

Antibodies and Disease

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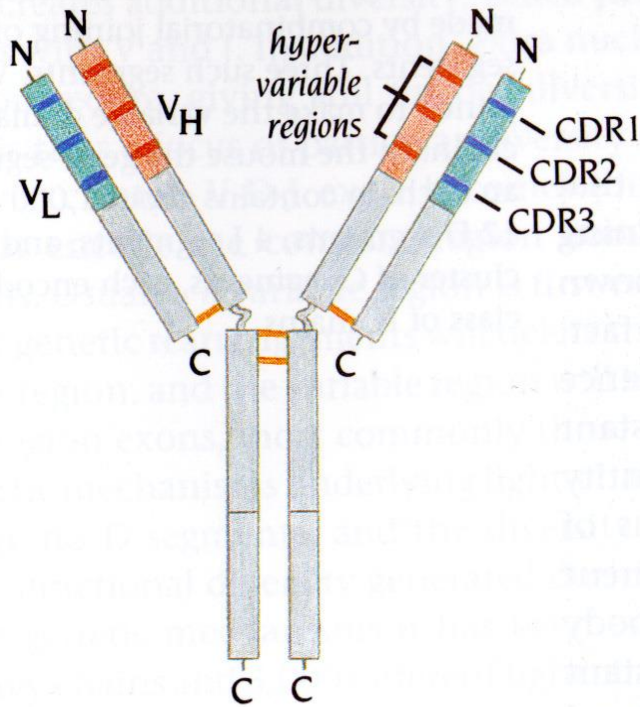


Lecture outline

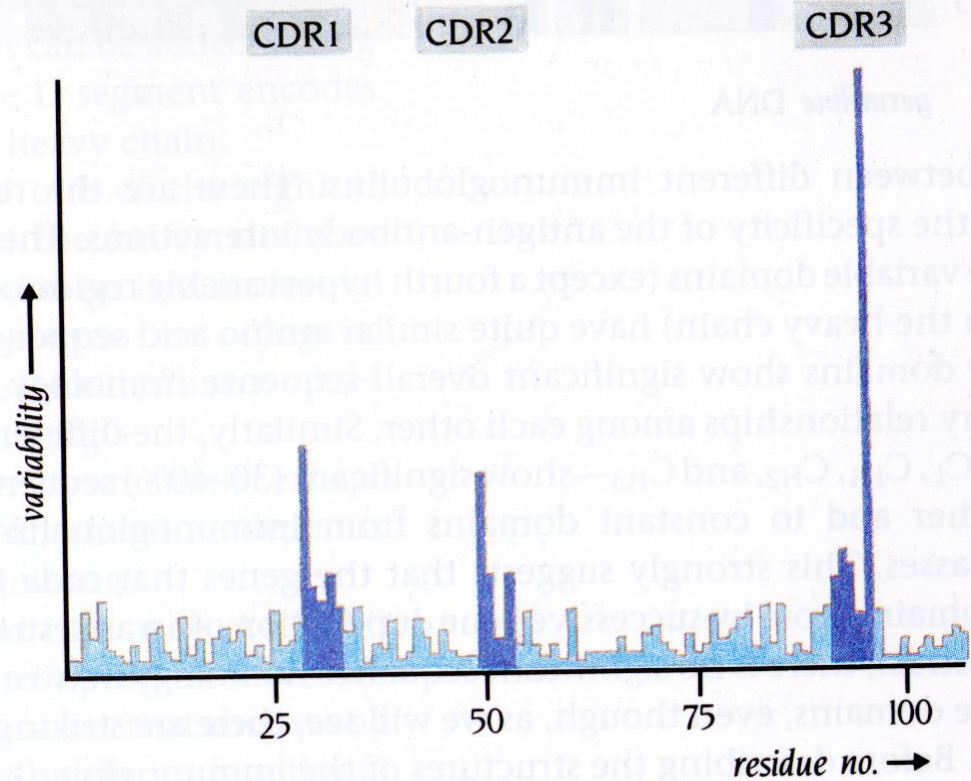
- ANTIBODIES
- ANTIBODIES AND DISEASE
- B CELL TOLERANCE
- ANTIBODIES AS THERAPEUTICS

Complementarity determining regions = CDRs = HVRs

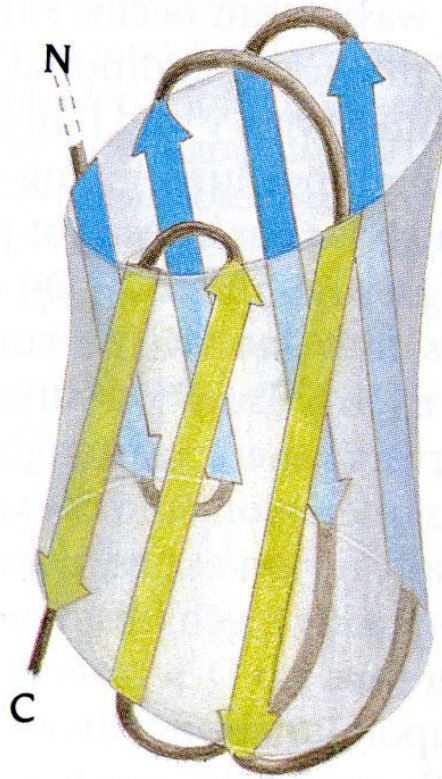
(a)



(b)

