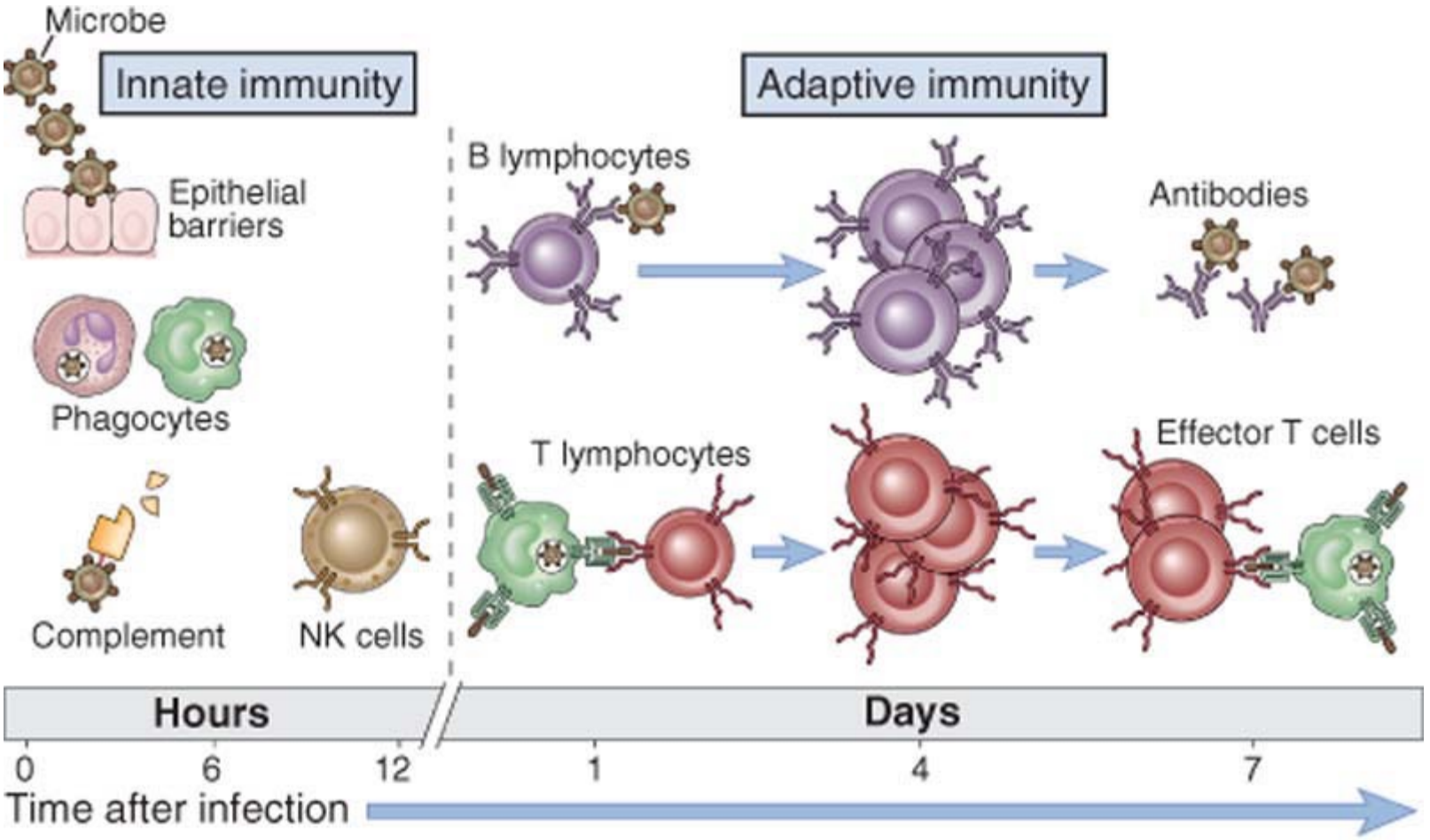
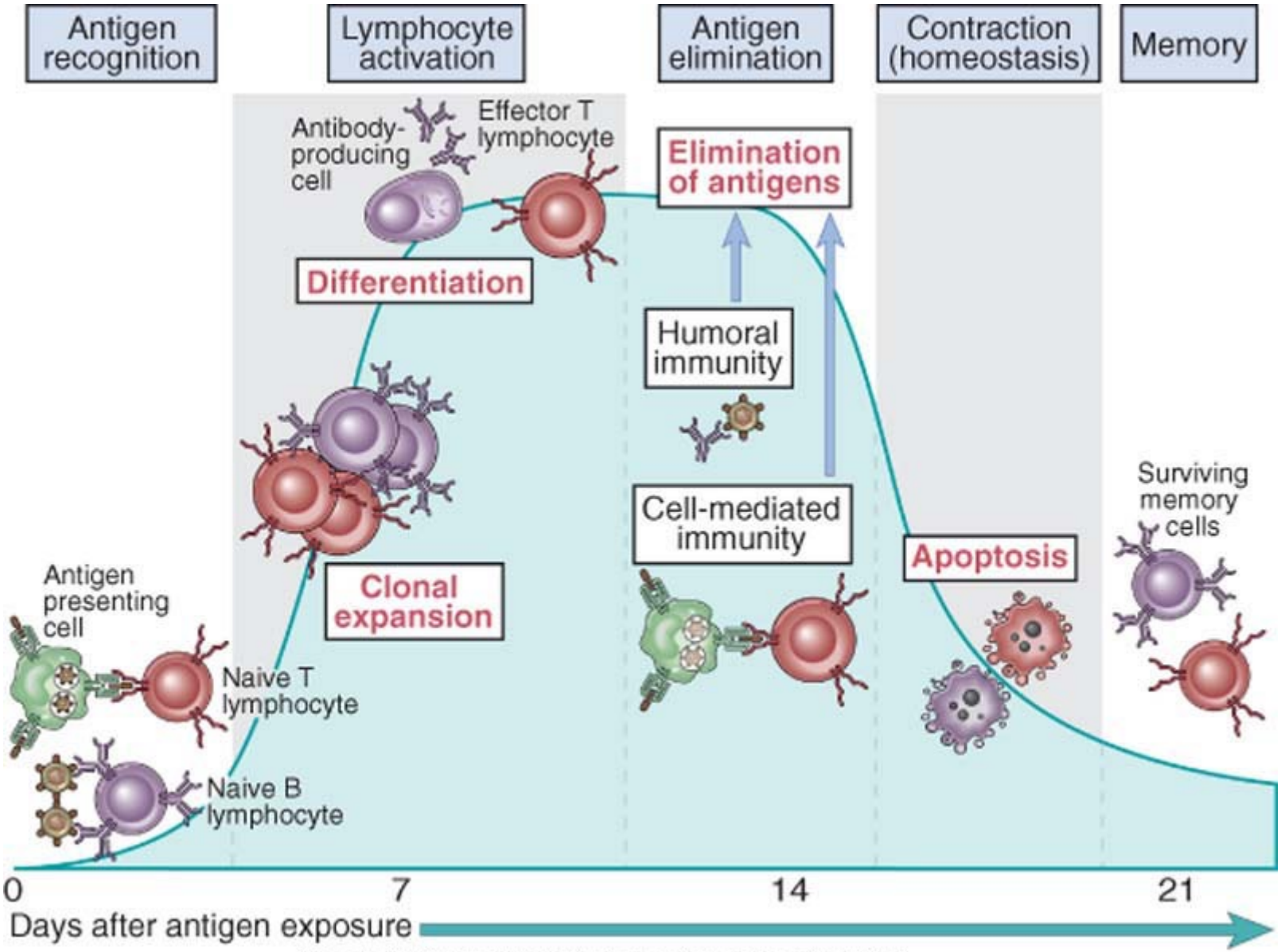
IPERsensitivity

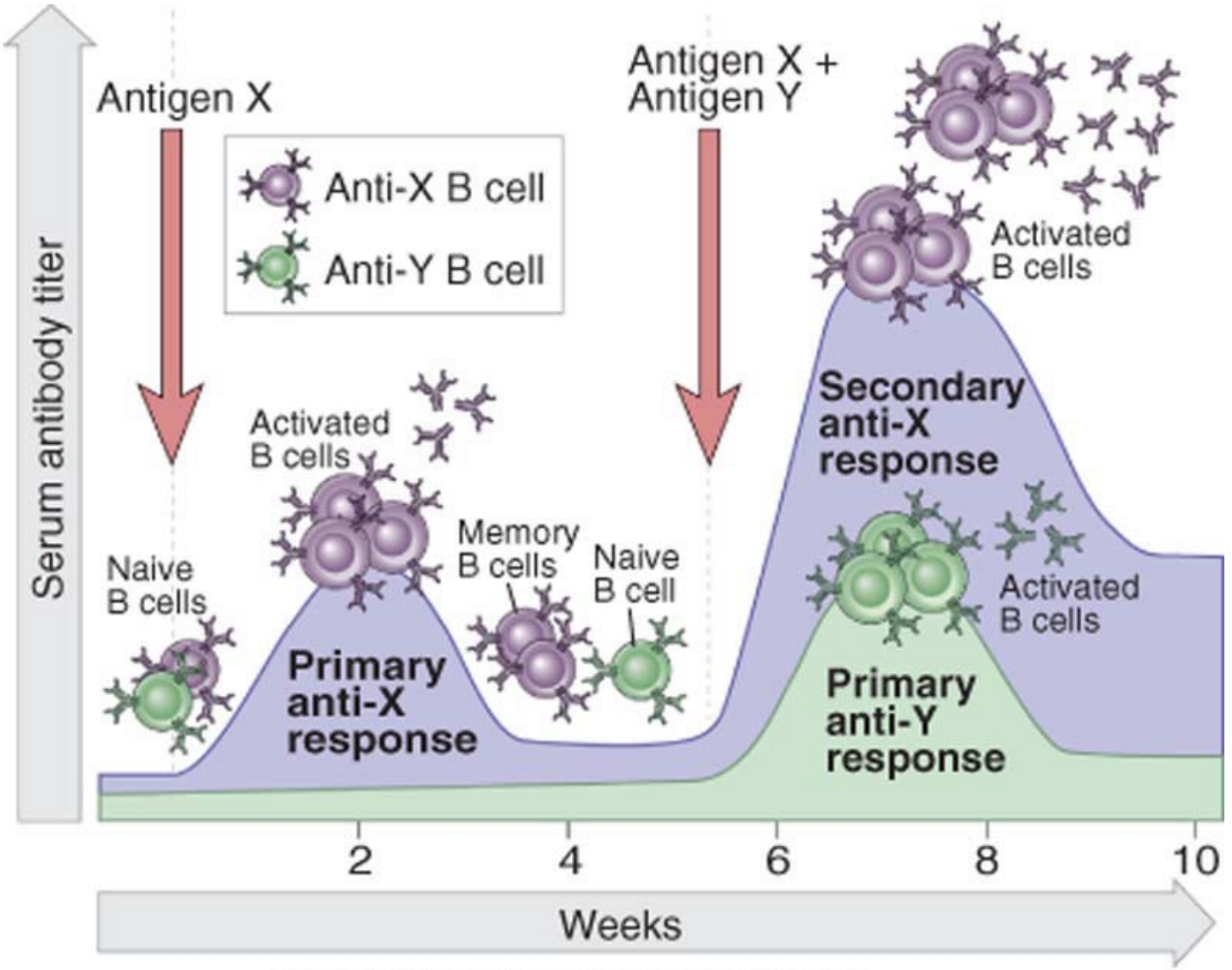
The immune system



Phases of adaptive immune response

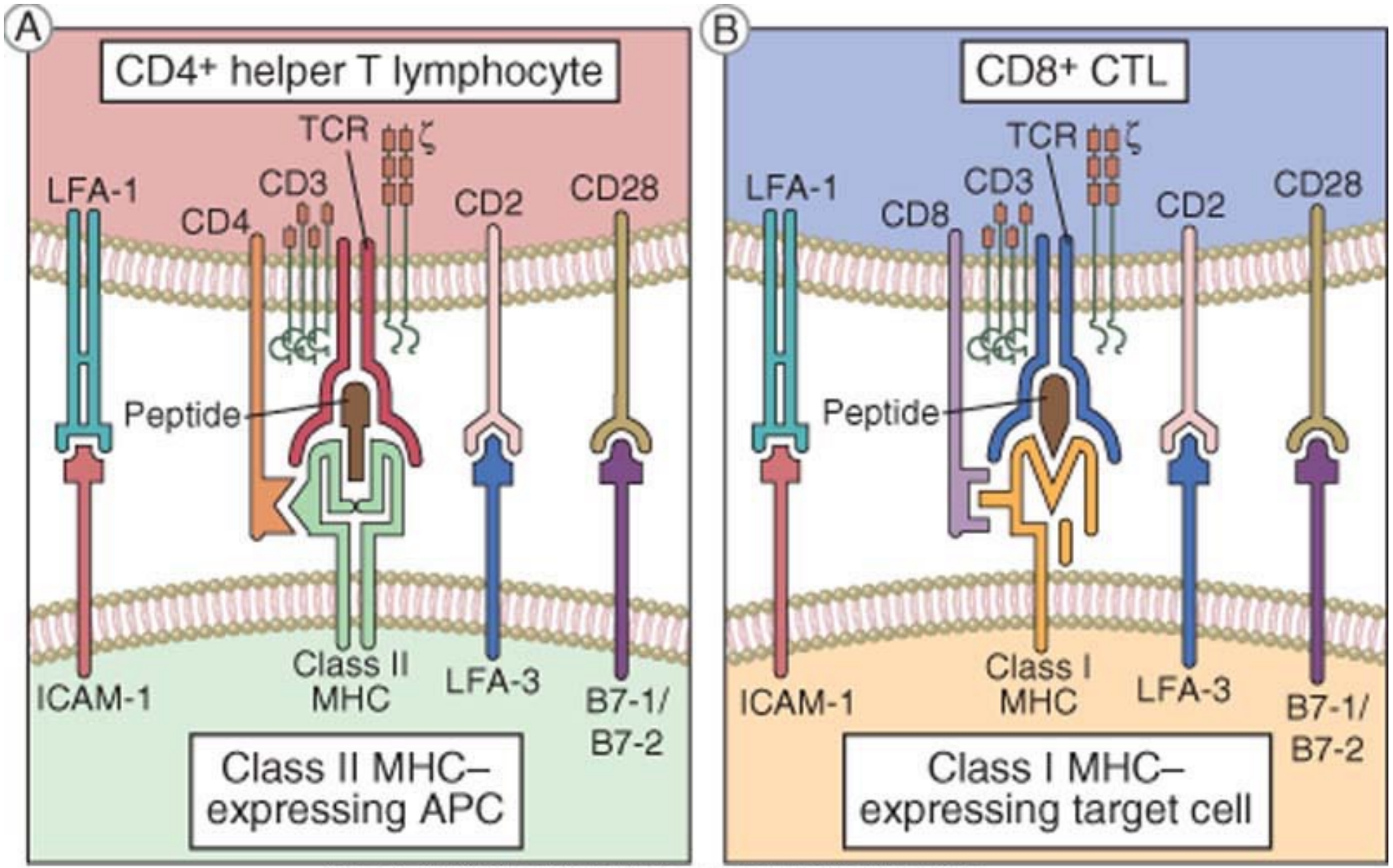


Specificity, resolution and memory



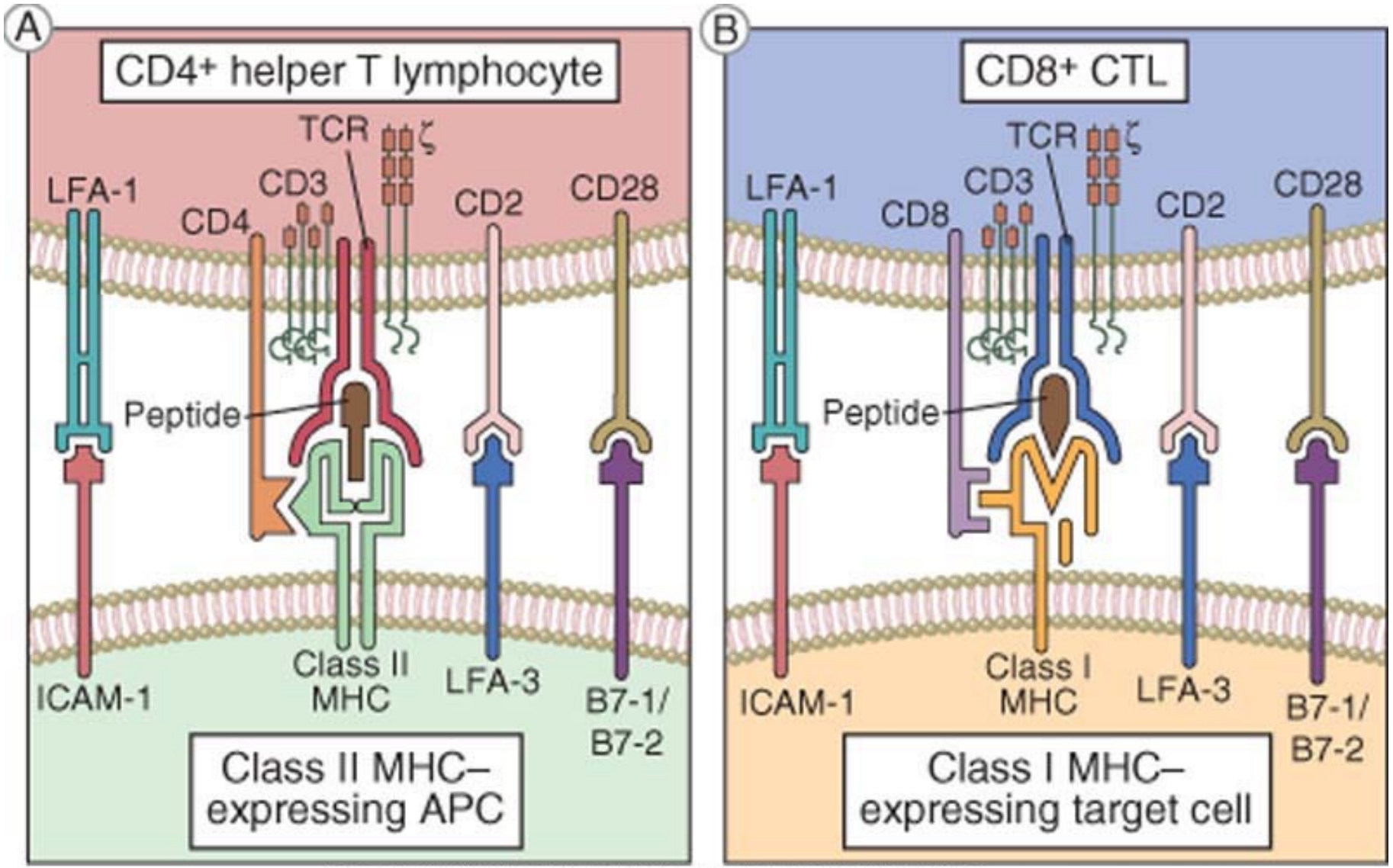
Control of Immune Response

- **Antigen**



Control of Immune Response

- **Antigen**
- **Lymphocytes half-life**
- **Treg Lymphocytes**
- **Complexity of the system (request of several costimulatory molecules)**



Hypersensitivity disorders: disorders caused by immune responses

….. Normally, immune responses eradicate infectious pathogens without serious injury to host tissues. However, these responses are sometimes inadequately controlled, inappropriately targeted to host tissues, or triggered by commensal microorganisms or environmental antigens that are usually harmless. In these situations, the normally beneficial immune response is the cause of disease.

