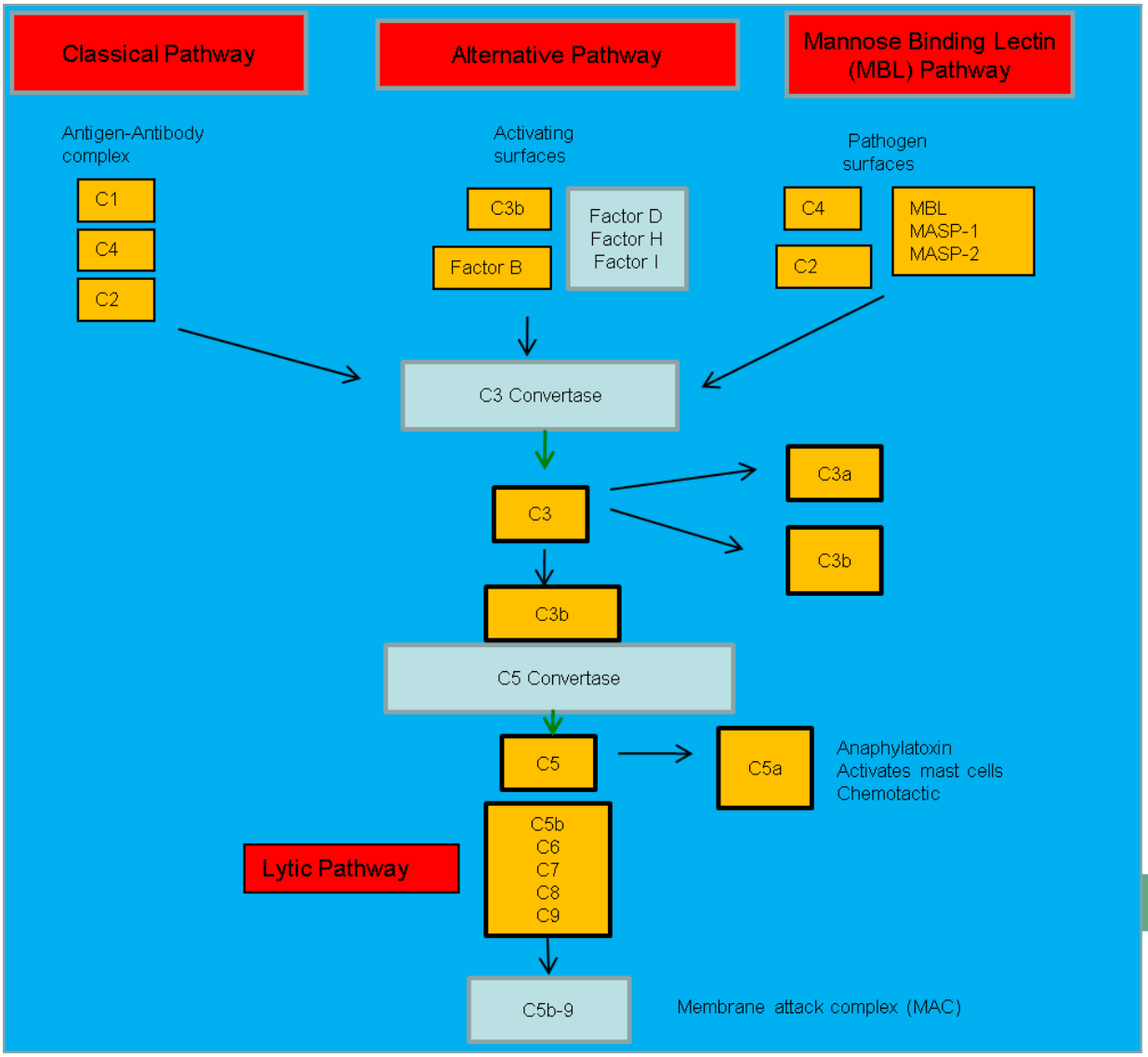
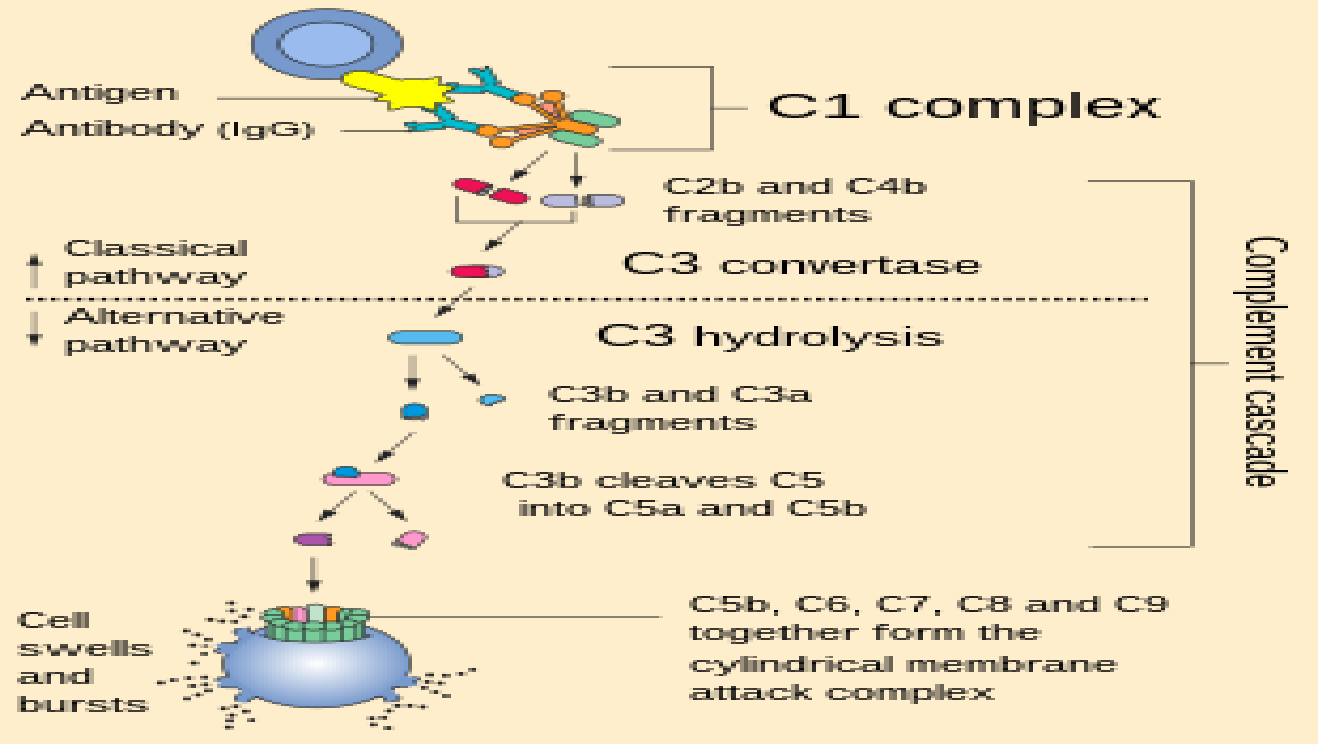
Lecture 3 The Complement System