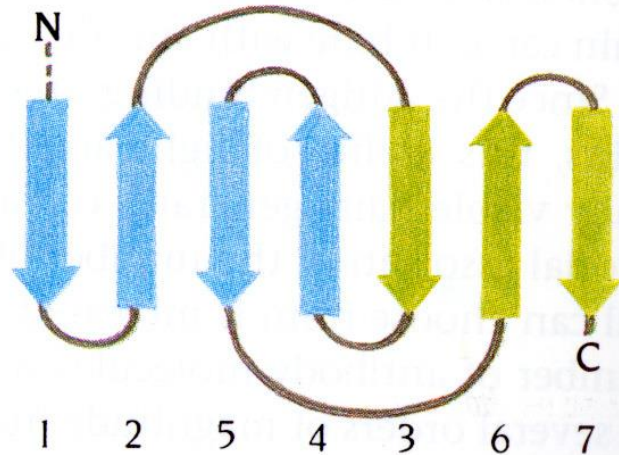


(a)



**Beta
Barrels**

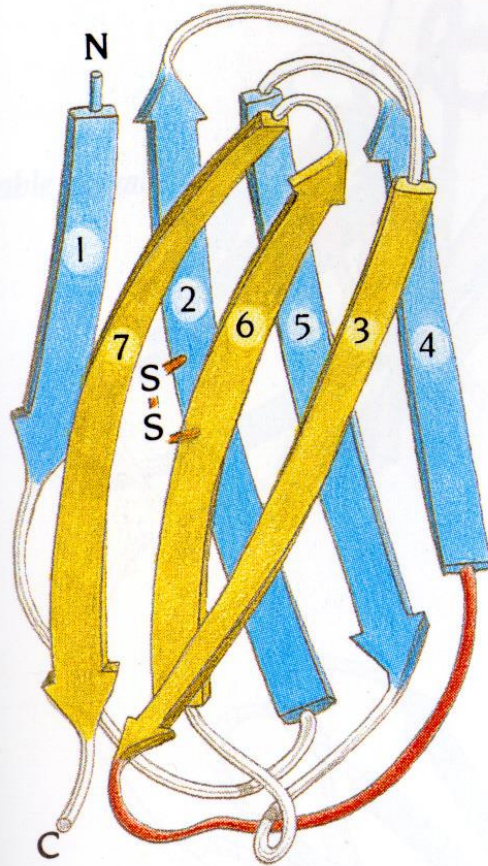
(b)



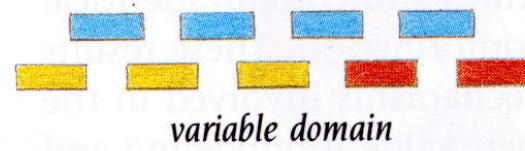
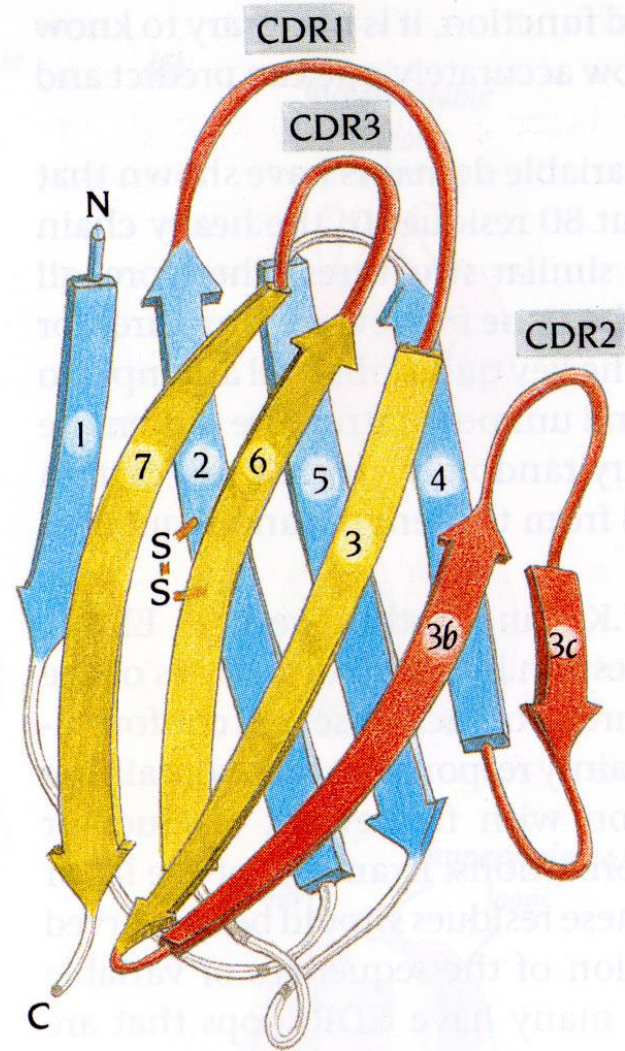
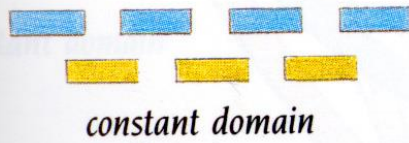
Ig folds

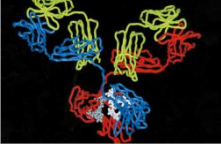
**Ig
domains**

(a)