TABLE 19.1 Classification of Hypersensitivity Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: Type I	IgE antibody, Th2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody-mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, for example, hormone receptor signaling, neurotransmitter receptor blockade
Immune complex–mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell–mediated: Type IV	1. $CD4^+$ T cells (Th1 and Th17 cells) 2. $CD8^+$ CTLs	1. Cytokine-mediated inflammation and macrophage activation 2. Direct target cell killing, cytokine-mediated inflammation

CTLs, Cytotoxic T lymphocytes; *Ig,* immunoglobulin.

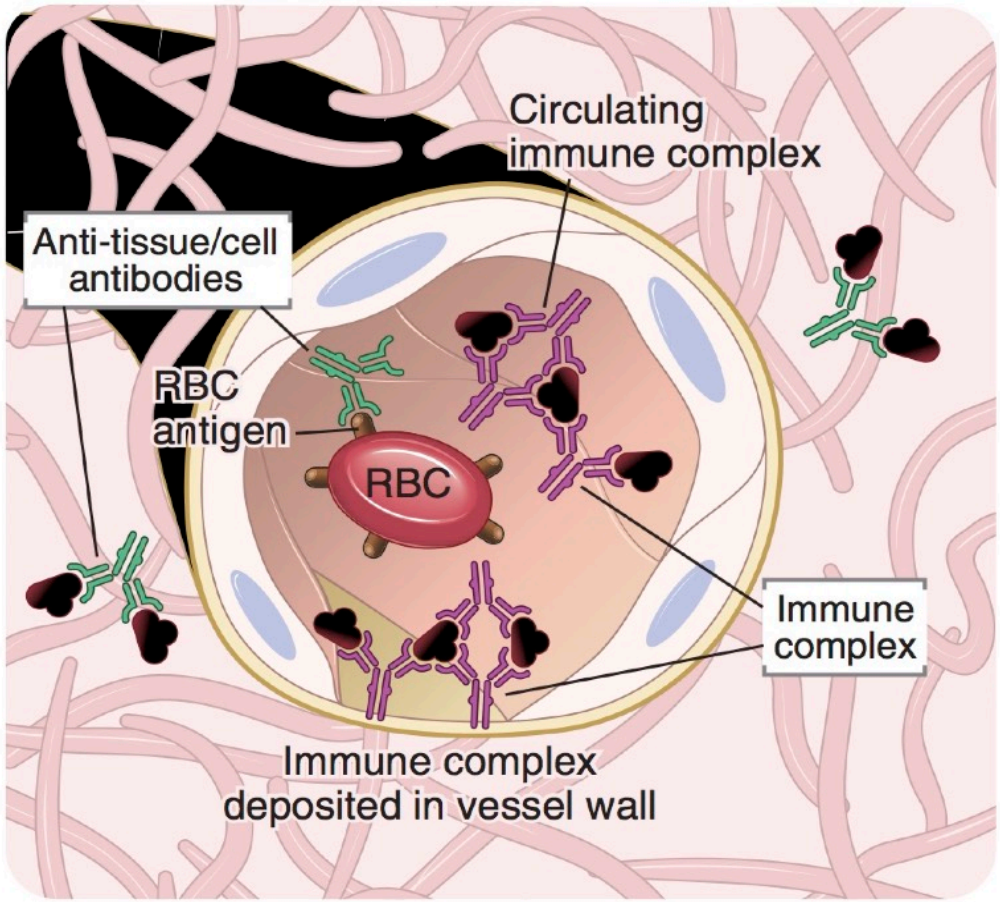
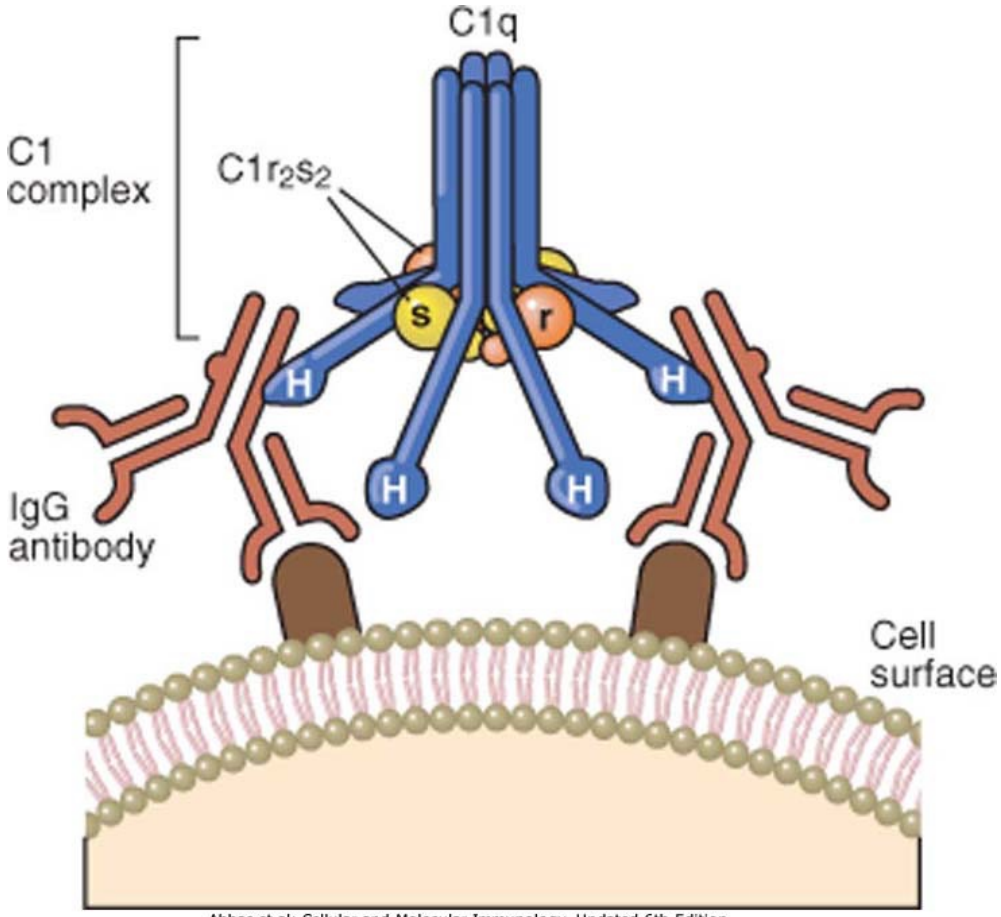
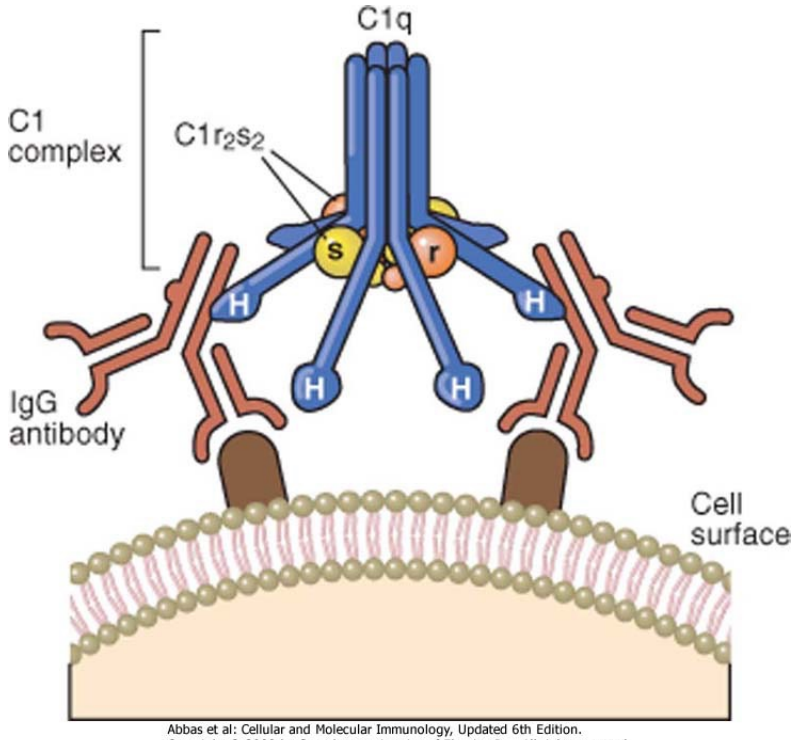


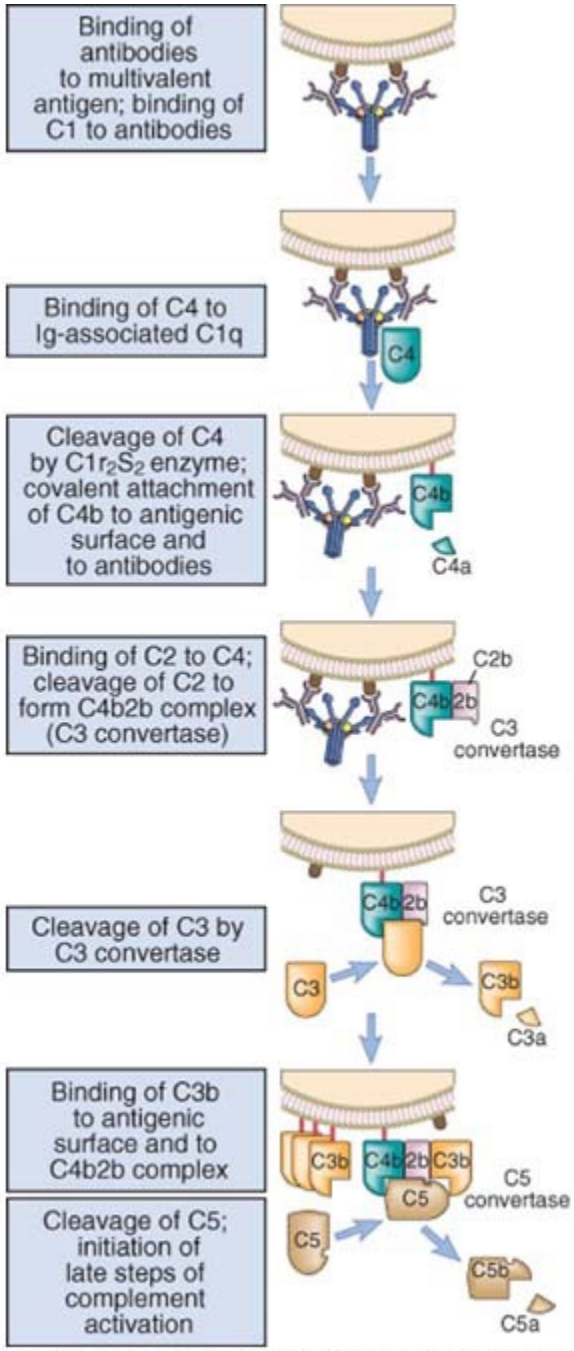
FIGURE 19.1 Types of antibodies that cause disease. This figure illustrates the different forms of antibodies that may cause disease. *Antitissue/cell antibodies*: Antibodies may bind specifically to extracellular tissue antigens and the recruited leukocytes cause tissue injury, or antibodies may bind to cells (in this example, circulating red cells) and promote depletion of these cells. *Immune complexes*: Complexes of antibodies and antigens may be formed in the circulation and deposited in the walls of blood vessels, where the complexes induce inflammation.

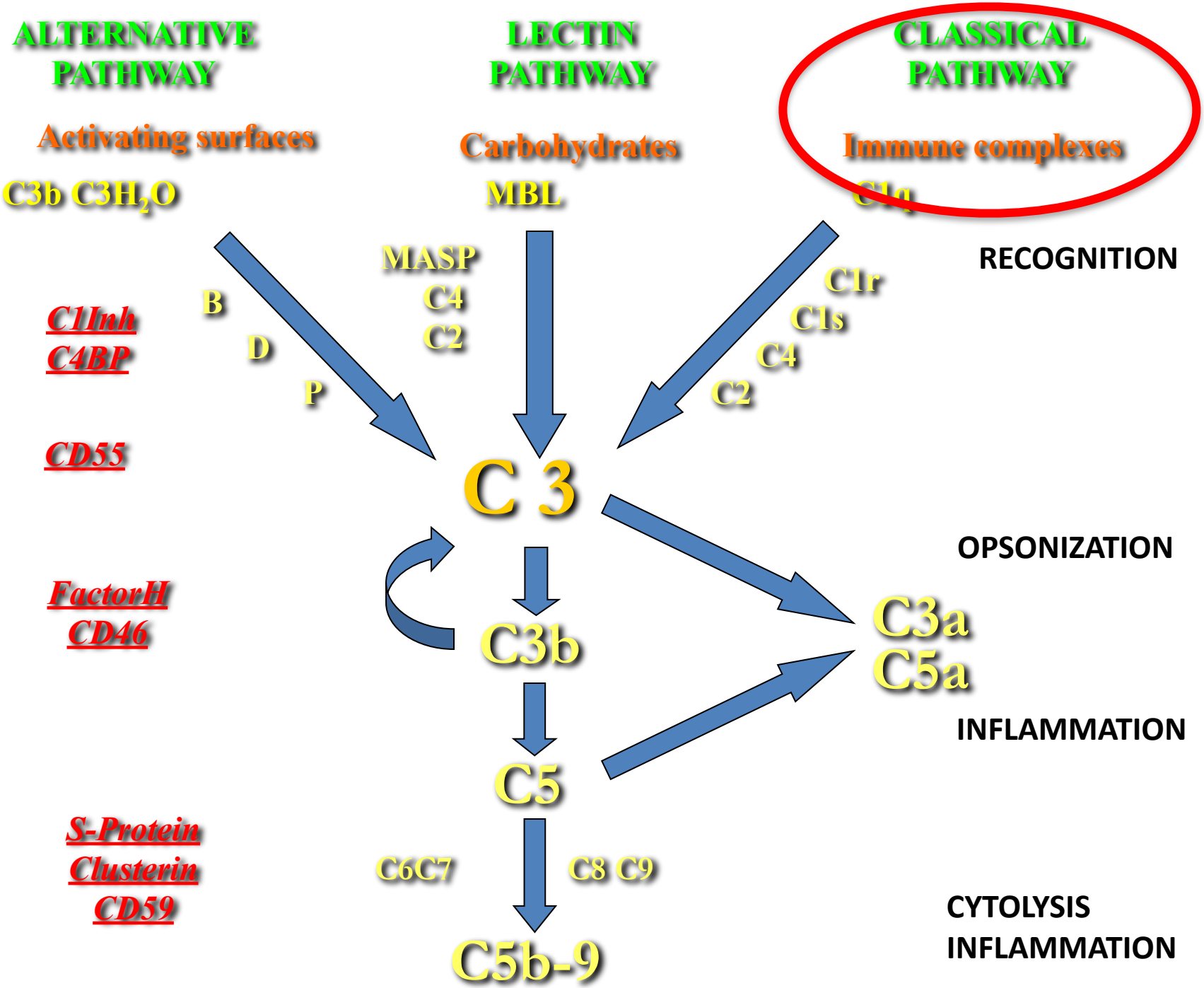
Type II Hypersensitivity

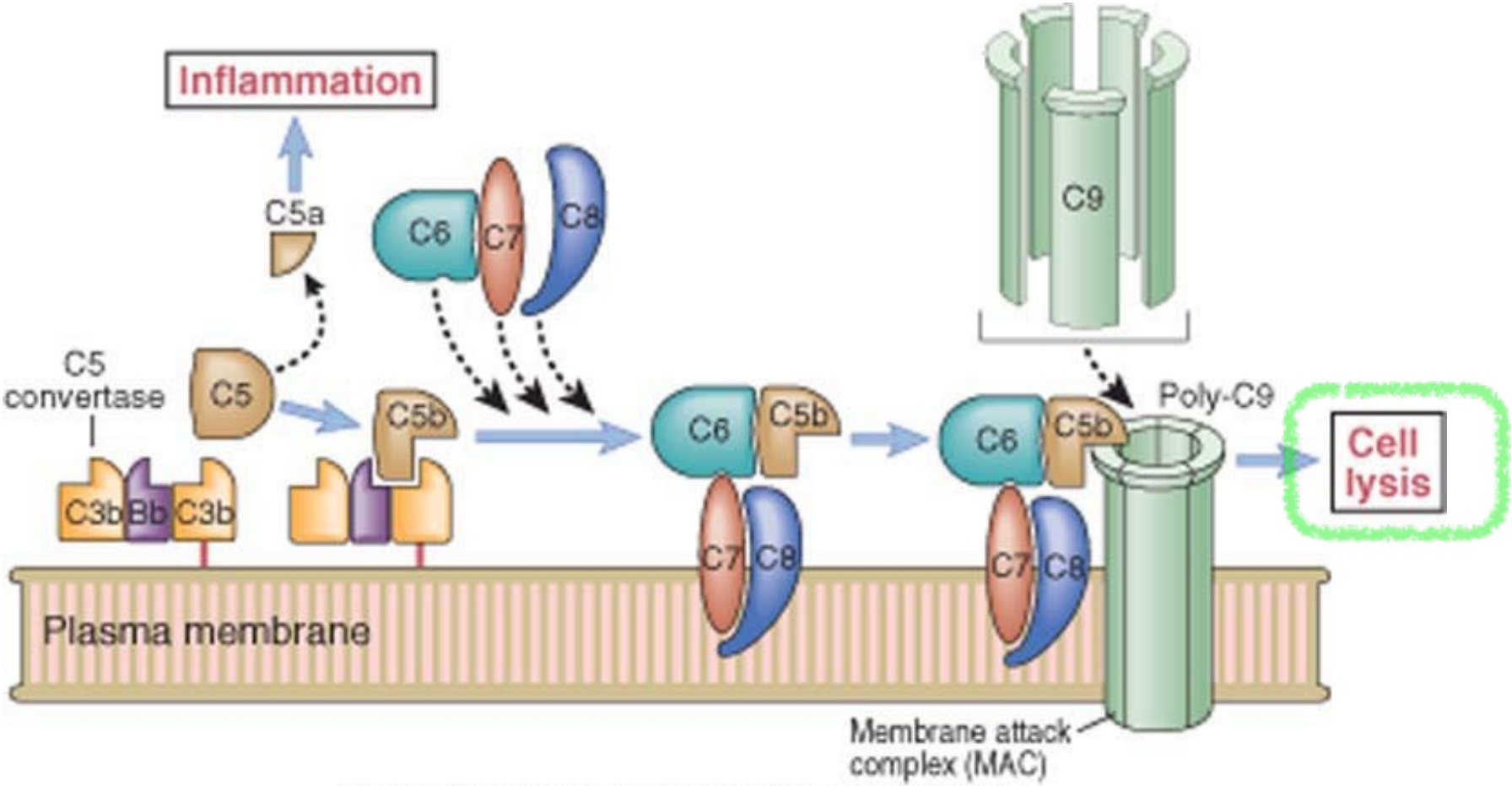
- Target antigens are found on cell or tissues
- Antibody binds to Target Antigen
  - **complement activated cell destruction (CDC)**