The Complement System

consists of over 30 proteins produced by the liver that circulate in blood serum and within tissues throughout the body. The system is so named because it "completes," or enhances, cells of the immune system in destroying microbes.

The complement system is not adaptable, never changing over a person's lifetime. Therefore it is considered part of the innate immune system. However, it can be recruited into action by the adaptive immune system. This is another example of the cooperation between the innate and adaptive immune systems. Together, proteins of the complement system destroy microbes by cytolysis, opsonization, and inflammation (Figure), and they also prevent excessive damage to host tissues. Complement proteins are inactive until split into fragments (products), which activates them. Activated fragments carry out the destructive actions. Complement proteins are usually designated by an uppercase letter C and are numbered C1 through C9, named for the order in which they were discovered. Activated fragments are indicated by lowercase letters a and b. For example, inactive complement protein C3 is split into activated fragments, C3a and C3b. Complement proteins act in a cascade, where one reaction triggers another, which in turn triggers another. More product is formed with each succeeding reaction in the cascade, amplifying the effects. The cascade of complement proteins that occurs during an infection is called complement activation. It may occur in three pathways that end in the activation of C3.


Classical Pathway
Alternative Pathway
Mannose Binding Lectin (MBL) Pathway
Antigen-Antibody complex
Activating surfaces
Pathogen surfaces
C1
C4
C2
C3b
Factor B
Factor D
Factor H
Factor I
C4
C2
MBL
MASP-1
MASP-2
C3 Convertase
C3
C3a
C3b
C3b
C5 Convertase
C5
C5a
Anaphylatoxin
Activates mast cells
Chemotactic
Lytic Pathway
C5b
C6
C7
C8
C9
C5b-9
Membrane attack complex (MAC)



activation pathway	Classic	Alternative	Lectin
Activator	Ag–Ab Complex	spontaneous hydrolysis of C3	MBL-Mannose Complex
C3-convertase	C4b2b	C3bBb	C4b2b
C5-convertase	C4b2b3b	C3bBbC3b	C4b2b3b
MAC development	C5b+C6+C7+C8+C9		

	Classical pathway	Alternative pathway	Lectin pathway
Activated by	Binding of antibody molecules (specifically IgM and IgG1, IgG2, IgG3) to a foreign particle	Invading microorganisms	Binding of MBP to the mannose groups of carbohydrates on microorganisms
Activation mechanism	Antibody-dependent	Antibody-independent	Antibody-independent
Limb of immunity	Adaptive immune response	Innate immune response	Innate immune response
Components	C1 (C1q, C1r, C1s) to C9	Factors B, D, P, H, I	C1 (C1r, C1s) to C9
Components that initiate enzyme cascade	C1 (q, r, s), C4, C2	C3, B, D	Lectin, MASP1, MASP2, C4, C2
C3 convertase	C4bC2a, C2b	C3bBb	C2b, C4bC2a
C5 convertase	C4bC2aC3b	C3bBbC3b	C4bC2aC3b
Terminal components	C5-C9, MAC	C5-C9, MAC	C5-C9, MAC (