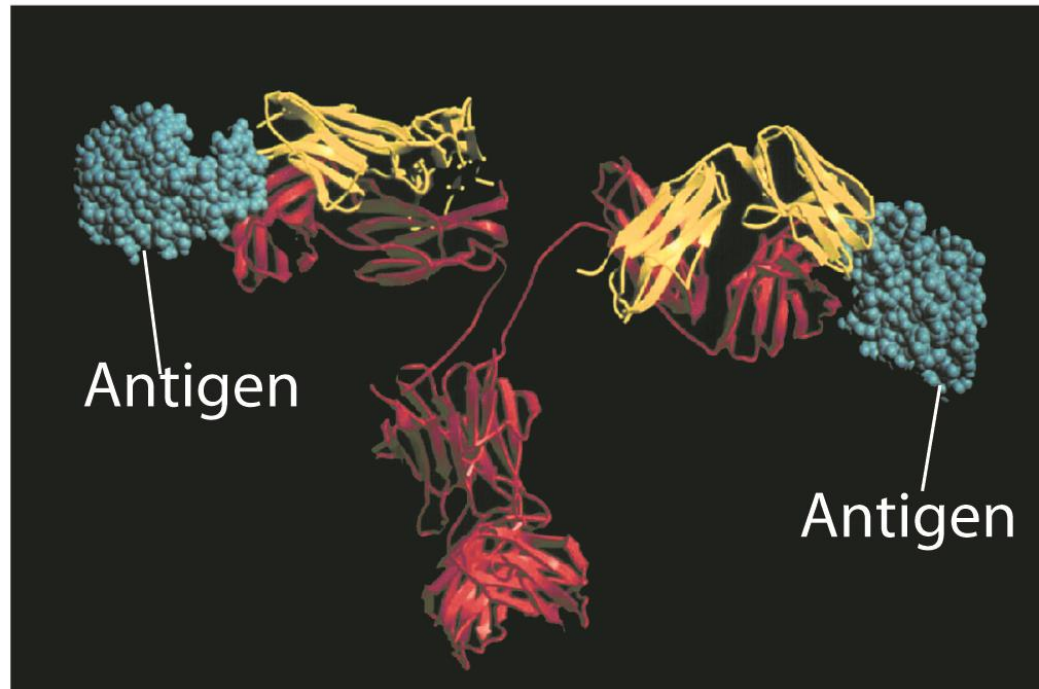
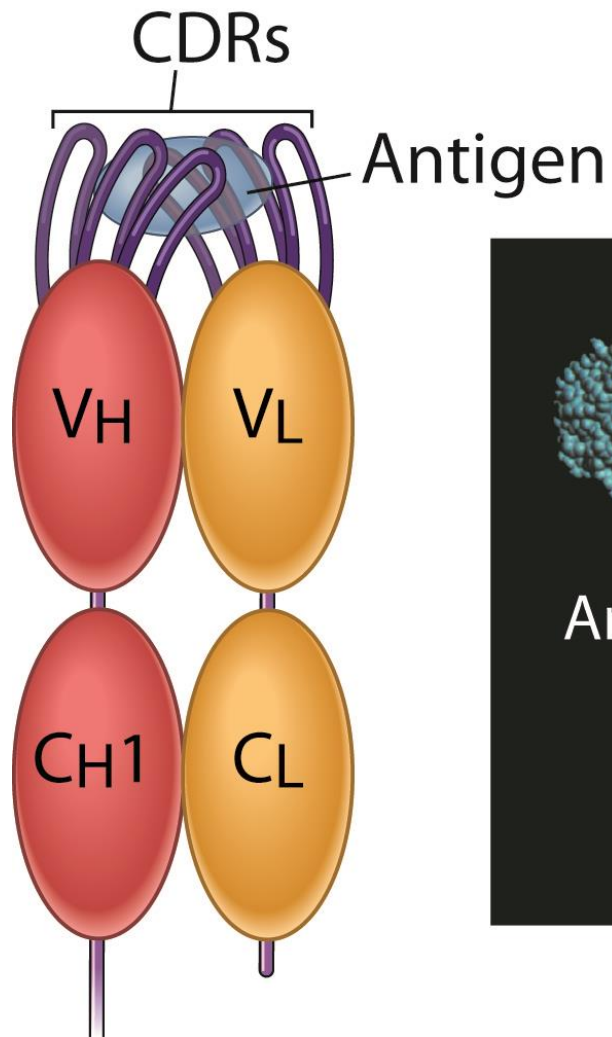


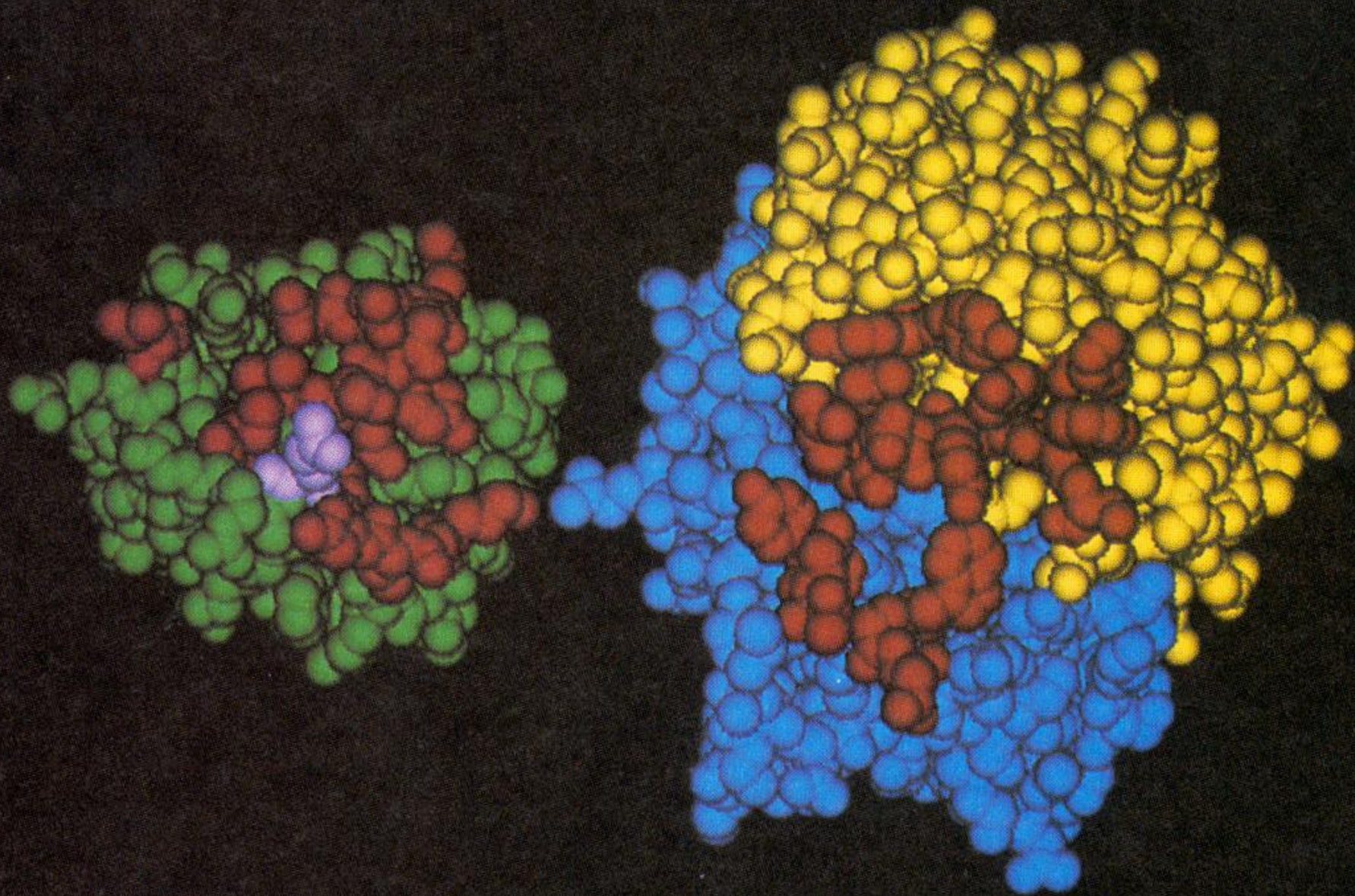
(b)