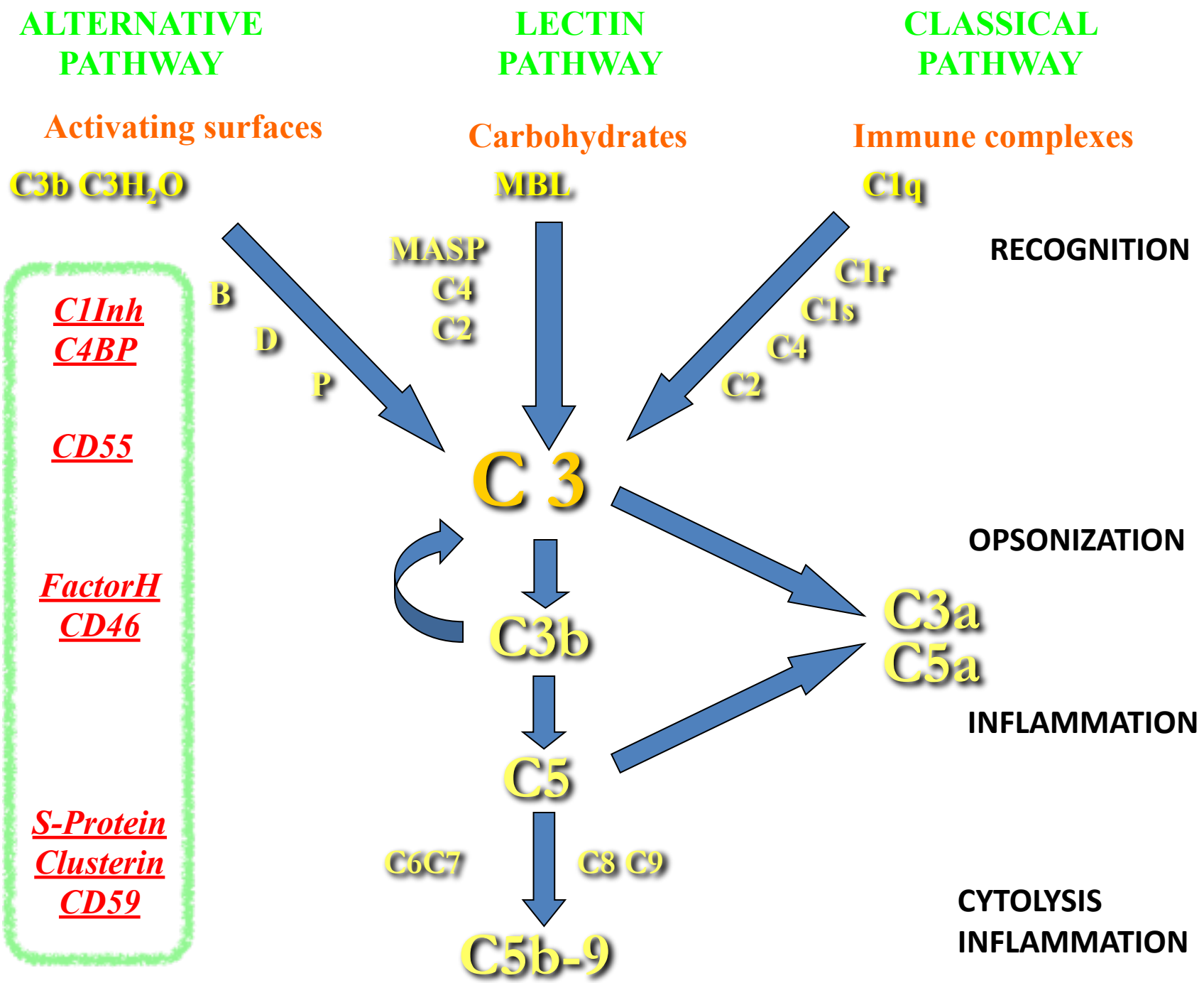







ALTERNATIVE PATHWAY
LECTIN PATHWAY
CLASSICAL PATHWAY
Activating surfaces
Carbohydrates
Immune complexes
C3b C3H2O
MBL
C1q
RECOGNITION
MASP
C4
C2
C1r
C1s
C4
C2
B
D
P
C1Inh
C4BP
CD55
C 3
OPSONIZATION
FactorH
CD46
C3b
C3a
C5a
INFLAMMATION
C5
S-Protein
Clusterin
CD59
C6C7
C8 C9
CYTOLYSIS
INFLAMMATION
C5b-9




ALTERNATIVE PATHWAY
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D
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C1s
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C4BP
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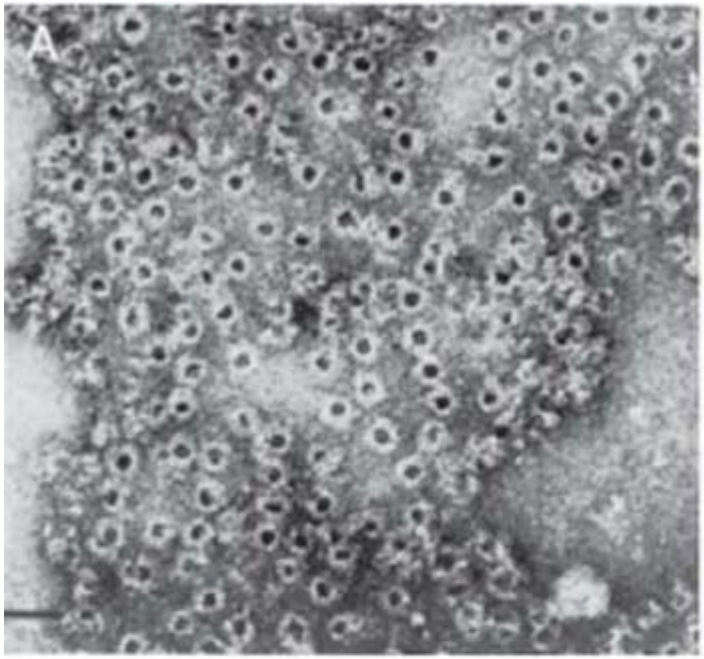
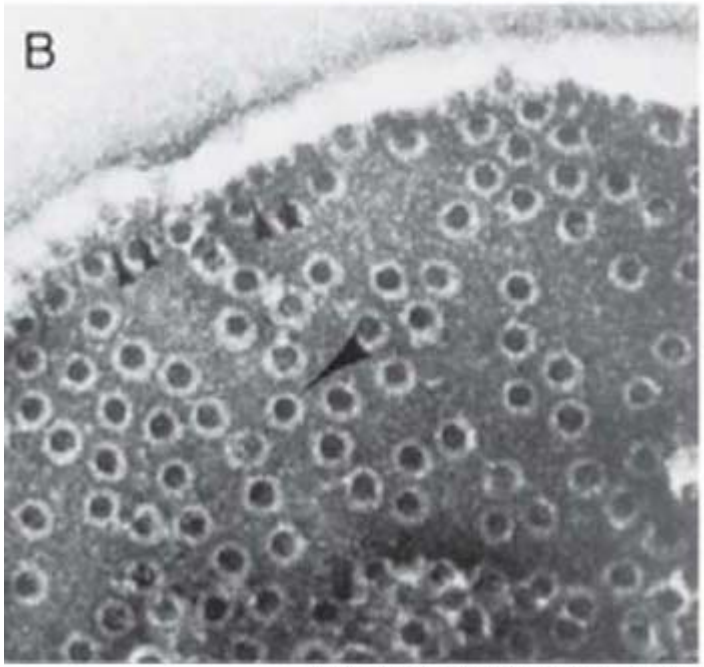
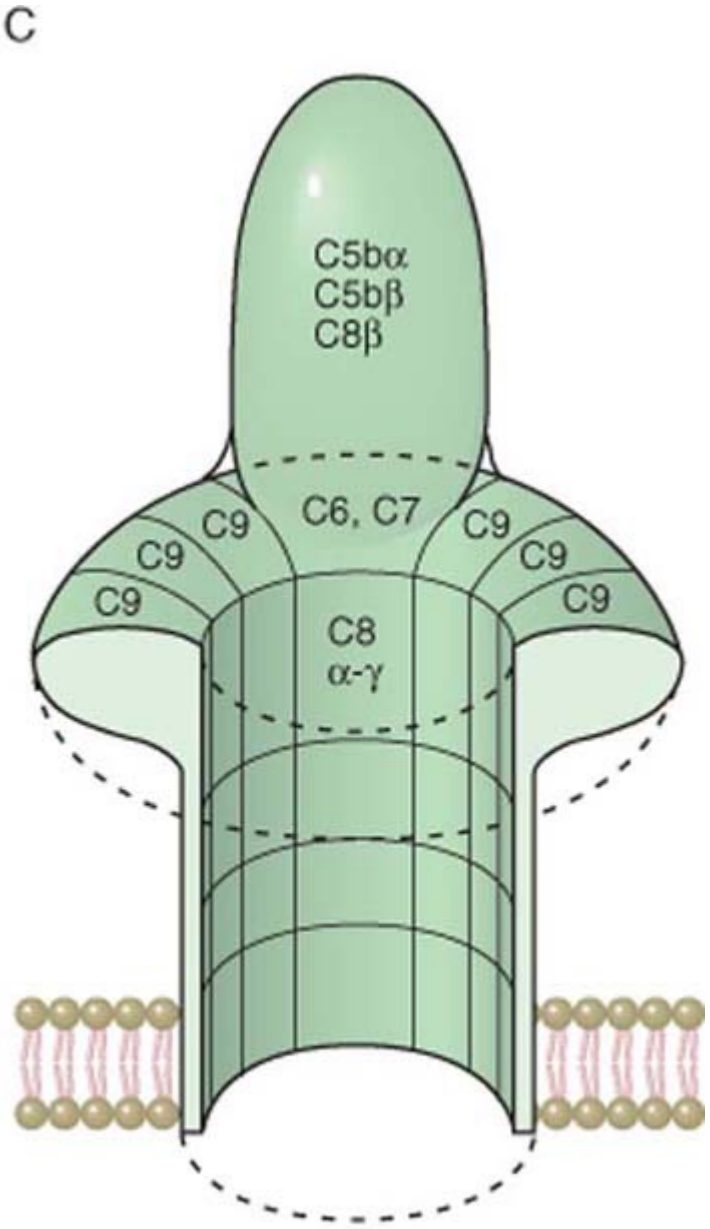
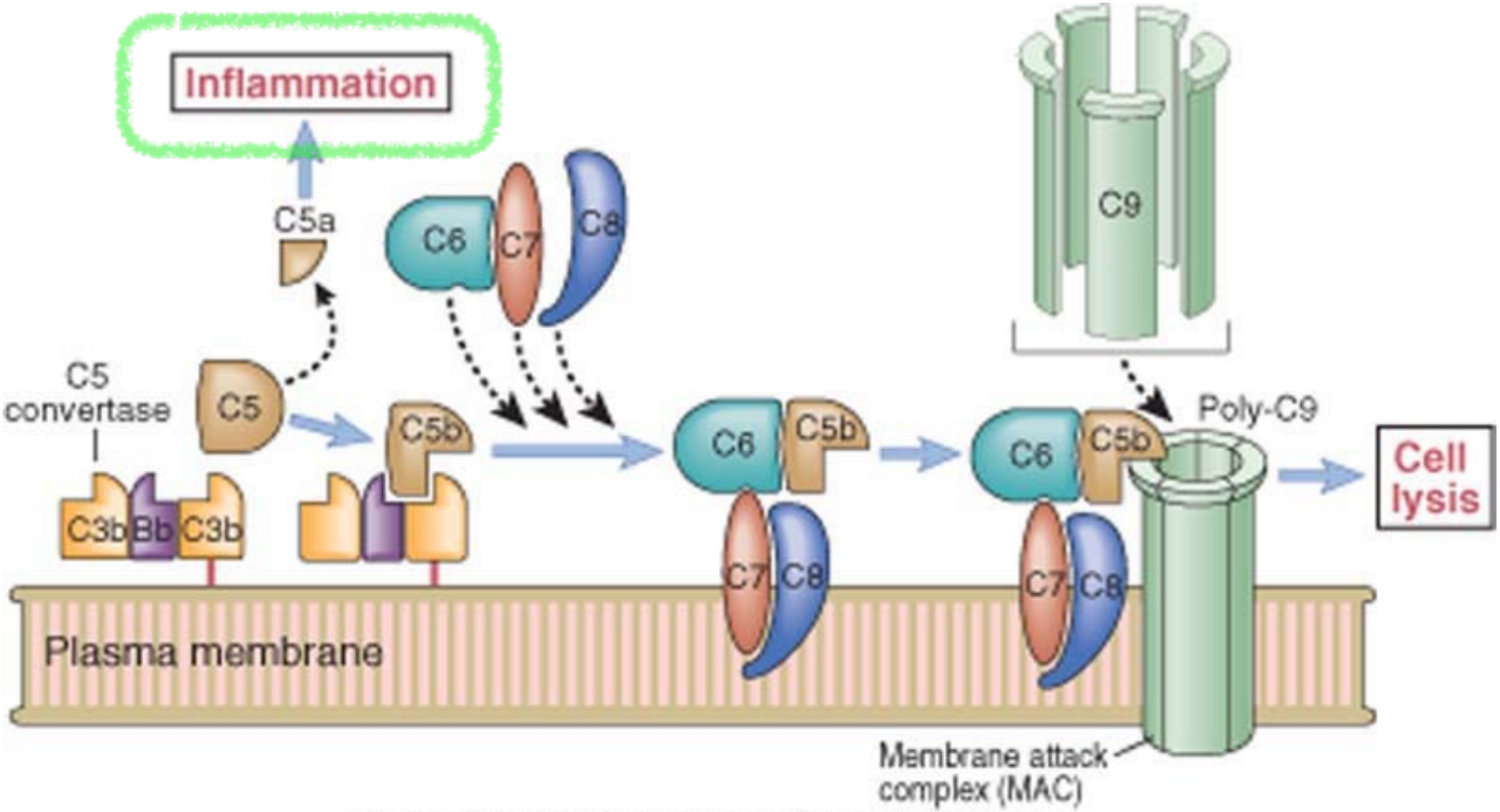
FactorH
CD46
S-Protein
Clusterin
CD59
C 3
C3b
C5
C3a
C5a
OPSONIZATION
INFLAMMATION
C6C7
C8 C9
C5b-9
CYTOLYSIS
INFLAMMATION









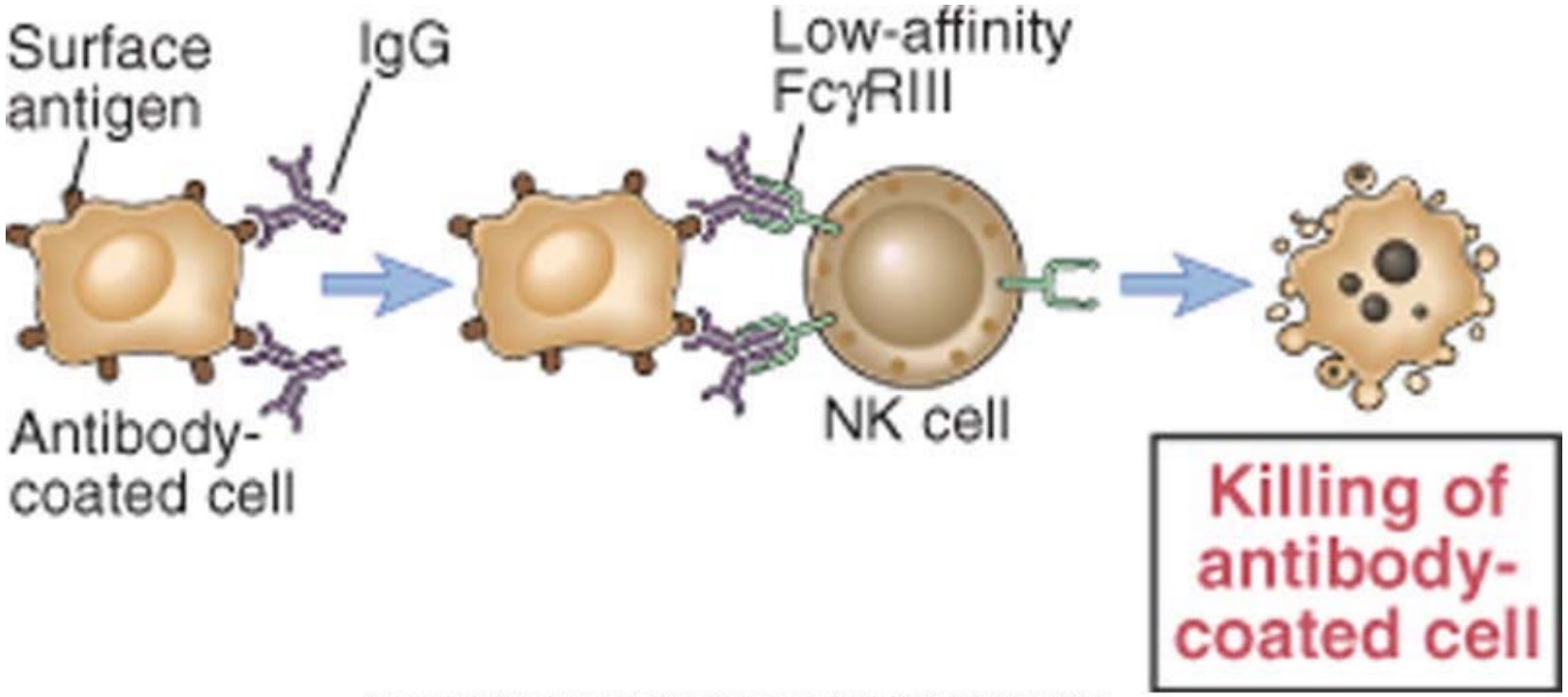
Type II Hypersensitivity

- Target antigens are found on cell or tissues
- Antibody binds to Target Antigen

