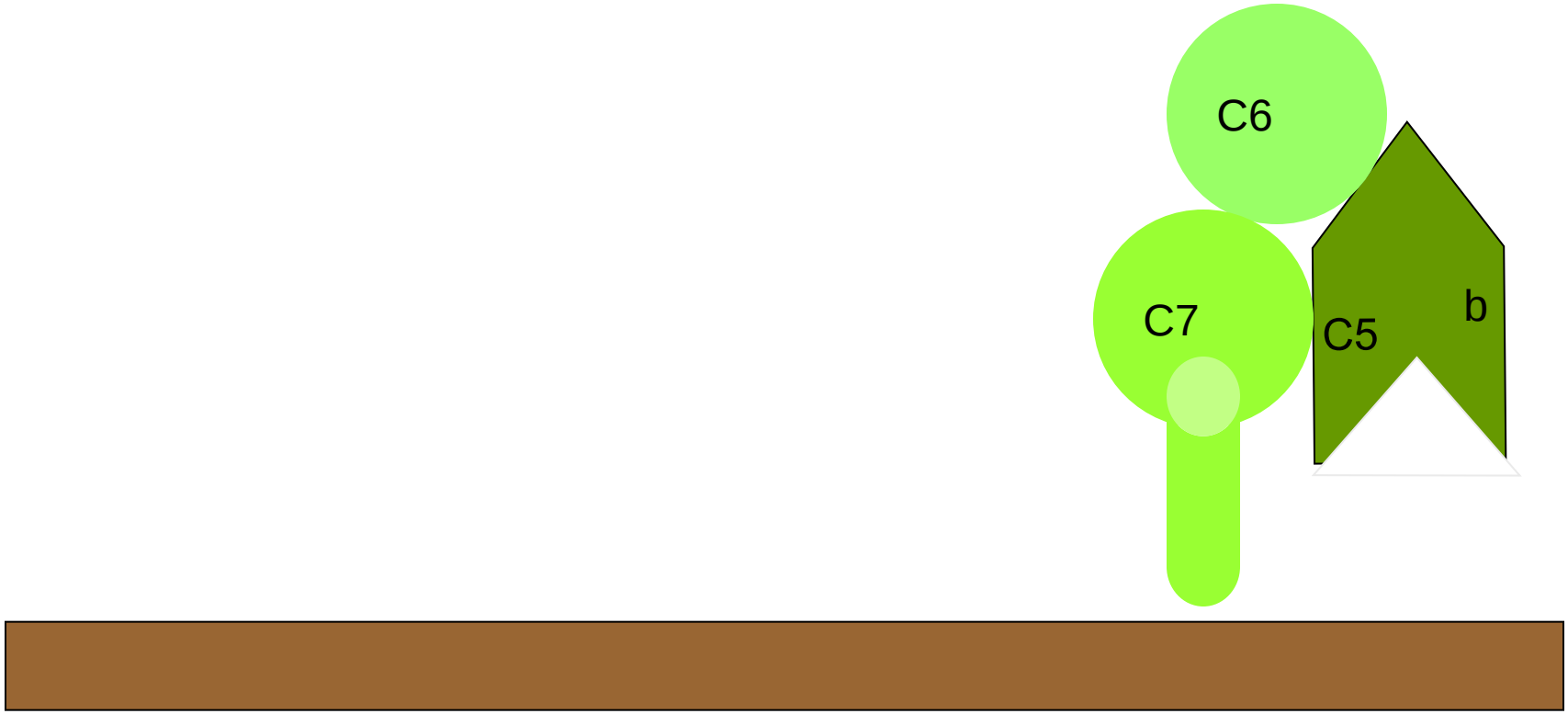
Lytic pathway

- C5 activation



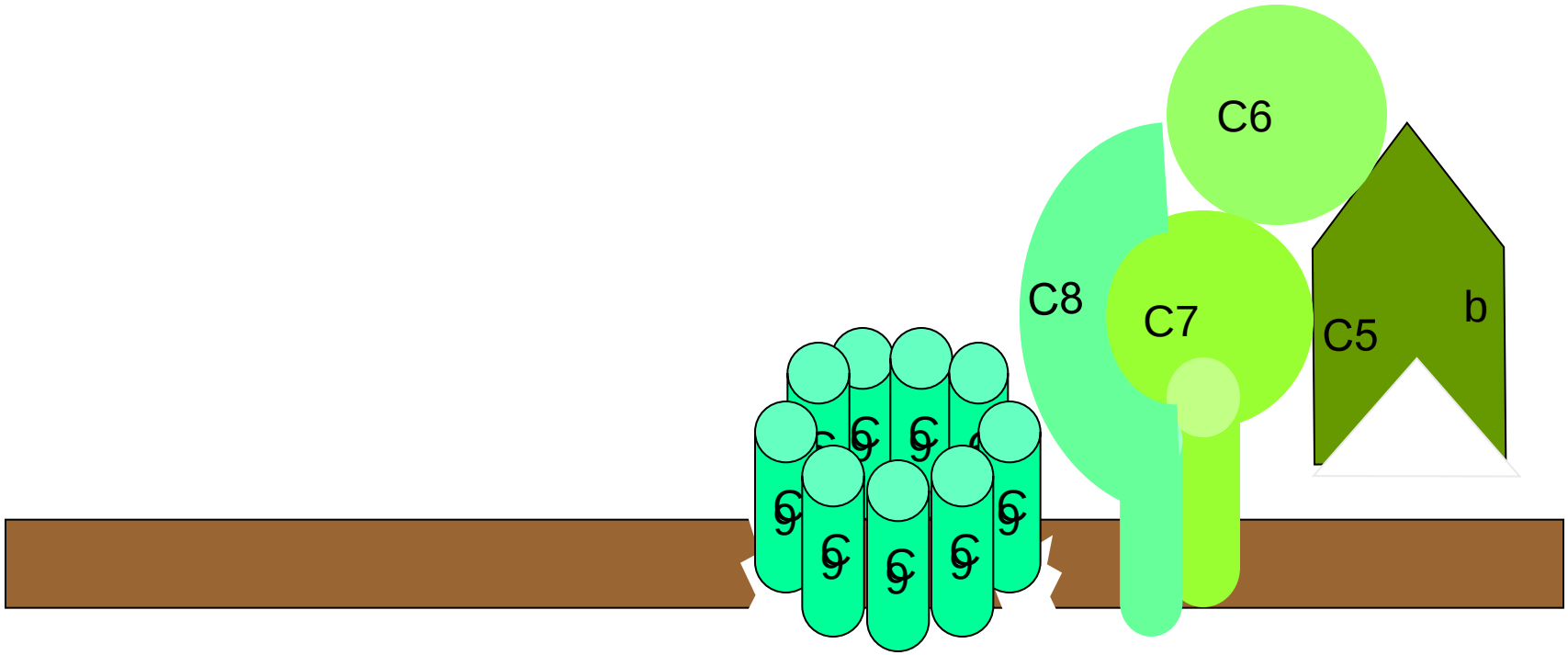
Lytic pathway

- Assembly of Lytic complex

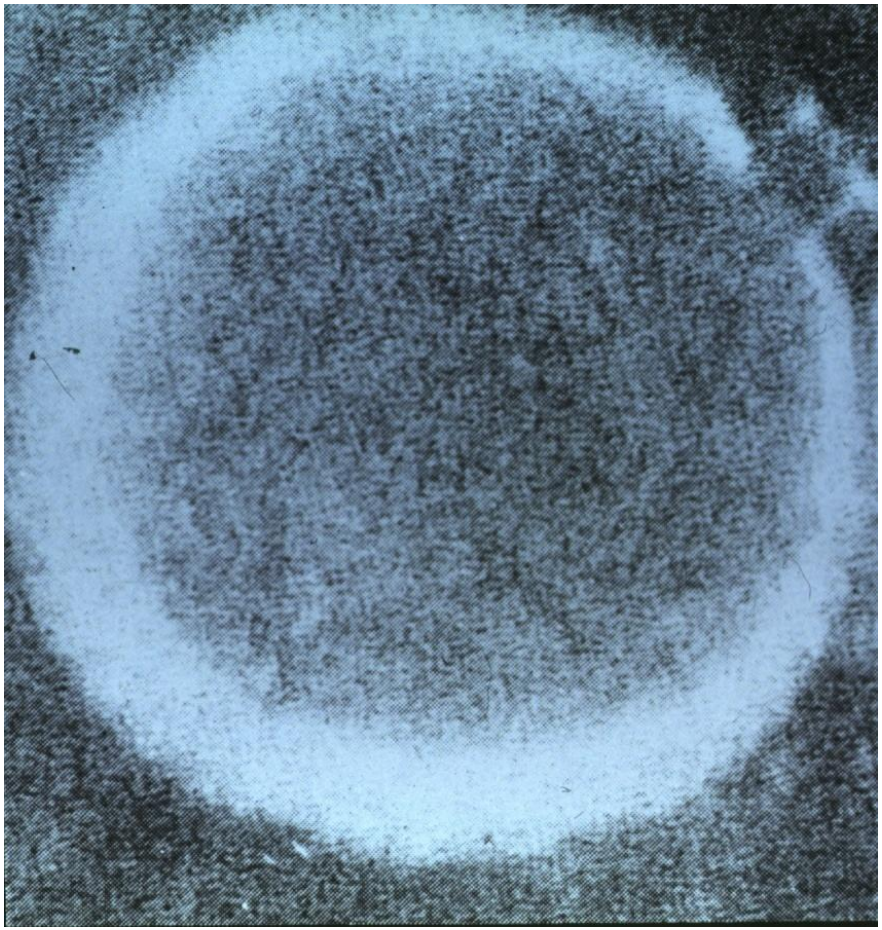


Lytic pathway

- Formation of MAC and insertion of lytic complex in to cell membrane



MAC



Complement pathway

- Several byproducts of complement system have biological properties

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	Anaphylotoxin
C4b	Opsonin

Complement pathway

- Angioedema due to deficiency of regulator of C

Next class…..

- Cell mediated immunity……