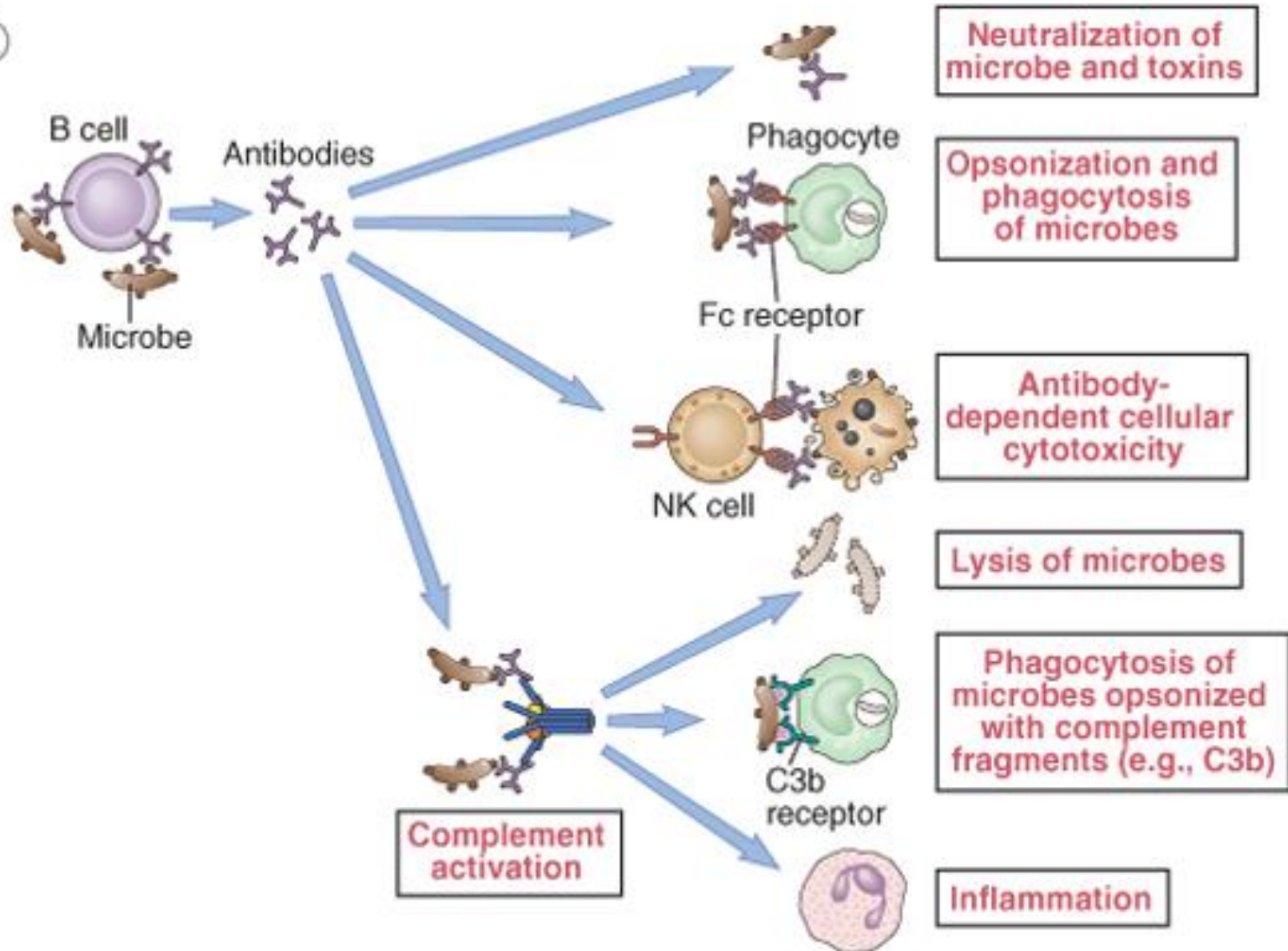
Binding of an Antigen by an Antibody





The effector functions of antibodies

(A)