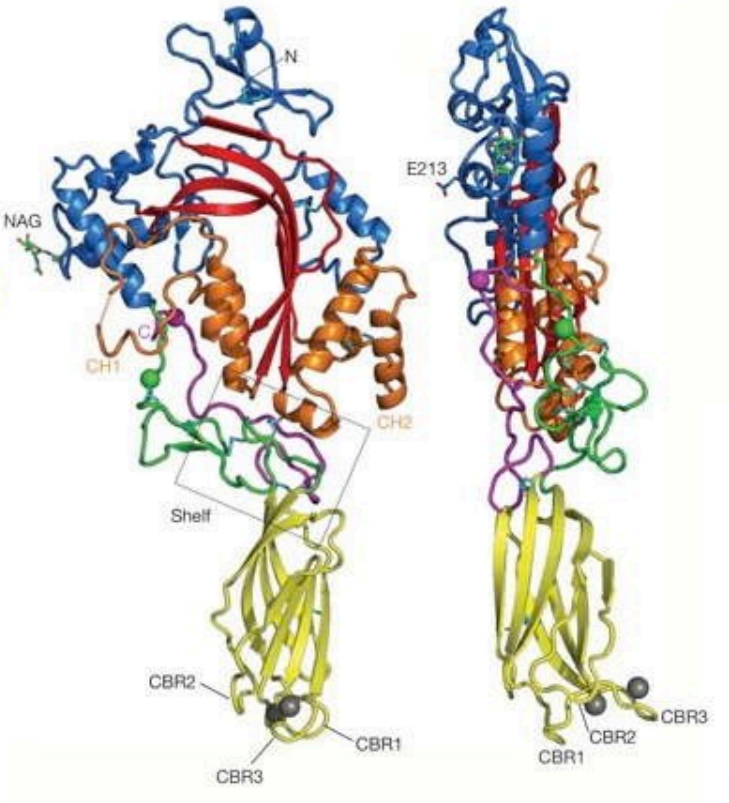
  - complement activated cell destruction

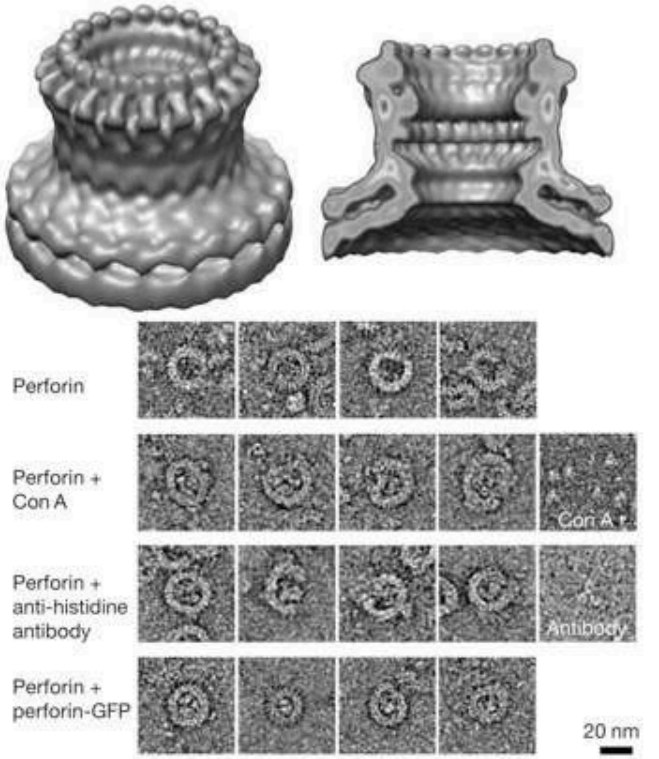
  - Ig binds to Fc receptors on effector cells

FcR	Affinity for immunoglobulin	Cell Distribution	Function
Fc γ RI (CD64)	High (Kd ~ 10^{-9} M) binds IgG1 and IgG3	Macrophages, neutrophils; also eosinophils	Phagocytosis, activation of phagocytes
Fc γ RIIA (CD32)	Low (Kd > 10^{-7} M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
Fc γ RIIB (CD32)	Low (Kd > 10^{-7} M)	B lymphocytes, dendritic cells, macrophages	Feedback inhibition of B cells, macrophages, dendritic cells
Fc γ RIIIA (CD16)	Low (Kd > 10^{-6} M)	NK cells	Antibody-dependent cell-mediated cytotoxicity
Fc γ RIIIB (CD16)	Low (Kd > 10^{-6} M) GPI-linked protein	Neutrophils, other cells	Phagocytosis (inefficient)
Fc ε RI	High (Kd > 10^{-10} M) binds monomeric IgE	Mast cells, basophils, eosinophils	Cell activation (degranulation)
Fc ε RII (CD23)	Low (Kd > 10^{-7} M)	B lymphocytes, eosinophils, Langerhans cells	Unknown
Fc α R (CD89)	Low (Kd > 10^{-6}M)	Neutrophils, eosinophils, monocytes	Cell activation?



Structures of the lymphocyte perforin monomer and pore network





Law RHP et al Nature 468: 447 (2010)

Type II Hypersensitivity: Antibody mediated cytotoxic

Transfusion reactions

Hemolytic disease of the newborn

Drug induced hemolytic anemia

Nephrotoxic (Masugi type) nephtris

Autoimmune hemolytic anemias

Anti receptors/ hormone autoimmune diseases

(Graves Disease / myasthenia gravis)

Transfusion Reactions

Major Incompatibility

(recipient has Abs to donor RBCs)

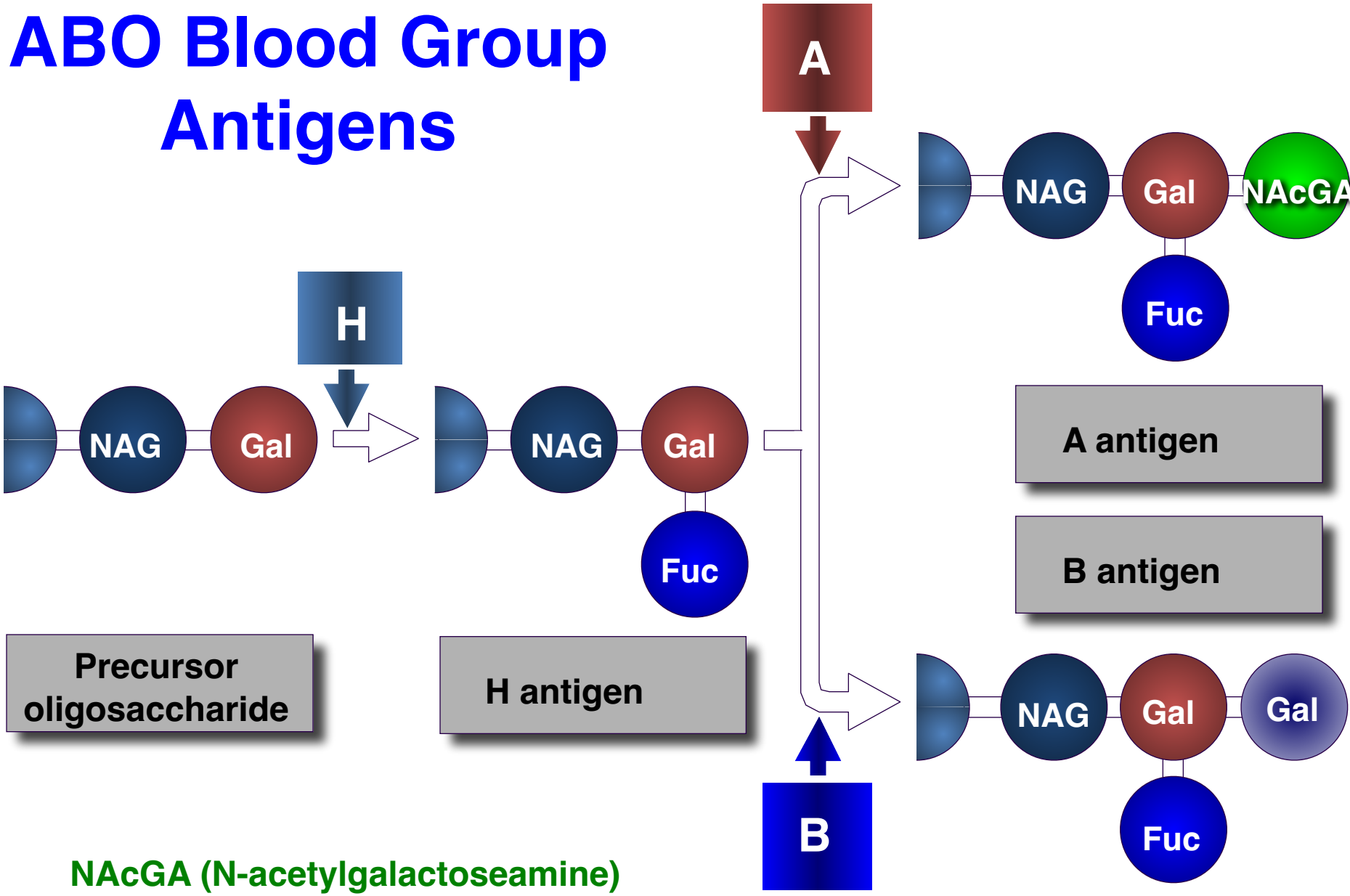
- chills, fever, pain & shock
- large amounts of hemoglobin released
- blood pressure drops, renal failure, coagulation

Minor Incompatibility

(donor has Abs to recipient RBCs)

- slowly falling hematocrit

ABO Blood Group Antigens



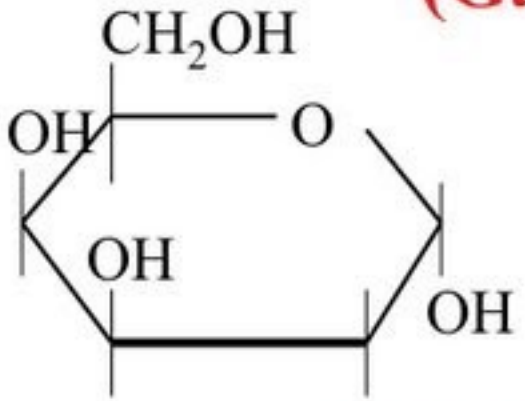
NAcGA (N-acetylgalactoseamine)

Gal (galactose)

Immunodominant Sugars

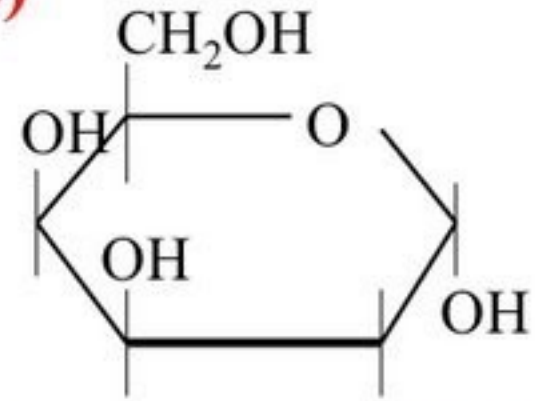
A

***N*-acetyl-D-galactosamine**
(GalNAc)

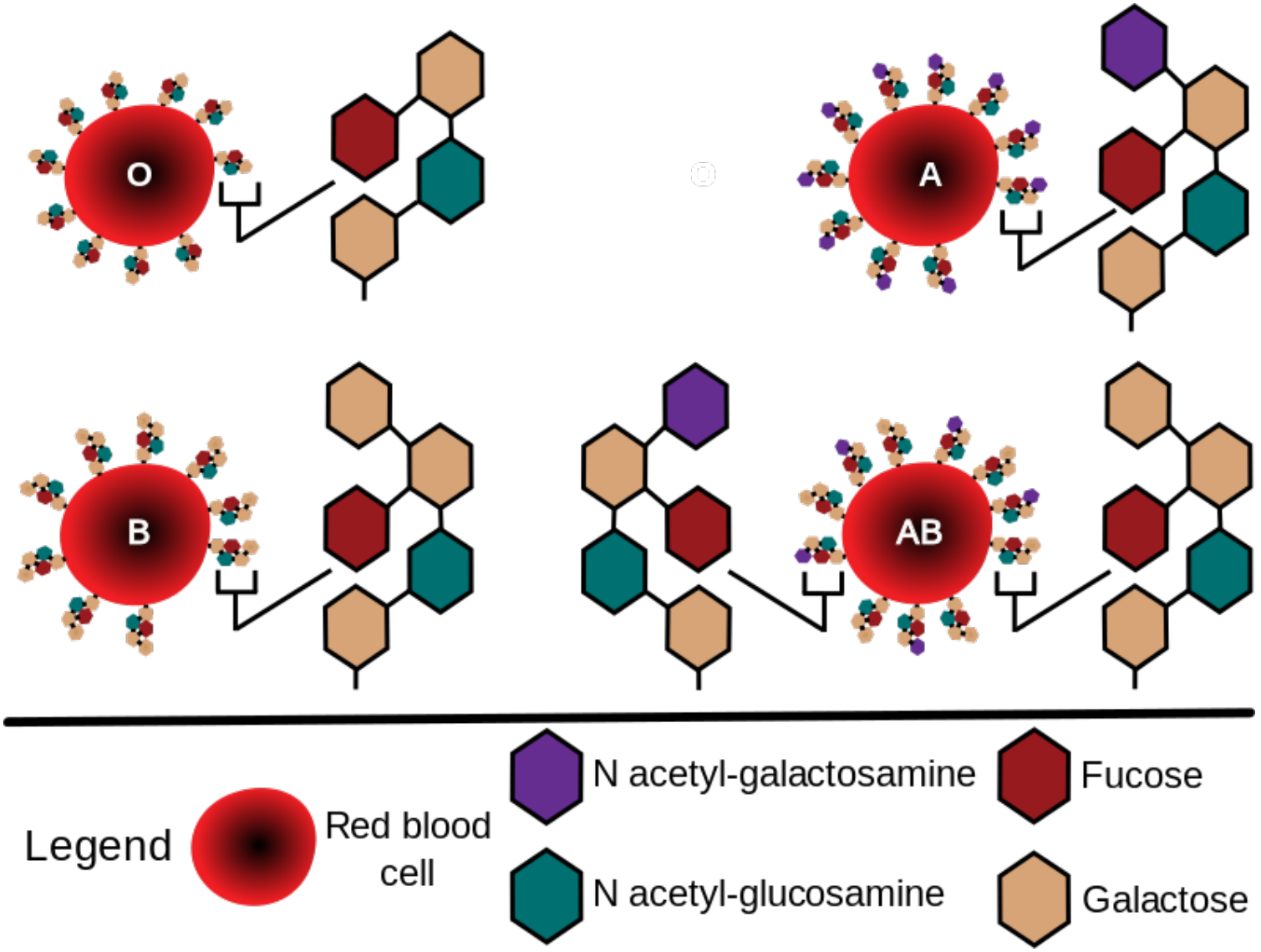


B

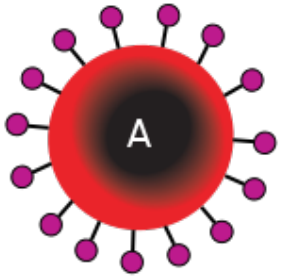
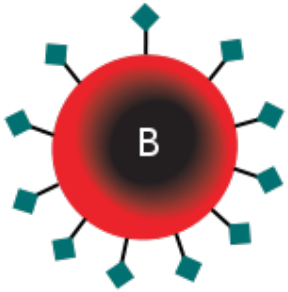
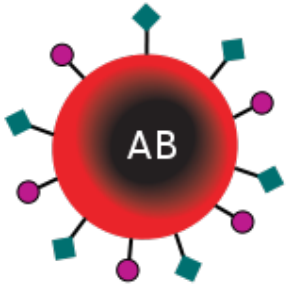
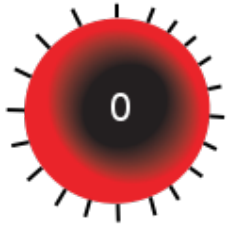
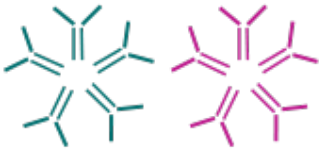
D-galactose



ABO Blood Group Antigens



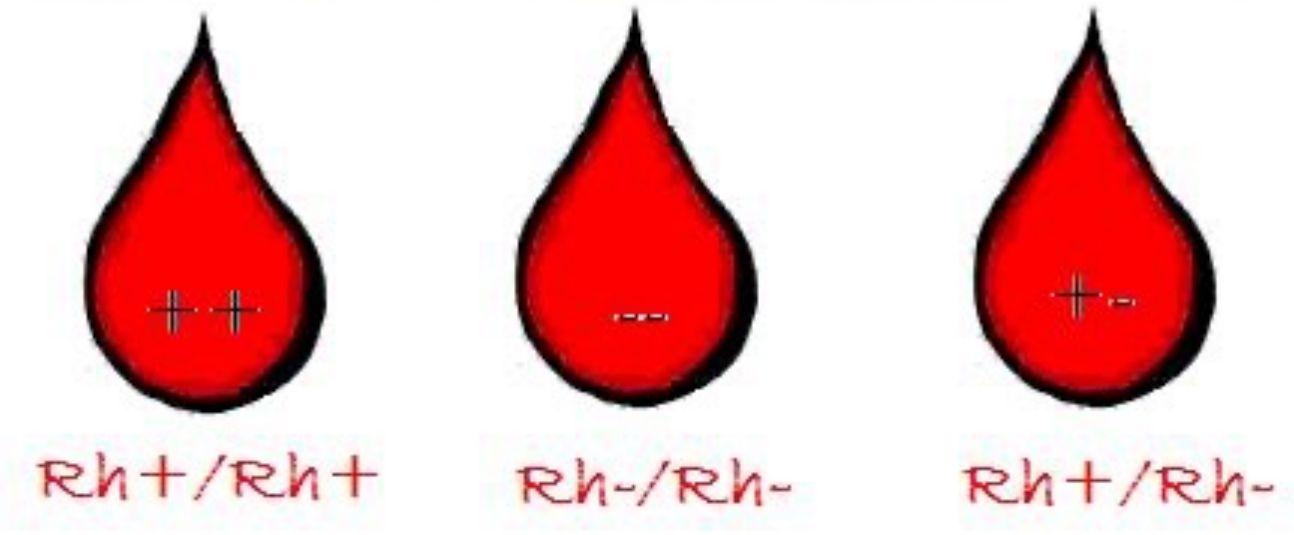
ABO Blood Group Reactivity

	Gruppo A	Gruppo B	Gruppo AB	Gruppo 0
Tipi di GLOBULI ROSSI				
Anticorpi presenti	 Anti-B	 Anti-A	Nessuno	 Anti-A e Anti-B
Antigeni presenti	 A	 B	 A e B	Nessuno