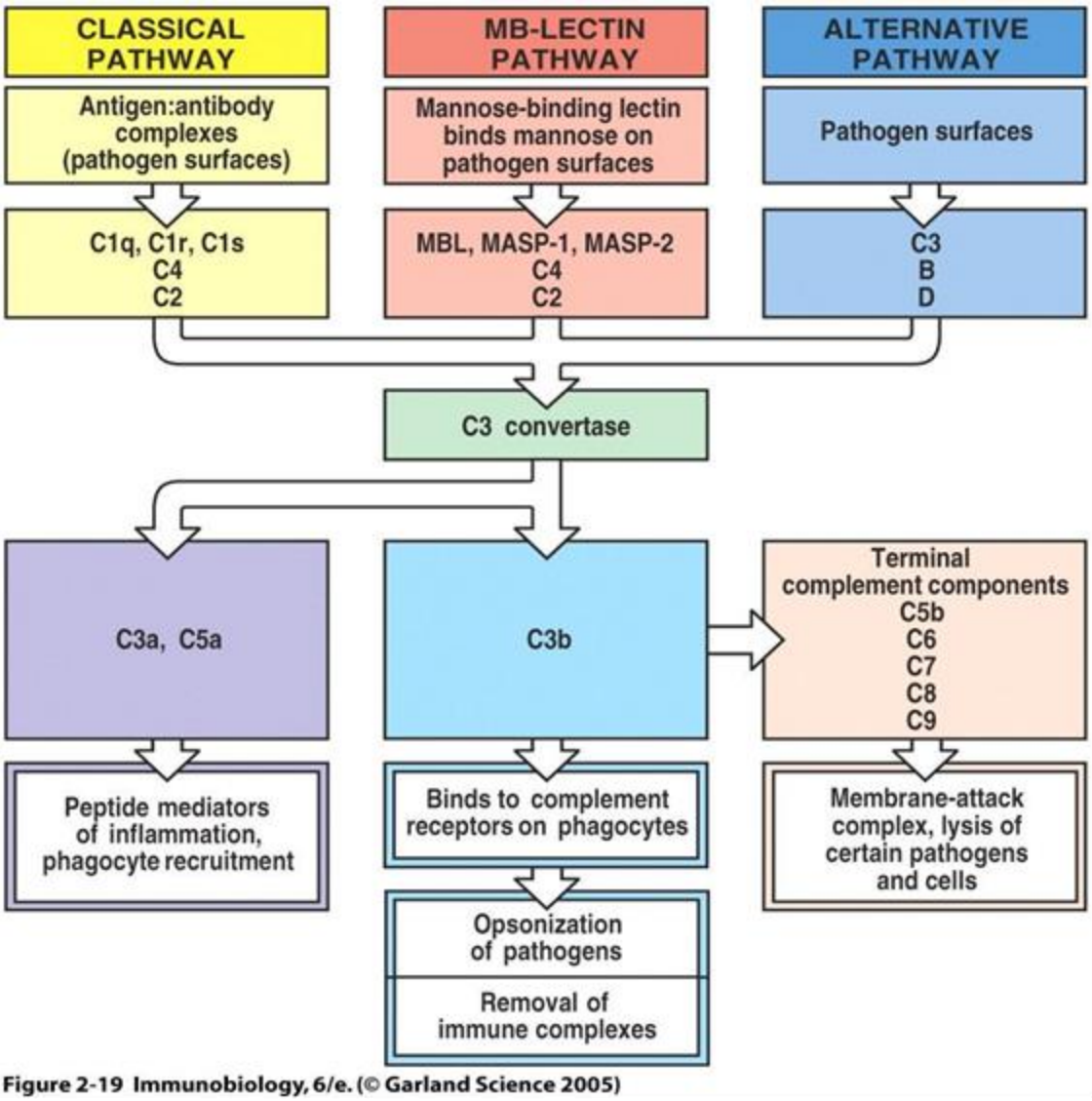


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