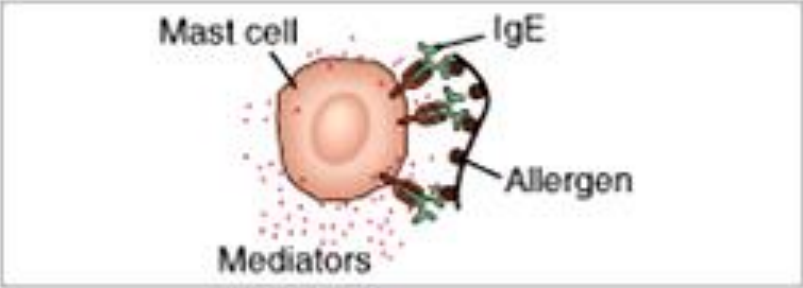


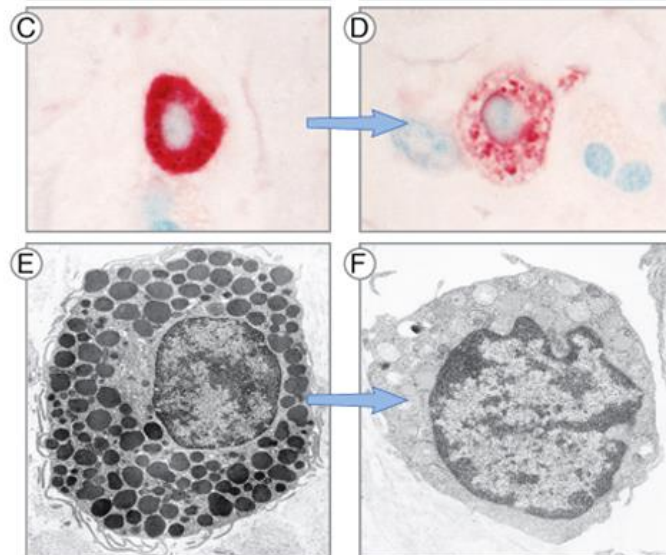
Doggerel for Dr. Ehrlich.....

Antibodies - Functional properties

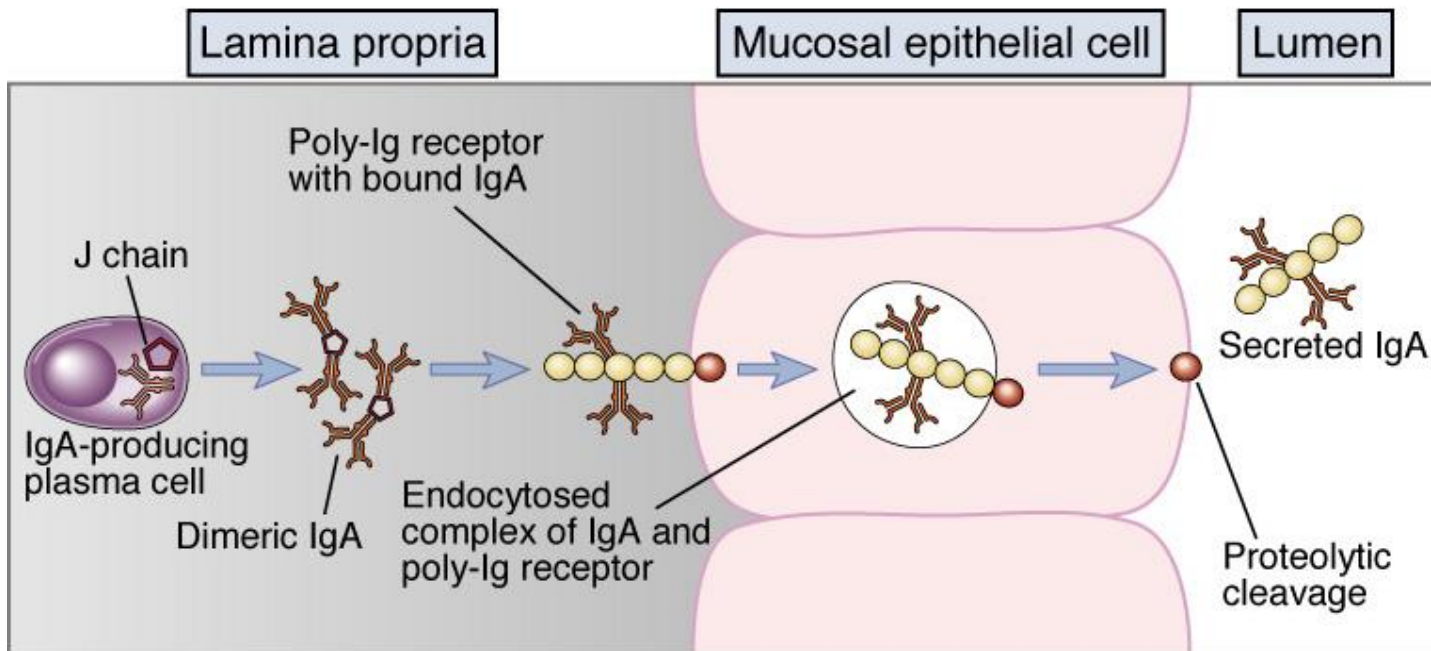
- 1. Complement fixation- IgM, IgG1, IgG3**
- 2. Opsonization- IgG1, IgG3**
- 3. Placental transfer- IgG1, IgG2, IgG4**
- 4. Mucosal immunity – IgA and IgM**
- 5. Immediate type hypersensitivity - IgE**
- 6. Antibody Dependent Cellular Cytotoxicity- IgG1, IgG3**

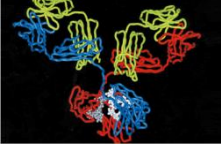
IgE-dependent Mast Cell Activation

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	<p>T_H2 cells, IgE antibody, mast cells, eosinophils</p> 	<p>Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines)</p> <p>Cytokine-mediated inflammation (eosinophils, neutrophils)</p>