AB0 distribution

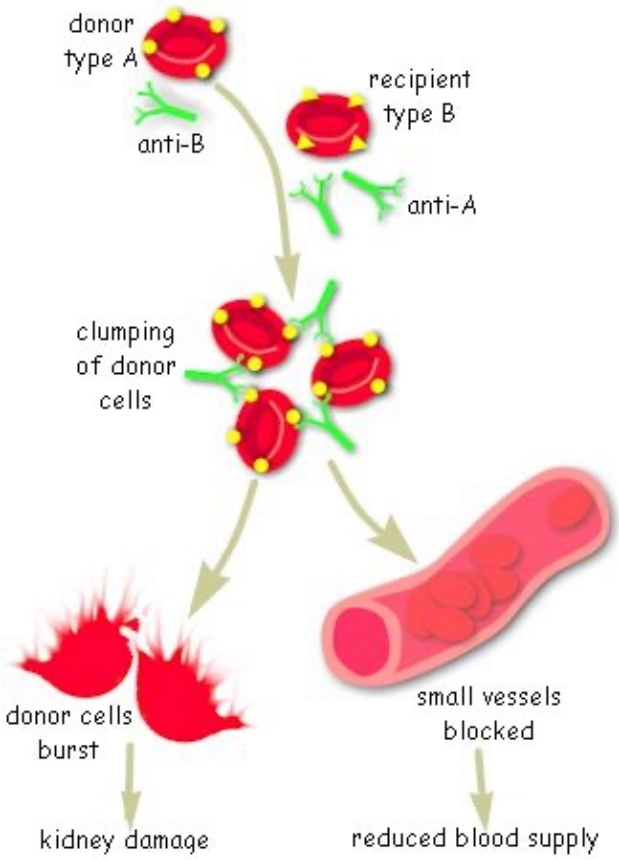
Grup	Population		
	White	Black	Eastern
A	45	29	35,4
B	8	17	22,5
AB	4	4	12,6
0	43	50	29,5

Ag Rhesus (Rh)



Type II Hypersensitivity:

Transfusion reactions



- Produced by mismatched blood types
  - Destroys foreign RBC by complement-mediated lysis triggered by IgG
    - Produces fever, intravascular clots, lower back pain, Hgb in urine
  - Free Hgb produced has 2 fates:
    - passes to the kidneys – hemoglobinuria
    - Breaks down to bilirubin..can be toxic

Type II Hypersensitivity:

Hemolytic Disease of the Newborn

- Occurs via maternal IgG Ab's crossing the placenta
- In severe cases causes **erythroblastosis fetalis**
  - Most commonly develops in Rh- mother with Rh+ fetus
  - Exposure to Rh+ fetal RBC's stimualtes production of memory/plasma cells
  - Activation of memory cells in subsequent pregnancy stimulate IgG production which can cross the placenta
  - mild-severe hemolytic anemia ensues along with bilirubin which affects the brain/CNS

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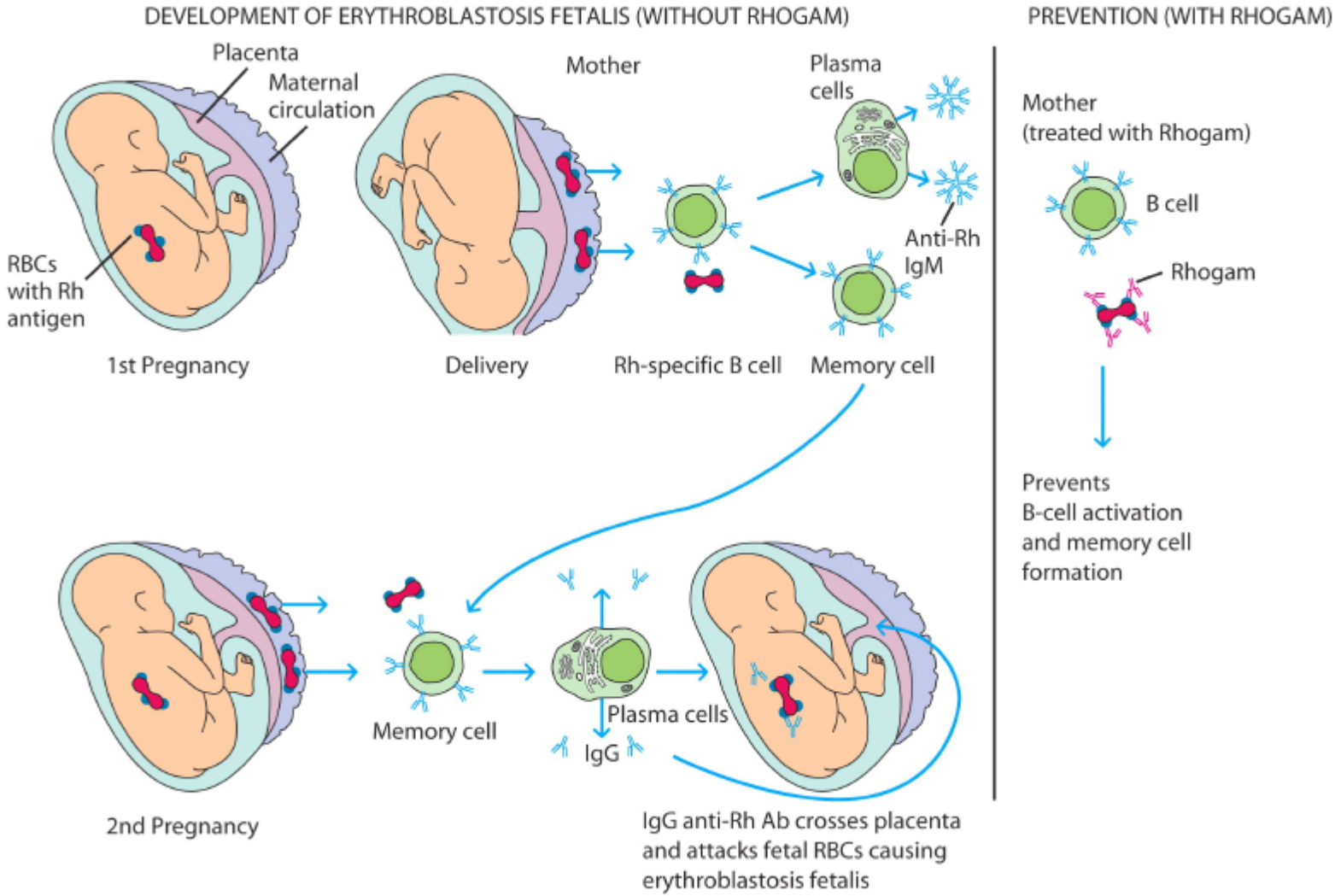
  - Activation of memory cells in subsequent pregnancy stim IgG Ab's which can cross the placenta
  - mild-severe hemolytic anemia ensues along with bilirubin which affects the brain/CNS

- Treatment centers on anti-Rh antibodies (RhoGAM)
- Mothers can be tested for anti-Rh antibodies to check for a rise in titre
- Isolated fetal RBC's can be checked for anti-Rh IgG w/ Coombs test

Hemolytic Disease of the Newborn



- RhoGAM is purified from human plasma containing anti-Rh
- RhoGAM is administered by intramuscular (IM) injection

Type II Hypersensitivity:

Drug-induced hemolytic anemia

- Drugs such as aspirin and antibiotics can bind to the surfaces of RBC's
- These interactions act similar to hapten-carrier conjugation
- Such complexes can trigger Ab-mediated cell lysis by complement activation

Type II Hypersensitivity:

Nephrotoxic Nephritis

Antibodies against glomerular basement membrane

Goodpasture's syndrome

(also lung basement membrane)

Linear binding of Ab

fixation of complement

Inflammatory cells

Type II Hypersensitivity:

Thyroiditis

Graves Disease

Antibodies to receptor of Thyroid Stimulating Hormone (TSH-R)

Hyperthyroidism

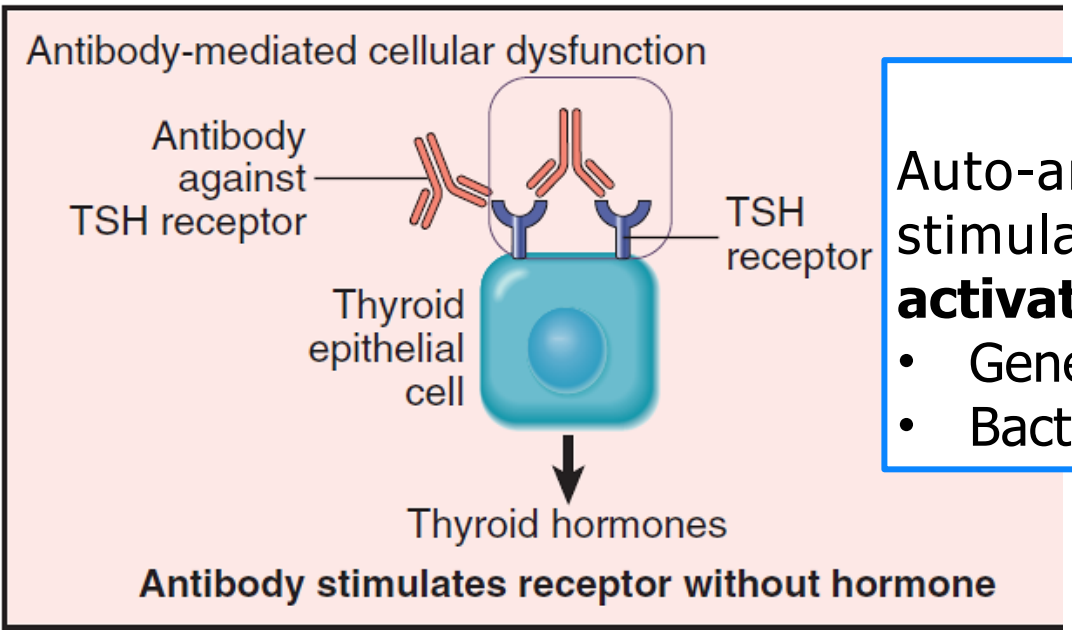
Hashimoto's Thyroiditis

Autoantibodies to thyroid proteins

T_{DTH} cells: lymphocyte infiltration

hypothyroidism- Goiter

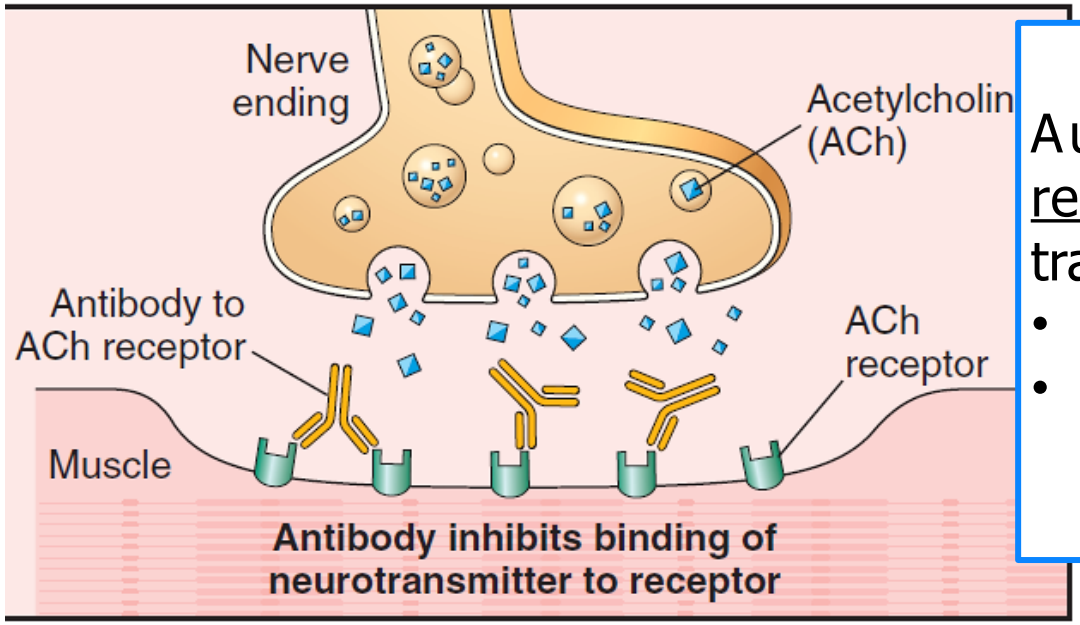
Antireceptor antibodies disturb the normal function of receptors



Graves disease

Auto-antibodies against the thyroid-stimulating hormone (TSH) receptor **activate** thyroid cells: **hyperthyroidism**

- Genetic susceptibility
- Bacterial and/or viral infections (?)



Myastenia gravis

Auto-antibodies against ACh receptor impair neuromuscular transmission: muscle **weakness**

- Genetic susceptibility
- **Treg dysfuntion** (low levels of transcription factor **FOXP3**, crucial for Treg function)

Effector mechanisms of Ab-mediated disorders

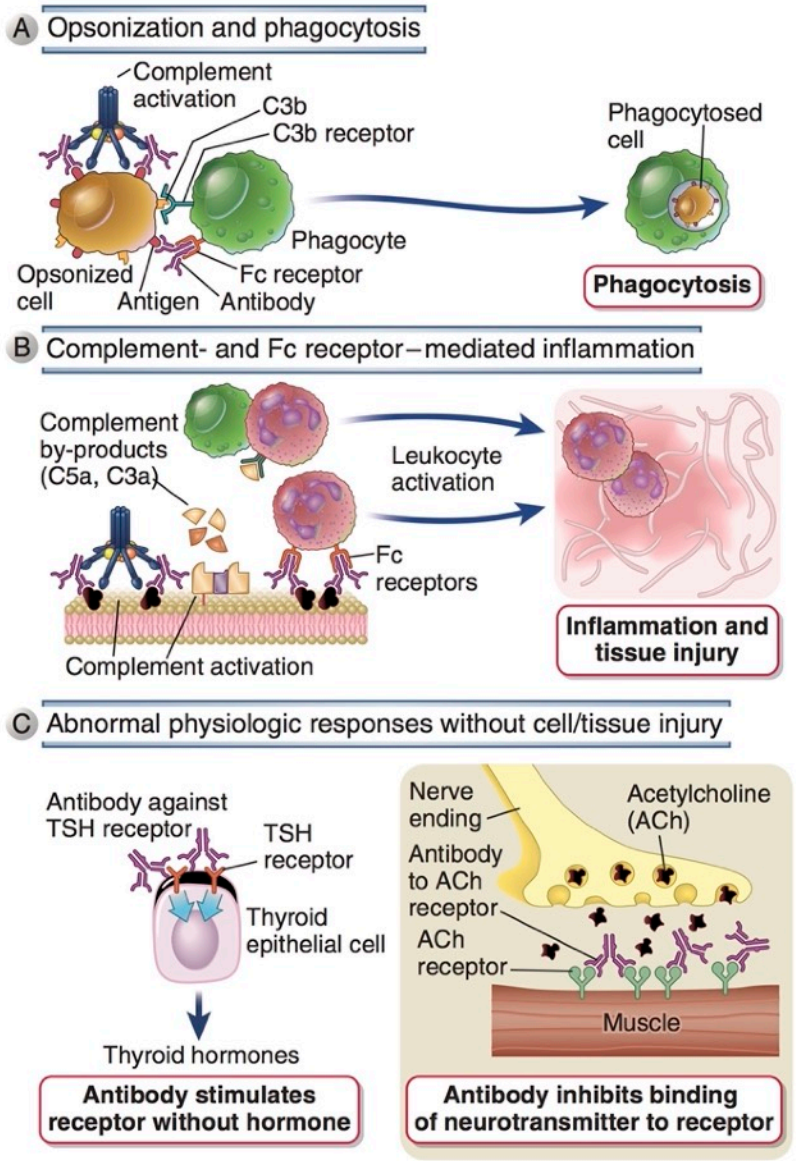


FIGURE 19.2 Effector mechanisms of antibody-mediated disease. A, Antibodies opsonize cells and may activate complement, generating complement products that also opsonize cells, leading to phagocytosis of the cells through phagocyte Fc receptors or C3b receptors. **B,** Antibodies recruit leukocytes by binding to Fc receptors or by activating complement and thereby releasing by-products that are chemotactic for leukocytes. **C,** Antibodies specific for cell surface hormone receptors or neurotransmitter receptors interfere with normal physiology. For example, in Graves' disease *(left panel)* autoantibodies specific for thyroid stimulating hormone (TSH) receptors in the thyroid gland stimulate the activity of the receptors even in the absence of TSH, causing excess thyroid hormone release (hyperthyroidism). In myasthenia gravis *(right panel)*, autoantibodies specific for the acetylcholine receptor on muscle cells block the action of acetylcholine, leading to paralysis.

TABLE 19.1 Classification of Hypersensitivity Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: Type I	IgE antibody, Th2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody-mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, for example, hormone receptor signaling, neurotransmitter receptor blockade
Immune complex–mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell–mediated: Type IV	1. $CD4^+$ T cells (Th1 and Th17 cells) 2. $CD8^+$ CTLs	1. Cytokine-mediated inflammation and macrophage activation 2. Direct target cell killing, cytokine-mediated inflammation

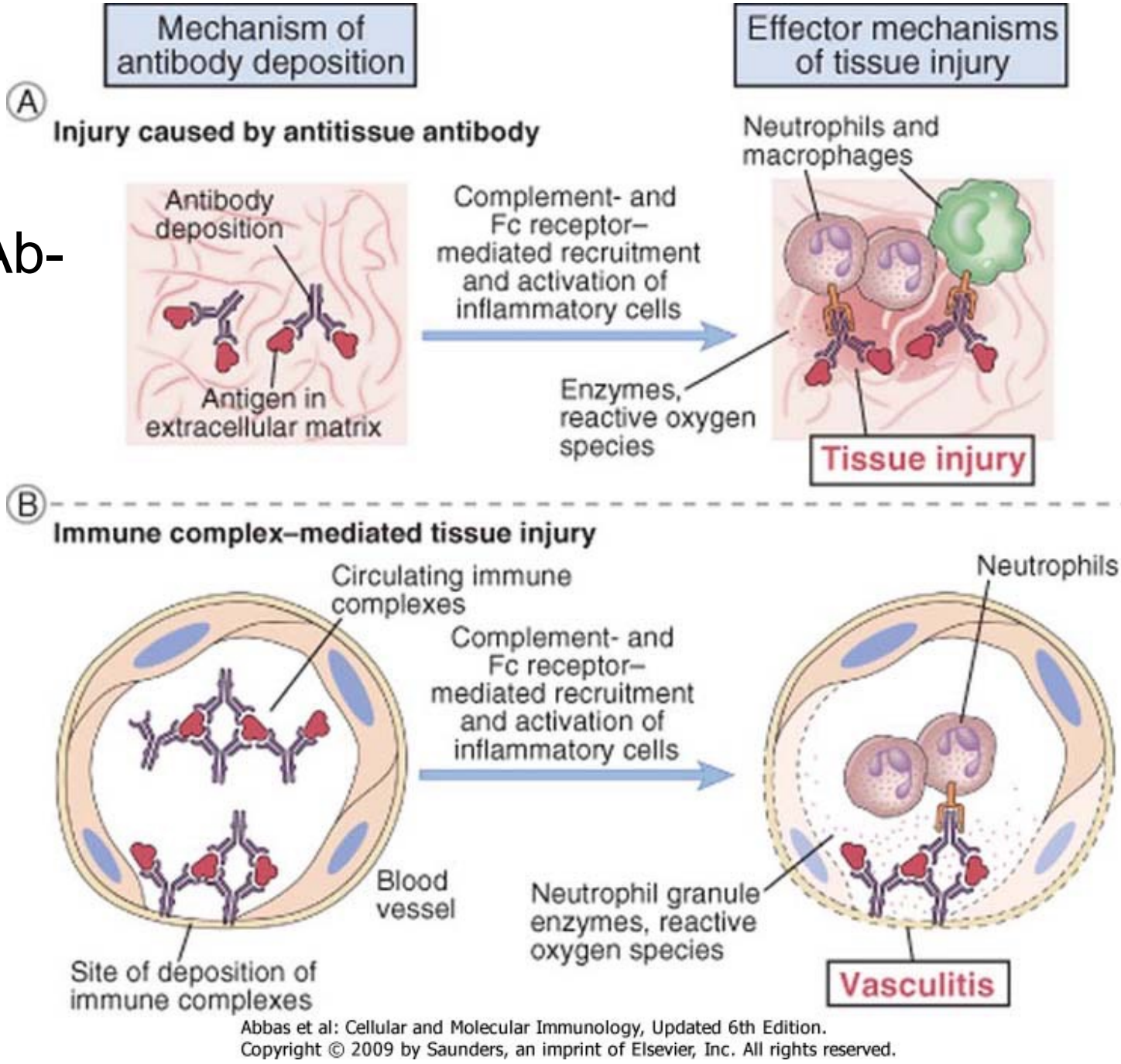
CTLs, Cytotoxic T lymphocytes; *Ig,* immunoglobulin.