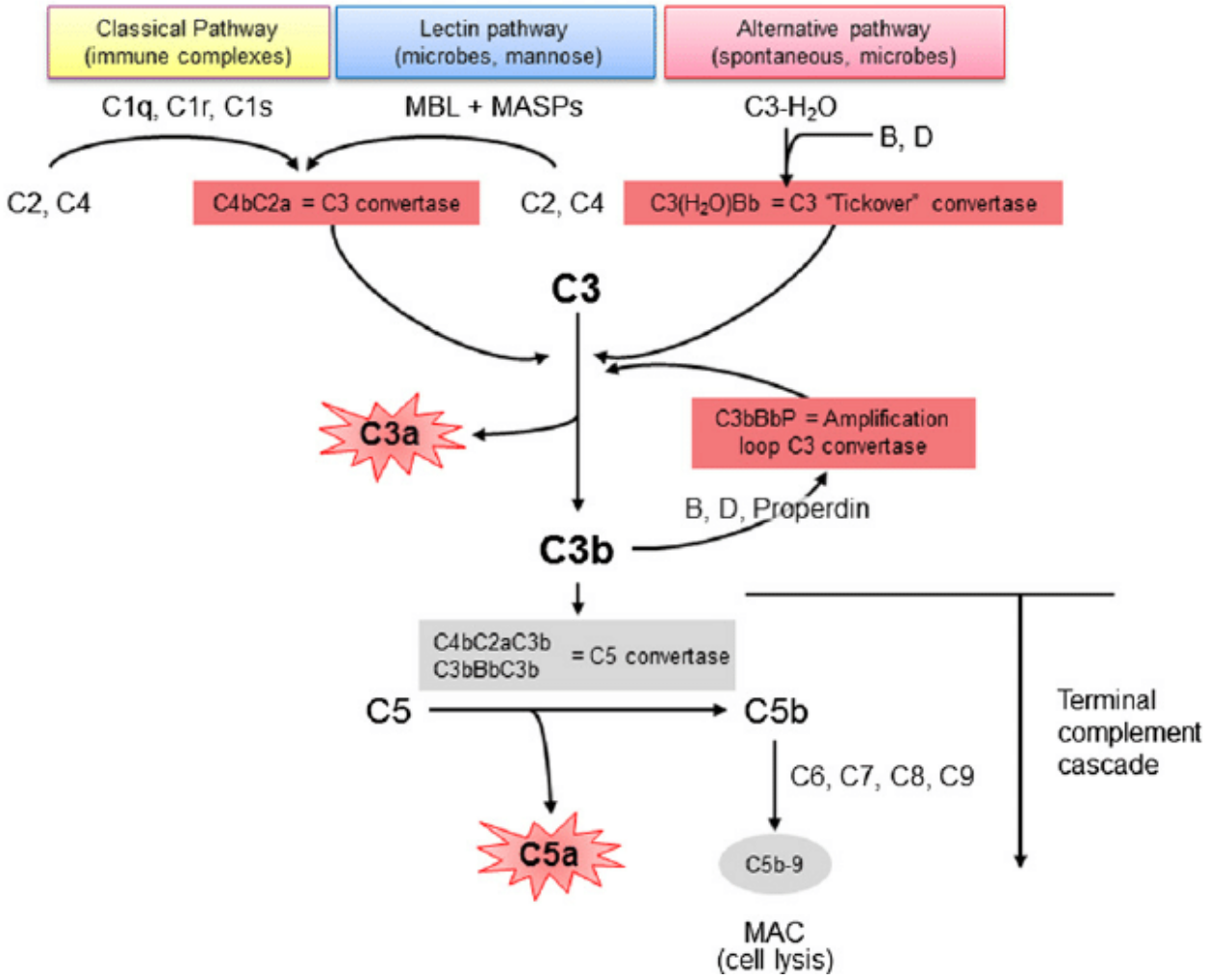
interferons (IFNs)