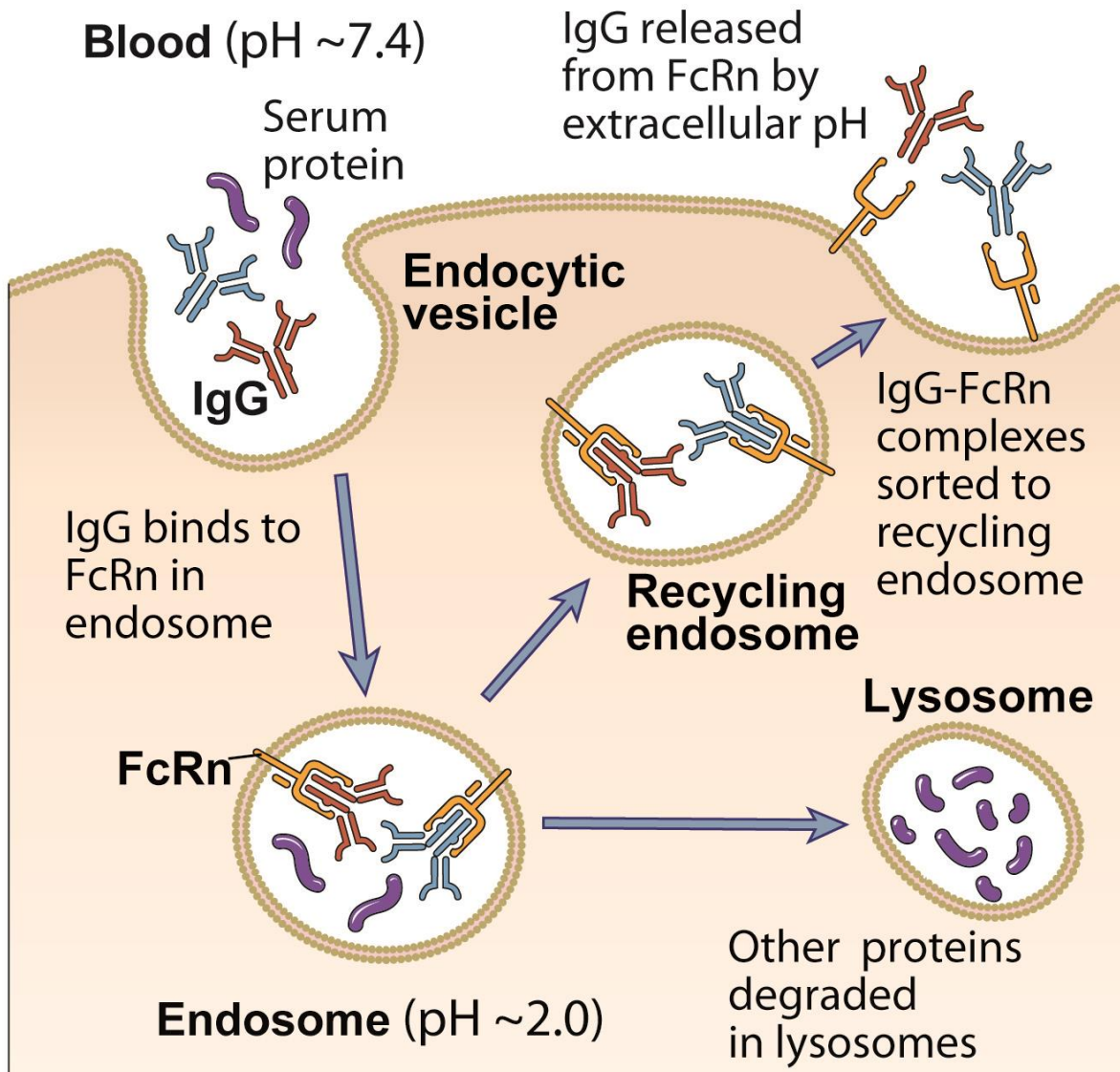


Poly Ig receptor mediates transcytosis

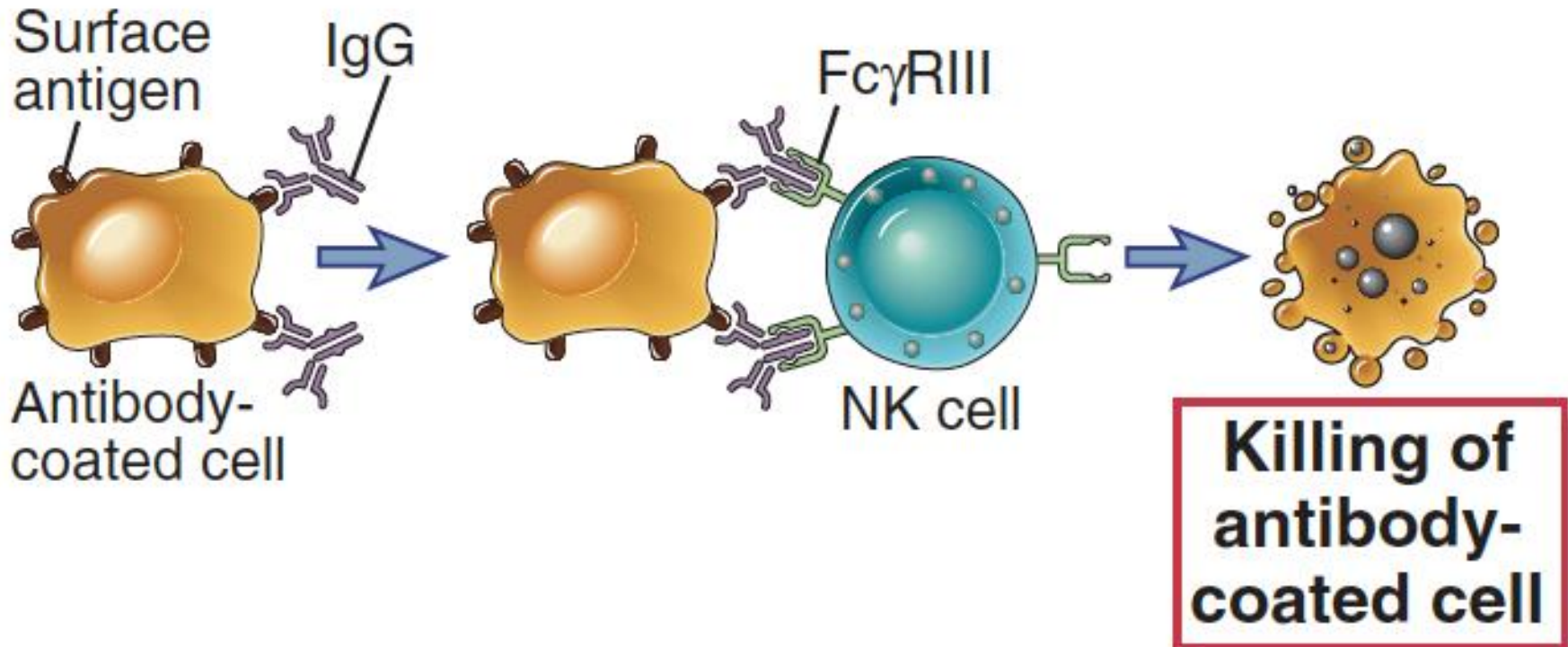