Type III Hypersensitivity

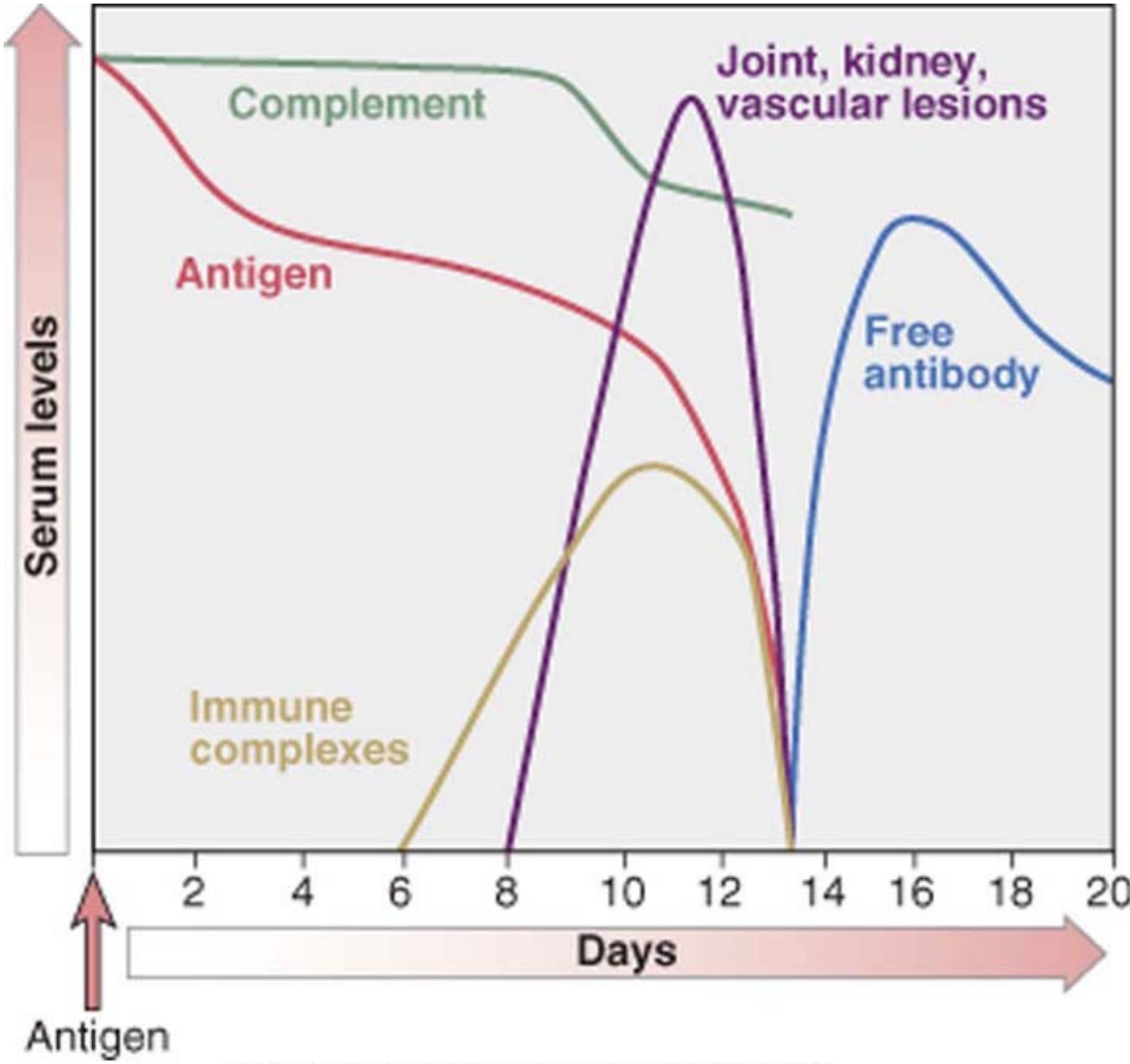
Immune Complex Reactions

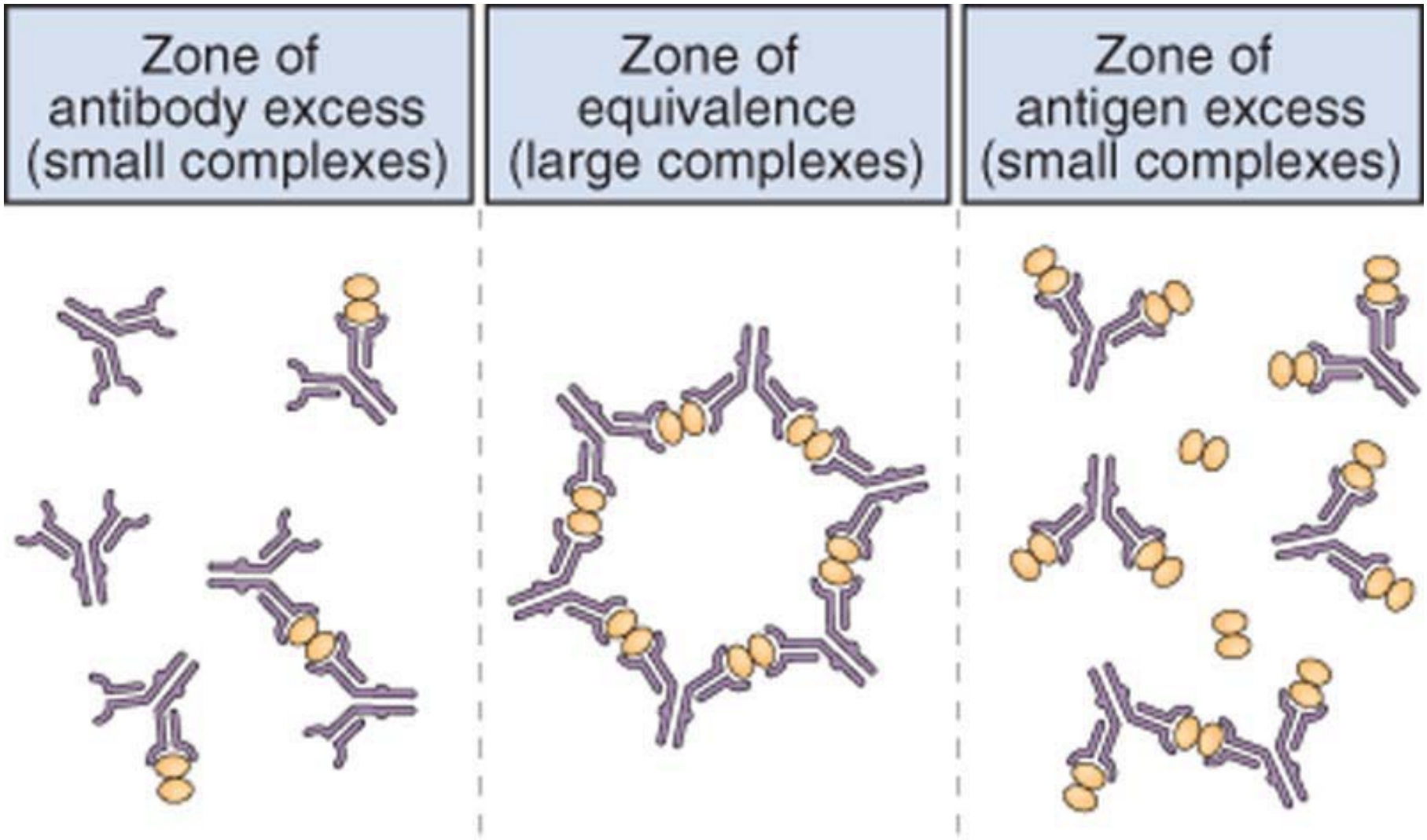
Antigens are in solution in plasma or interstitial fluids. Abs combine with these Ags, fix complement and initiate the consequences of the complement cascade

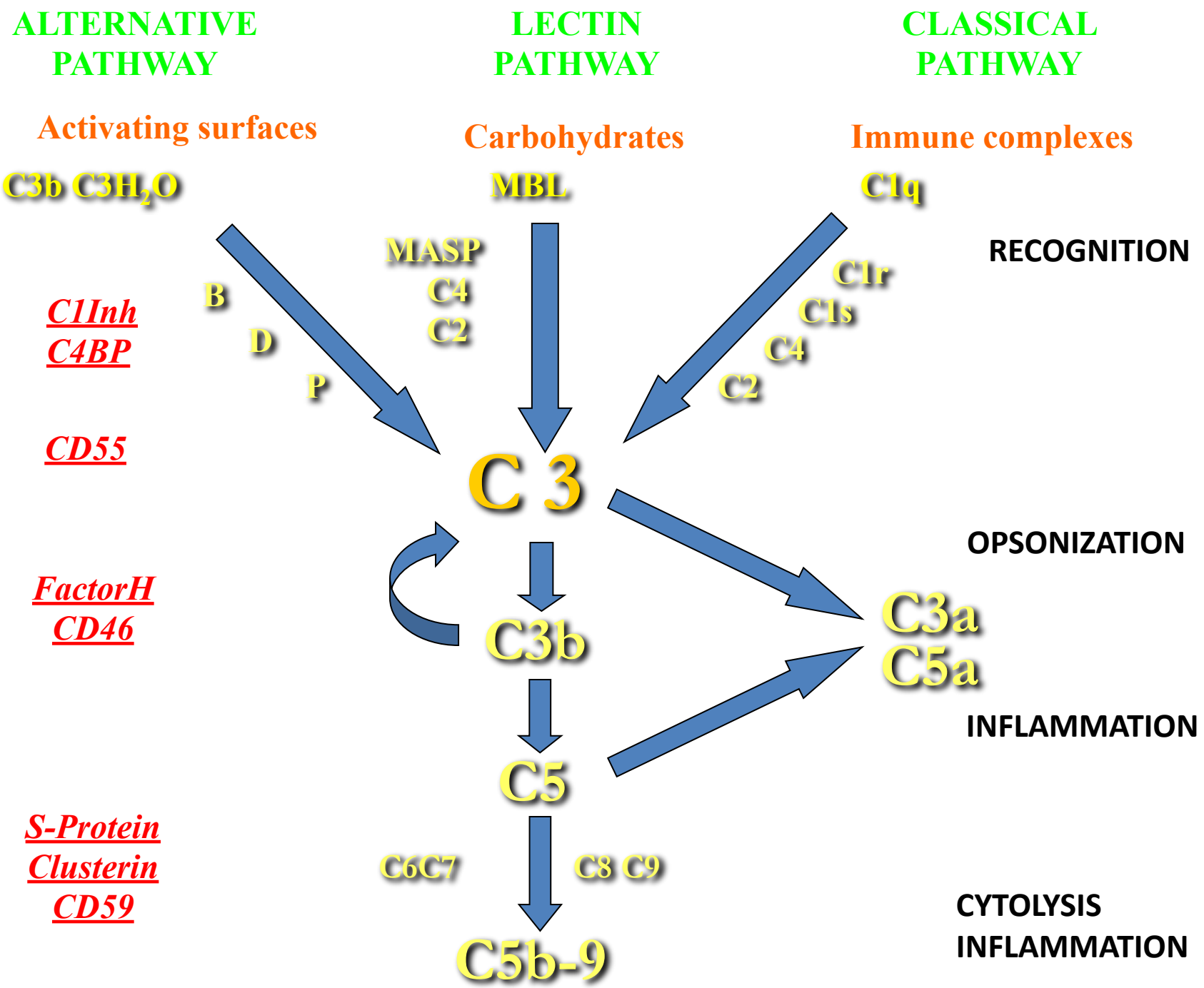
Examples of Ab-mediated disorders



Sequence of the immunological response






ALTERNATIVE PATHWAY
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C4BP
CD55
C 3
OPSONIZATION
FactorH
CD46
C3b
C3a
C5a
INFLAMMATION
C5
S-Protein
Clusterin
CD59
C6C7
C8 C9
CYTOLYSIS
INFLAMMATION
C5b-9

Inflammatory Mechanisms in Type III

- Complement activation
  - Anaphylatoxins
  - Chemotactic factors

- Neutrophils attracted
  - difficult to phagocytize tissue-trapped complexes
  - frustrated phagocytosis leads to tissue damage

Diseases associated with immune complexes

- Persistent infection
  - microbial antigens
  - deposition of immune complexes in kidneys
- Autoimmunity
  - self antigens
  - deposition of immune complexes in kidneys, joints, arteries and skin
- Extrinsic factors
  - environmental antigens
  - deposition of immune complexes in lungs

TABLE 19.2 Examples of Diseases Caused by Cell- or Tissue-Specific Antibodies

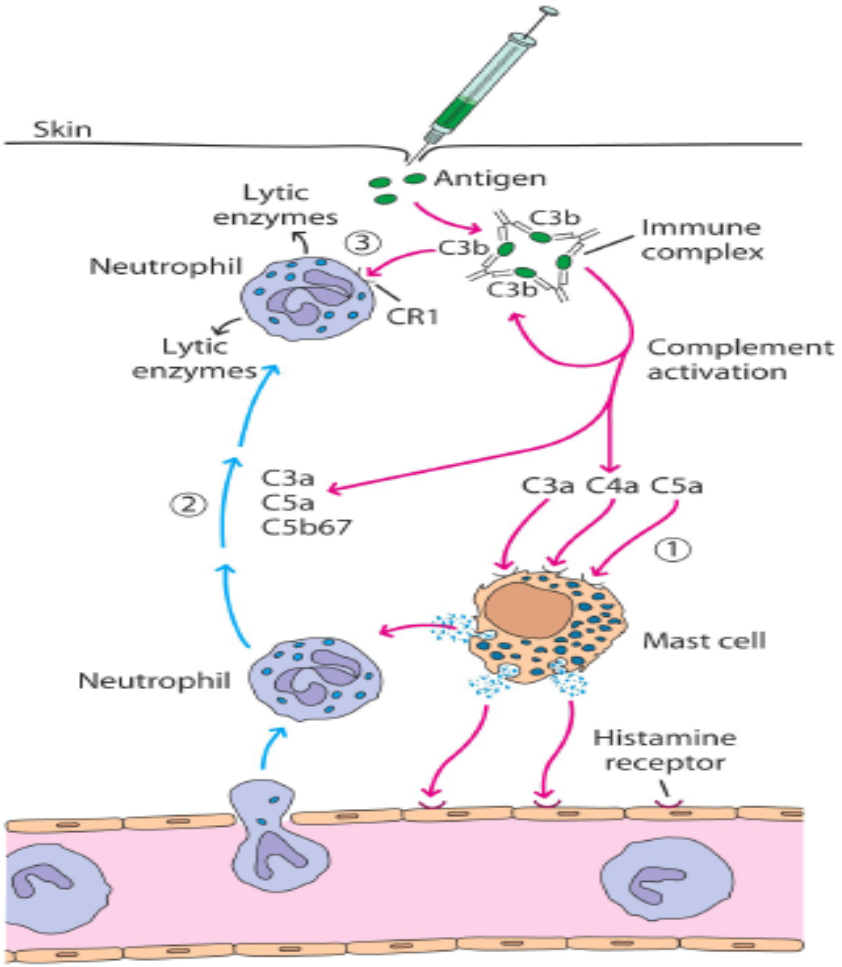
Disease	Target Antigen	Mechanisms of Disease	Clinicopathologic Manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins	Opsonization and phagocytosis of erythrocytes, complement-mediated lysis	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb-IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (desmoglein)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin blisters (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture syndrome	Noncollagenous NC1 protein of basement membrane in glomeruli and lung	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor; decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia, neurologic symptoms

ANCA, Anti-neutrophil cytoplasmic antibodies; *TSH*, thyroid-stimulating hormone.