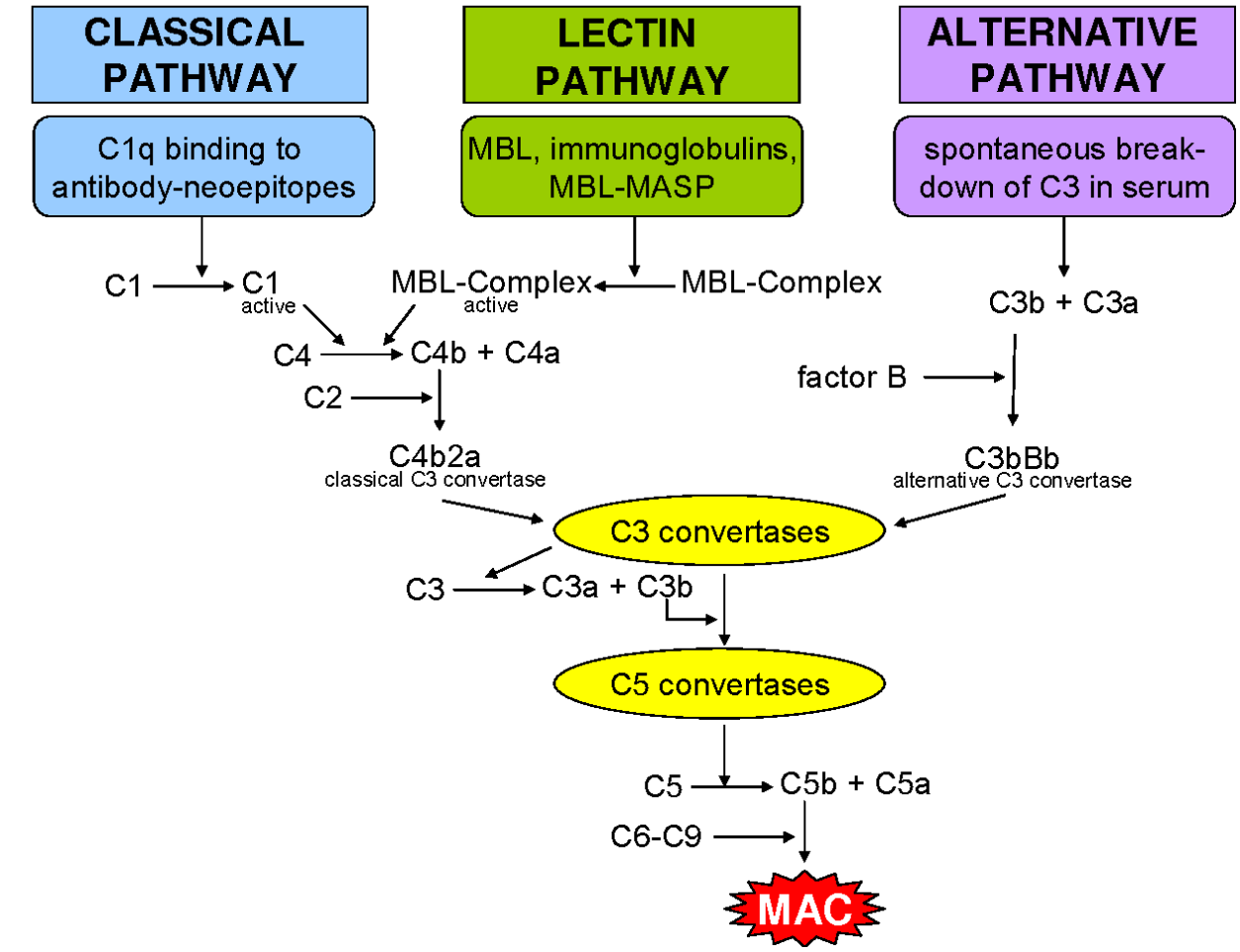
These are a class of proteins produced by certain animal cells, such as lymphocytes and macrophages Interferons produced by people protect human cells, but they produce little antiviral activity for cells of other species. However, the interferons of a species are active against a number of different viruses. They typically play a major role in viral infections There are three main types of human interferons: alpha interferon (IFN- α), beta interferon (IFNβ), and gamma interferon (IFN- γ). There are also various subtypes of interferons within each of the principal groups. In humans, interferons are produced by fibroblasts in connective tissue and by lymphocytes and other leukocytes.