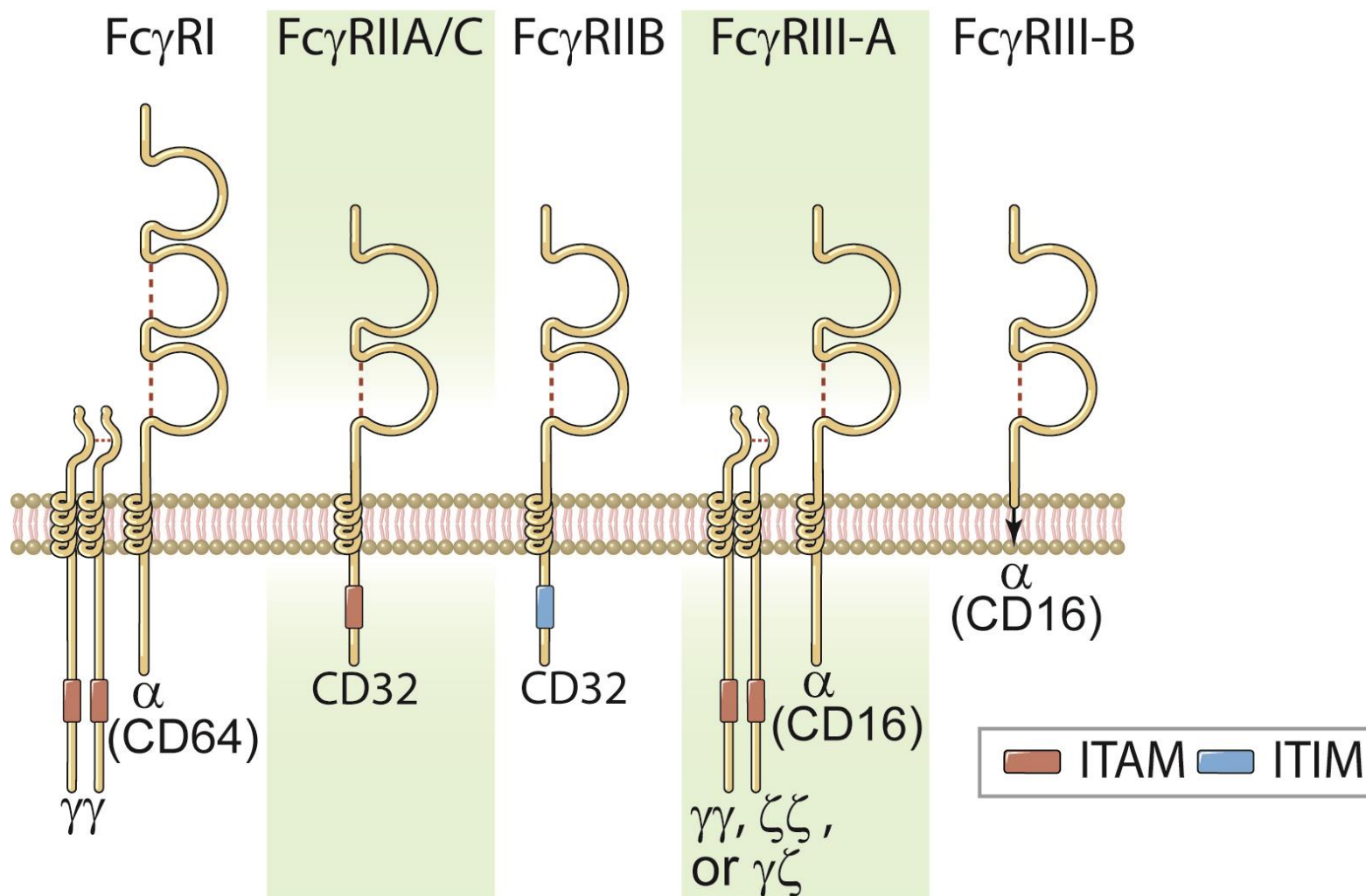
FcRn Prolongs Half-Life of IgG Molecules