Type III Hypersensitivity

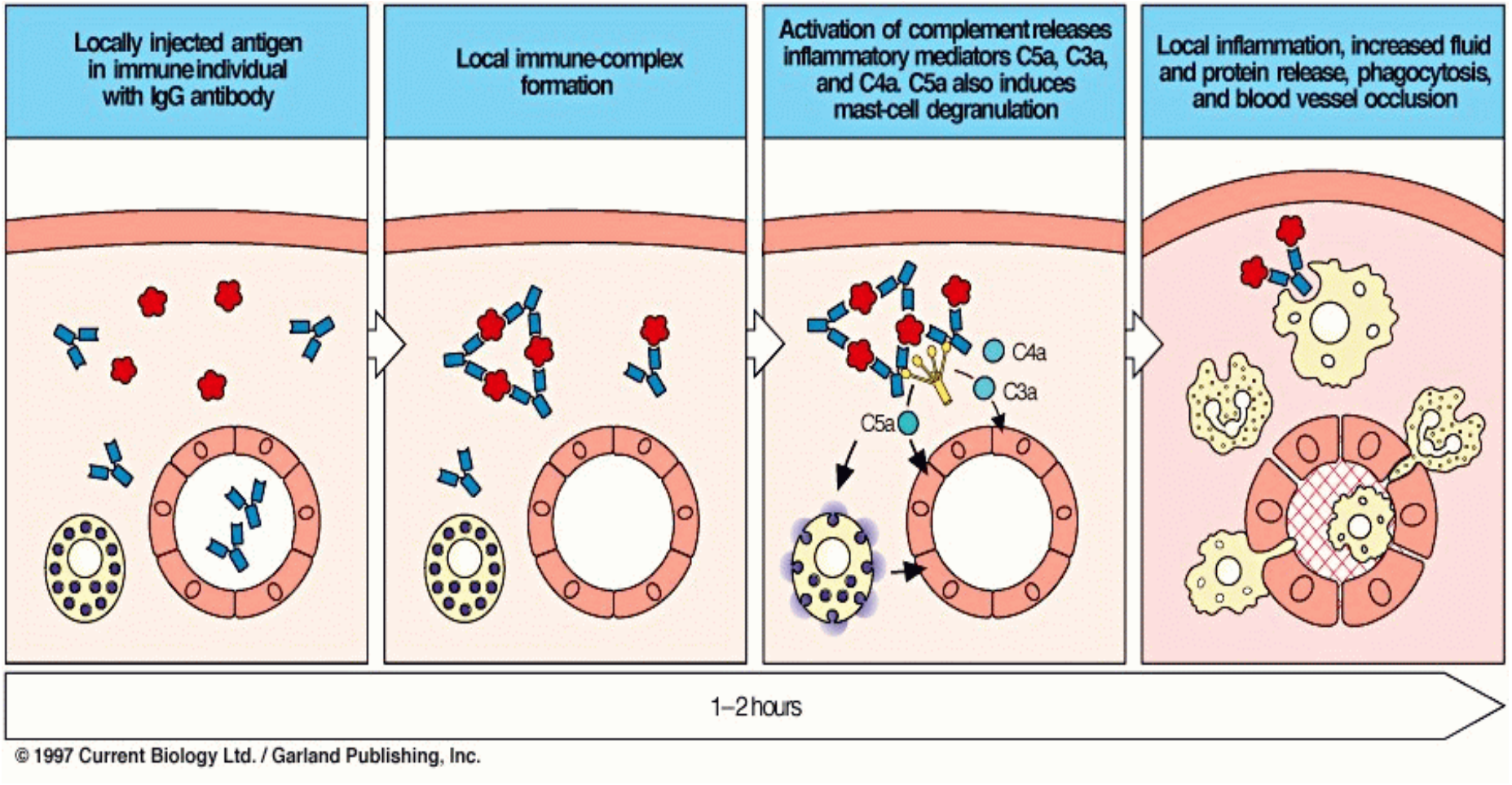
- Localized reactions
  - Arthus type skin reactions
  - complex mediated glomerulonephritis
  - bumpy deposits

Type III Hypersensitivity:
Localized reactions



- Arthus reactions:
  - Exposure to an Ag for which there already is a high concentration of Ab
  - Produces edema/erythema from damage
    - Insect bites
    - Inhalation of bacteria, fungi, dried fecal matter

Arthus Reaction



Type III Hypersensitivity

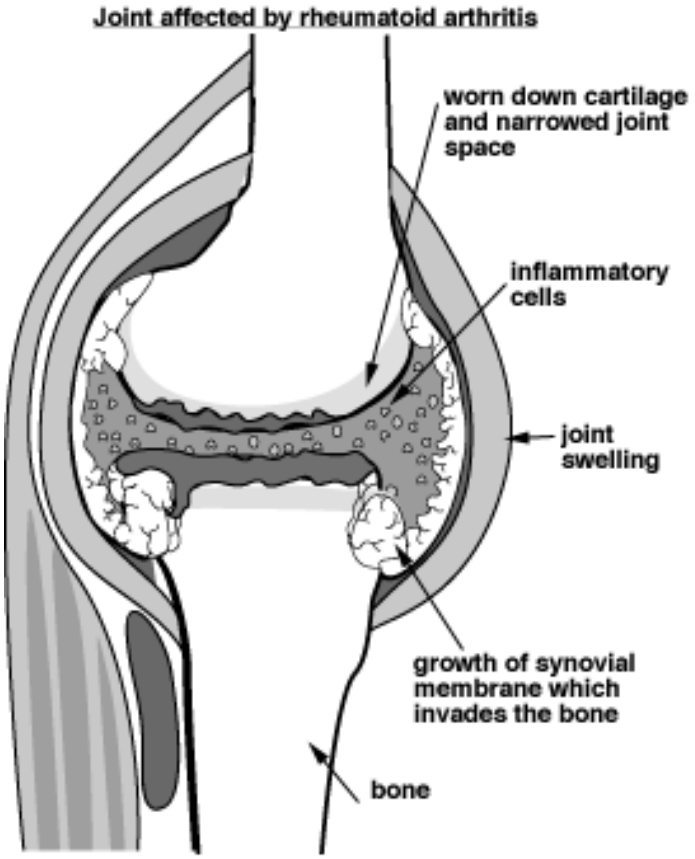
- Localized reactions
  - Arthus type skin reactions
  - complex mediated glomerulonephritis
  - bumpy deposits

- Generalized reactions
  - Serum sickness (injection of large amount of Ag)

Generalized or Systemic Type III

- Acute Systemic Reactions
  - drug reactions penicillin
  - Post streptococcal acute glomerulonephritis
  - Aggregate “anaphylaxis”- cyro-precipitates
- Chronic Systemic Reactions
  - Infections
  - Autoimmune conditions SLE or RA
  - Cutaneous vasculitis

Type III Hypersensitivity:
Systemic (generalized) reactions



- Produced when large amounts of Ag enter the bloodstream
  - The sites of deposition vary; usually in tissues where plasma is filtered
  - Esp. in kidneys, blood vessels, and joints
- Can cause tissue damaging reactions:
  - Serum sickness
  - Autoimmune diseases
  - Drug reactions
  - Infectious diseases

TABLE 19.1 Classification of Hypersensitivity Diseases

Type of Hypersensitivity	Pathologic Immune Mechanisms	Mechanisms of Tissue Injury and Disease
Immediate: Type I	IgE antibody, Th2 cells	Mast cells, eosinophils, and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody-mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, for example, hormone receptor signaling, neurotransmitter receptor blockade
Immune complex–mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement- and Fc receptor–mediated recruitment and activation of leukocytes
T cell–mediated: Type IV	1. $CD4^+$ T cells (Th1 and Th17 cells) 2. $CD8^+$ CTLs	1. Cytokine-mediated inflammation and macrophage activation 2. Direct target cell killing, cytokine-mediated inflammation

CTLs, Cytotoxic T lymphocytes; *Ig,* immunoglobulin.

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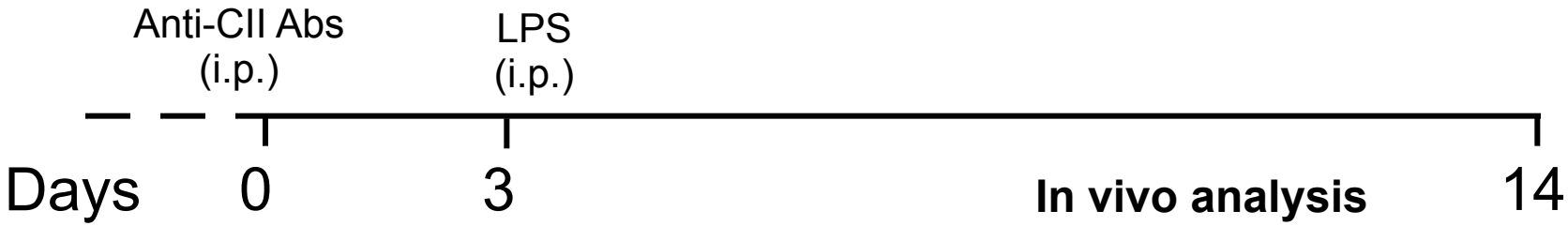
Anti-CII arthritis (Arthrogen)



Anti-Collagen II arthritis

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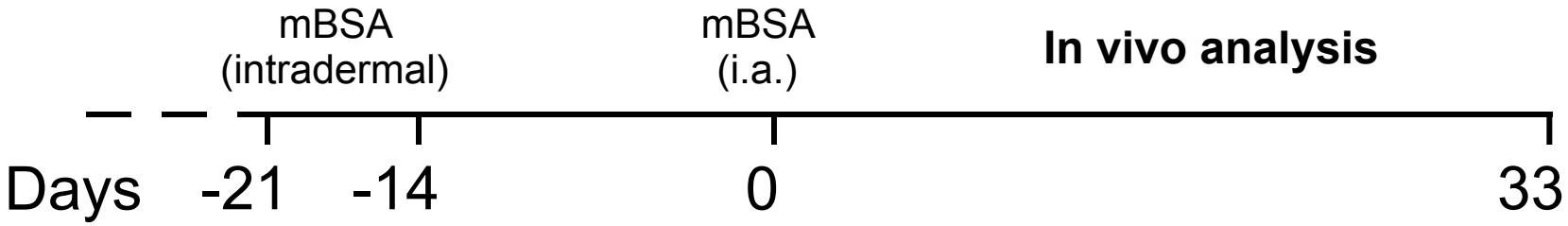
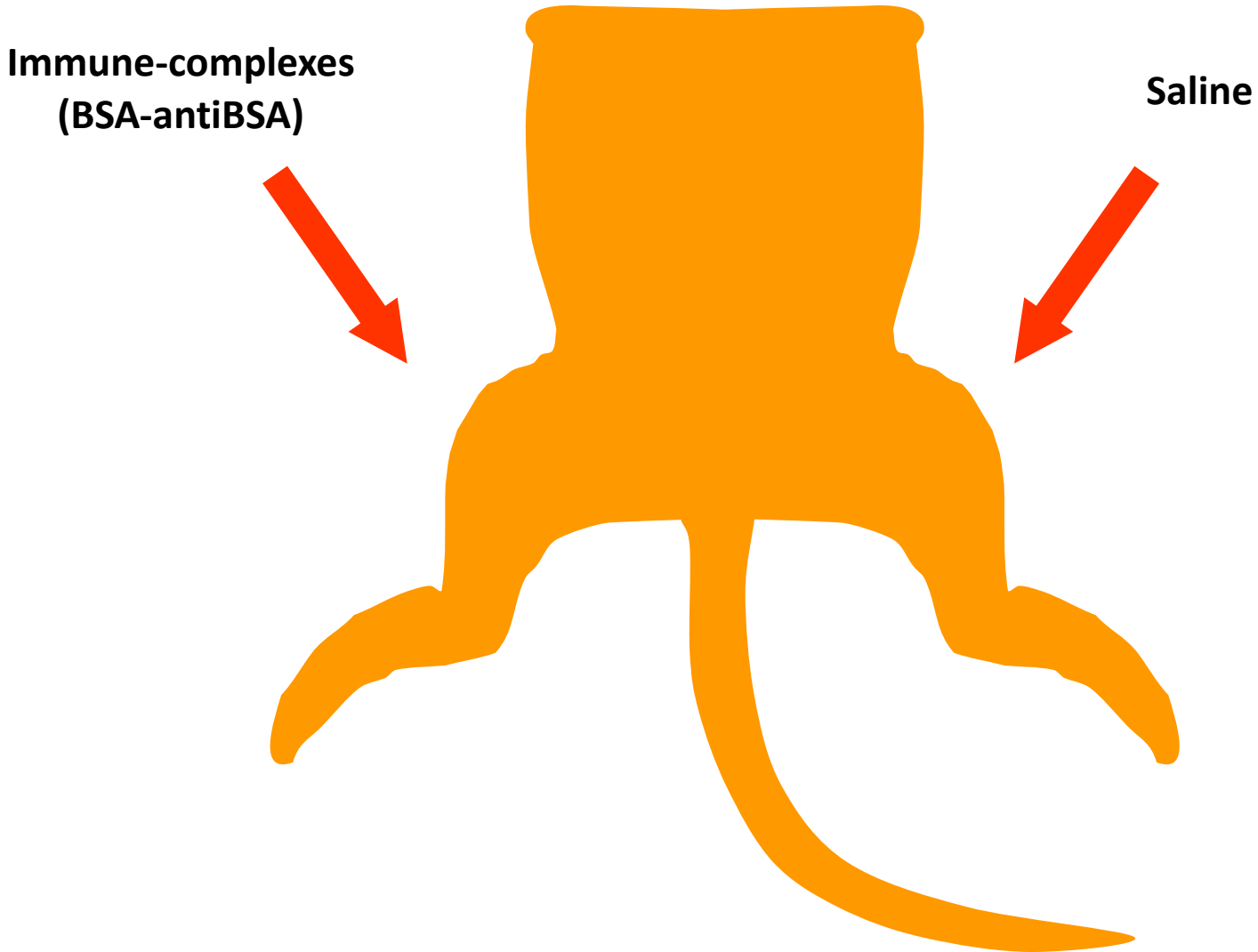
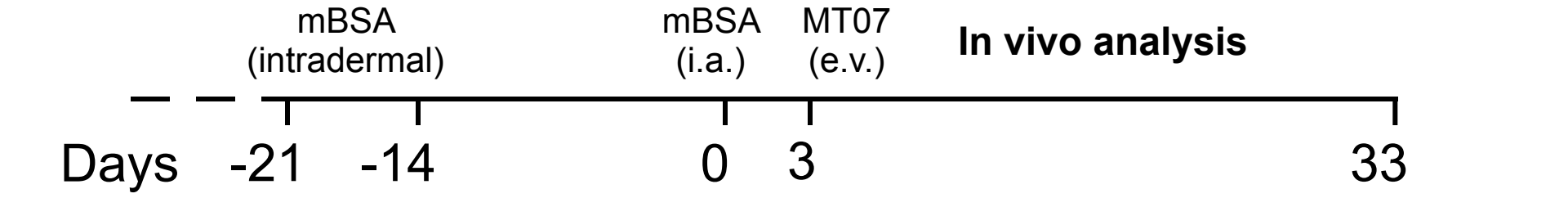
Rat model of antigen-induced arthritis

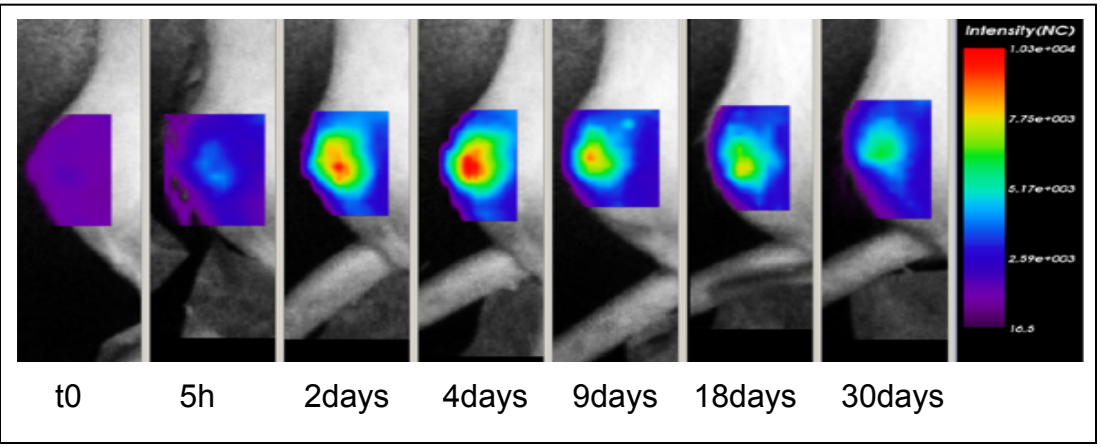


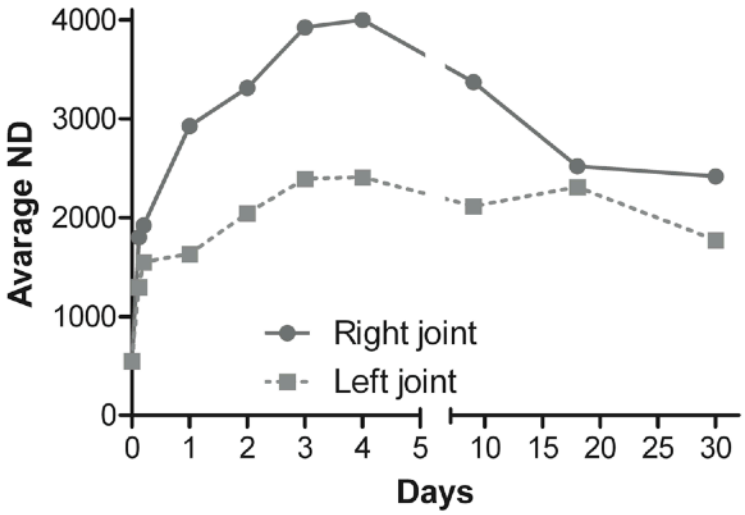
Antigen induced model of arthritis in rats