Both IFN-α and IFN-β are produced by virus-infected host cells only in very small quantities that diffuse to uninfected neighboring cells (Figure).

Both types are host-cell–specific but not virusspecific. They react with plasma or nuclear membrane receptors, inducing the uninfected neighboring cells to manufacture mRNA for the synthesis of antiviral proteins (AVPs). These proteins are enzymes that disrupt various stages of viral multiplication. For example, one AVP, called oligoadenylate synthetase, degrades viral mRNA. Another, called protein kinase, inhibits protein synthesis.

Both IFN-α and IFN-β stimulate NK cells, which produce IFN-γ. Gamma interferon is produced by lymphocytes and induces neutrophils and macrophages to kill bacteria. IFN-γ causes macrophages to produce nitric oxide that appears to kill bacteria as well as tumor cells by inhibiting ATP production. IFN-γ increases the expression of MHC molecules and antigen presentation. Interferons are stable for short periods of time in the body, so their effect is limited. When injected, interferons have side effects such as nausea, fatigue, headache, vomiting, weight loss, and fever. High concentrations of interferons are toxic to the heart, liver, kidneys. Another problem is that interferons have no effect on viral multiplication in cells already infected, and some viruses (such as adenoviruses) have resistance mechanisms that inhibit antiviral proteins


Classical Pathway
(immune complexes)
Lectin pathway
(microbes, mannose)
Alternative pathway
(spontaneous, microbes)
C1q, C1r, C1s
MBL + MASPs
C3-H2O
B, D
C2, C4
C4bC2a = C3 convertase
C2, C4
C3(H2O)Bb = C3 "Tickover" convertase
C3
C3a
C3bBbP = Amplification loop C3 convertase
B, D, Properdin
C3b
C4bC2aC3b
C3bBbC3b
= C5 convertase
C5
C5b
Terminal complement cascade
C6, C7, C8, C9
C5a
C5b-9
MAC
(cell lysis)


CLASSICAL PATHWAY
LECTIN PATHWAY
ALTERNATIVE PATHWAY
C1q binding to antibody-neoepitopes
MBL, immunoglobulins, MBL-MASP
spontaneous break-down of C3 in serum
C1
C1 active
MBL-Complex active
MBL-Complex
C3b + C3a
C4
C4b + C4a
C2
factor B
C4b2a
classical C3 convertase
C3bBb
alternative C3 convertase
C3 convertases
C3
C3a + C3b
C5 convertases
C5
C5b + C5a
C6-C9
MAC