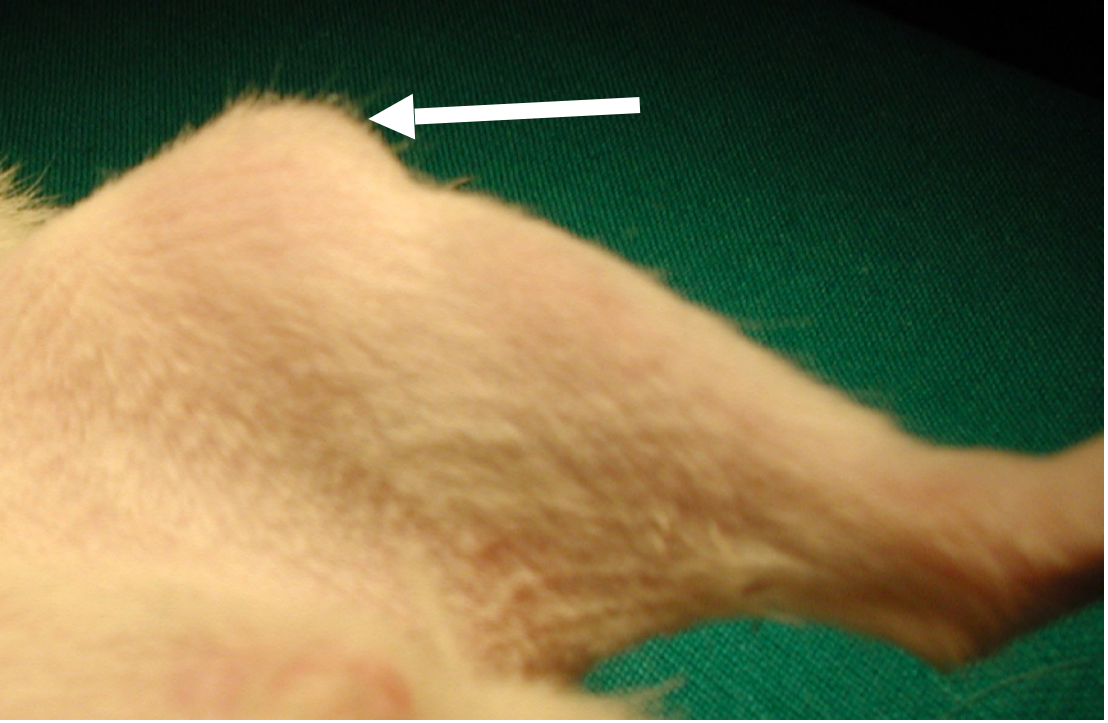


Bio-distribution of MT07 in a rat model of antigen-induced arthritis

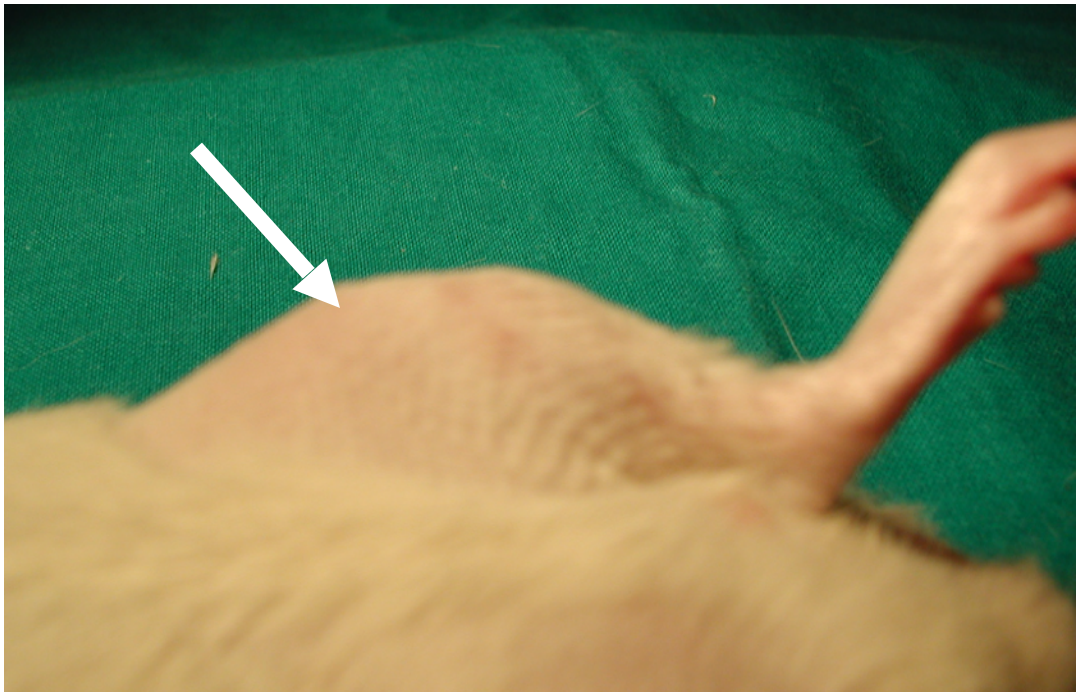








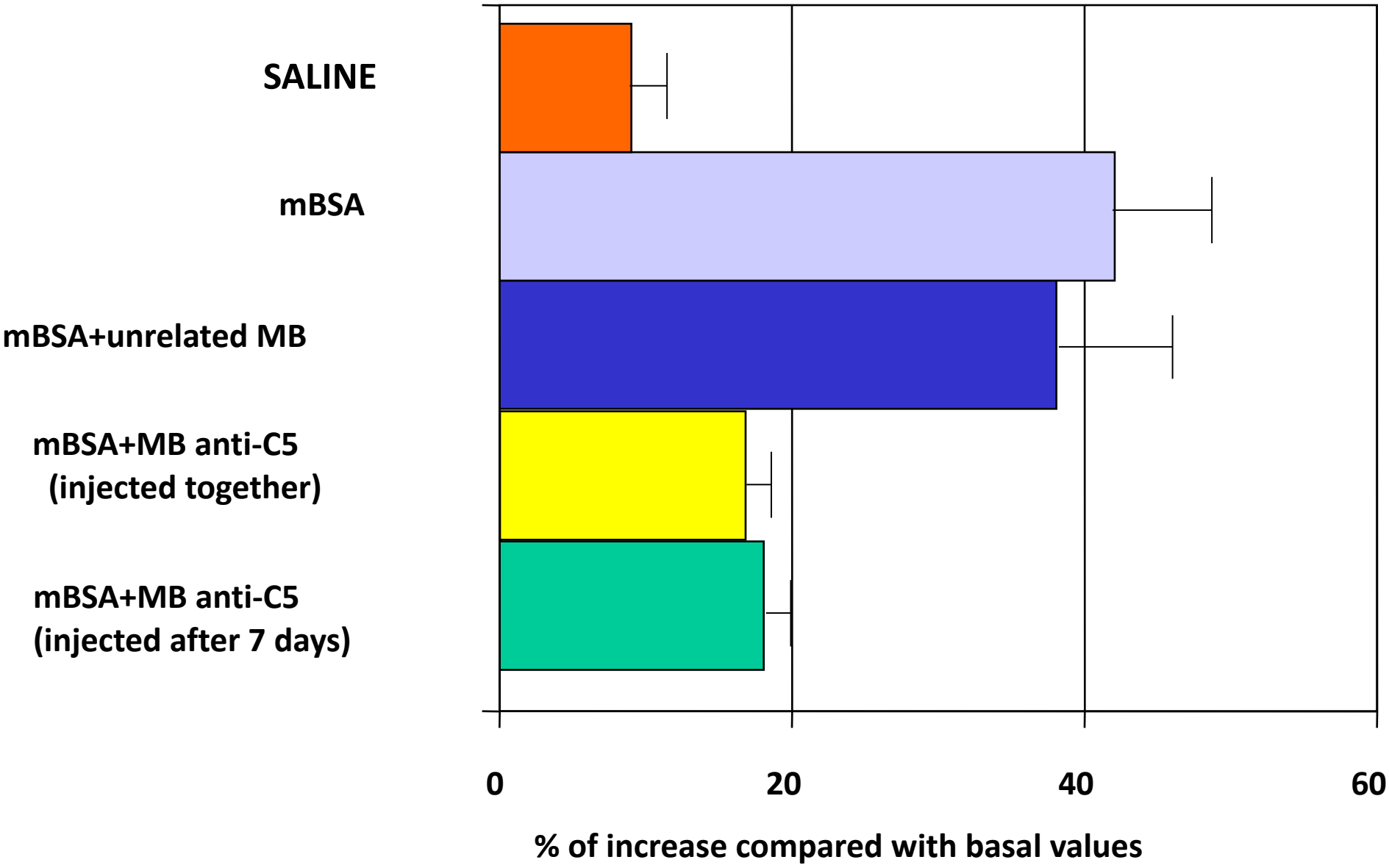
Knee joint 60 hr after intraarticular injection of mBSA



Knee joint 60 hr after intraarticular injection of mBSA + MB anti-C5

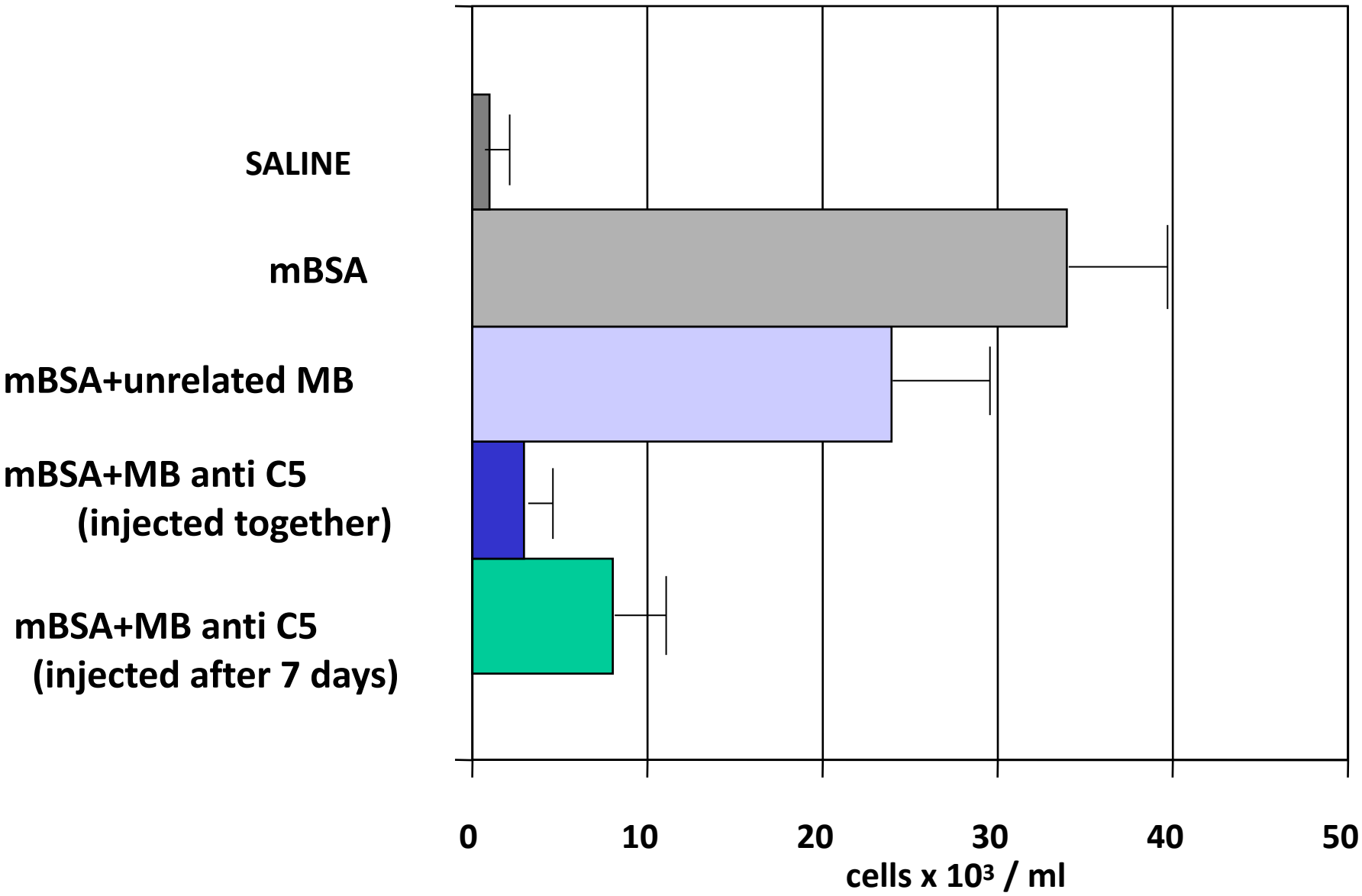
Joint swelling

(21 days after induction of arthritis)



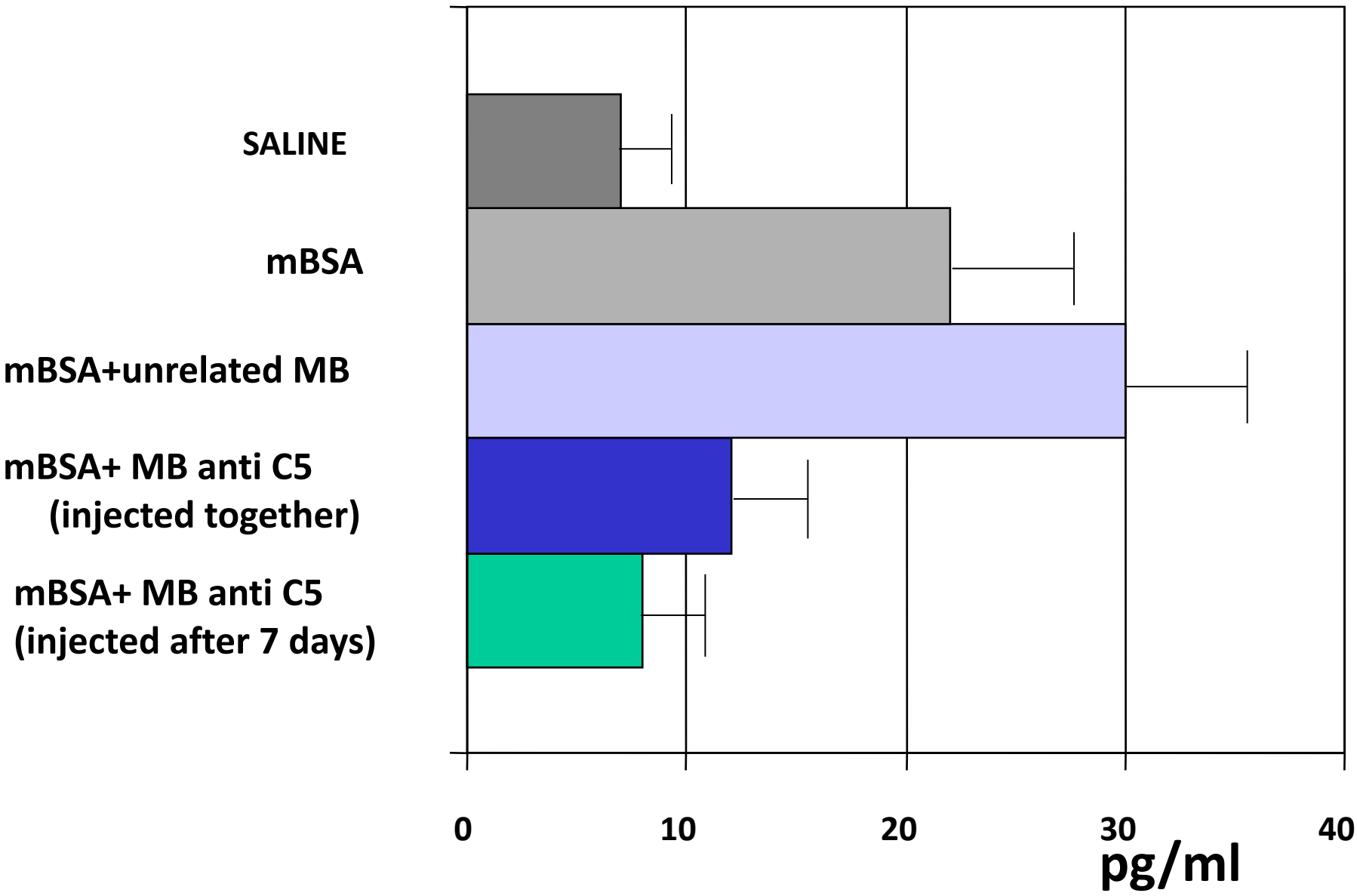
PMN in the synovial fluid washings

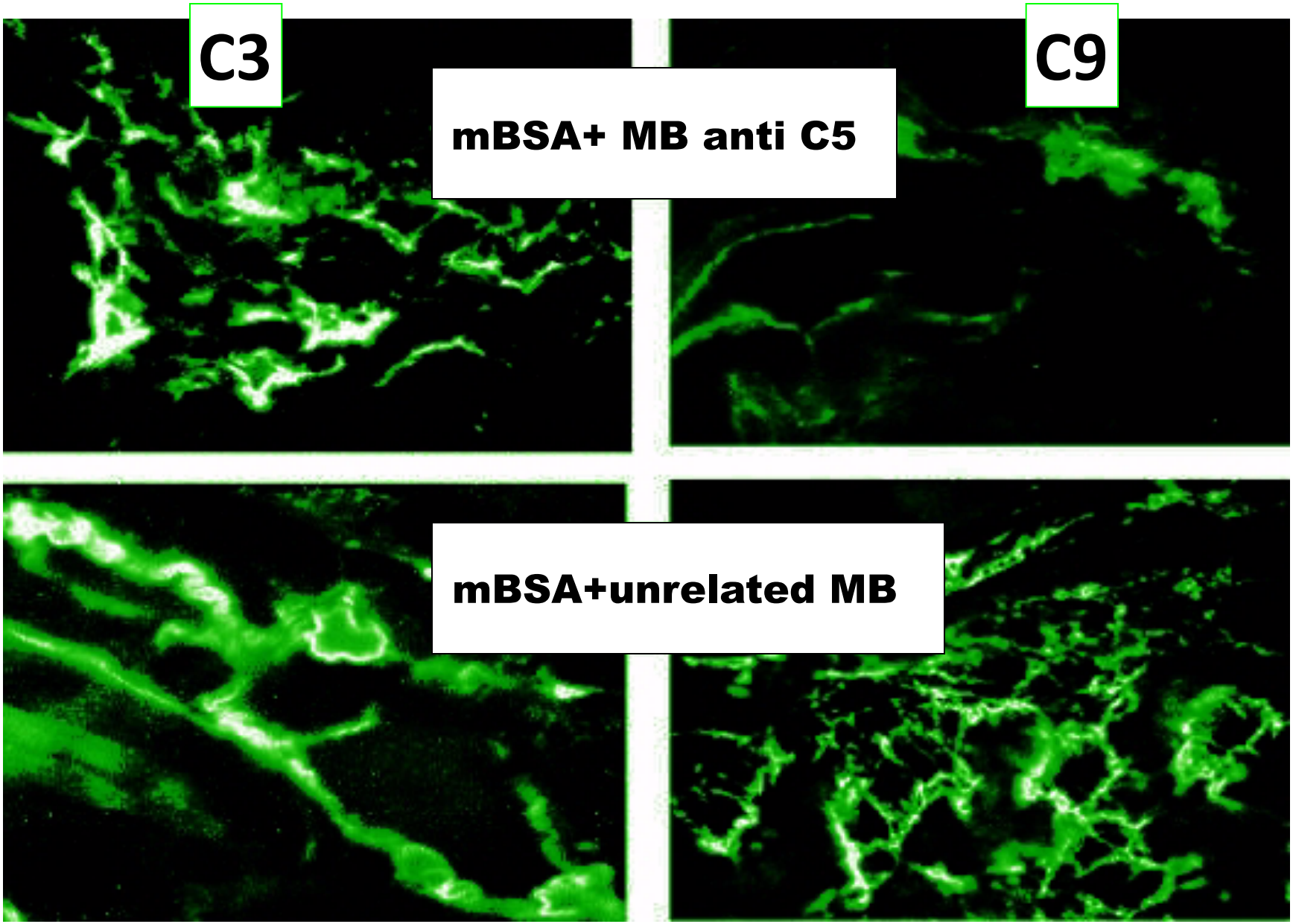
(21 days after induction of arthritis)



TNF-α concentration in the synovial fluid washings

(21 days after induction of arthritis)





Immunofluorescence analysis of rat synovial tissue 48 hr after mBSA injection