ADCC- Antibody Dependent Cellular Cytotoxicity



Subunit Composition of Fc γ receptors



Opsonization and Phagocytosis by Antibodies

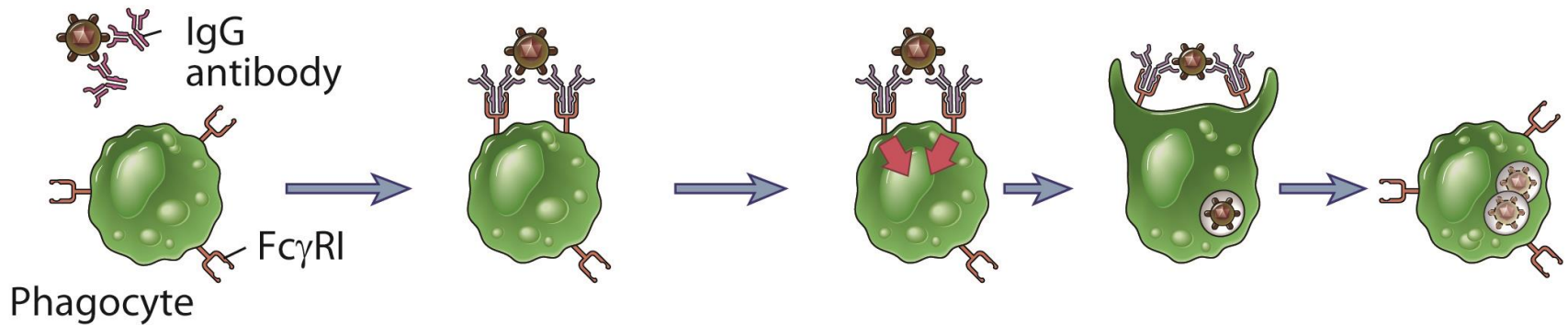
Opsonization of microbe by IgG

Binding of opsonized microbes to phagocyte Fc receptors (Fc γ RI)

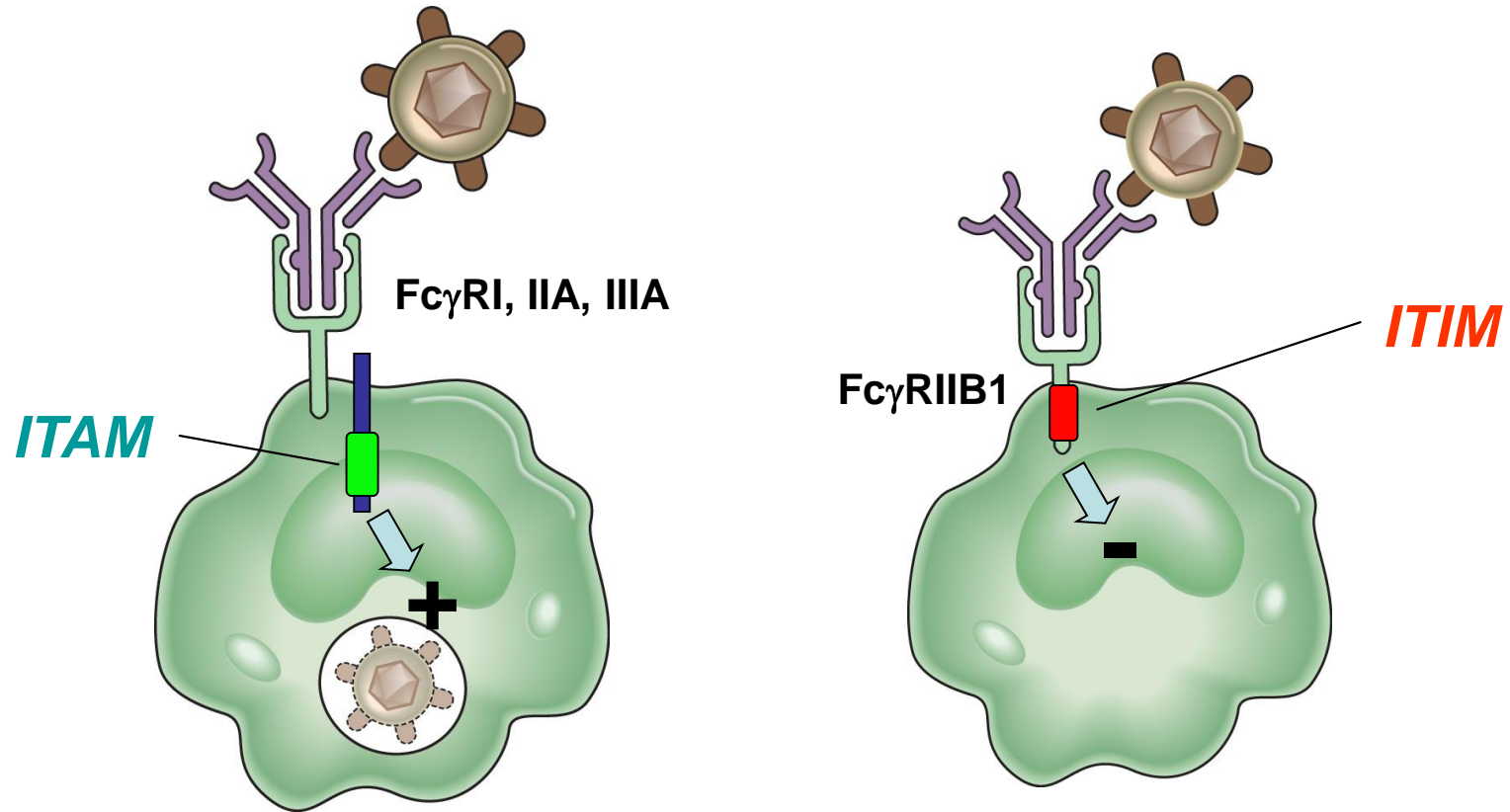
Fc receptor signals activate phagocyte

Phagocytosis of microbe

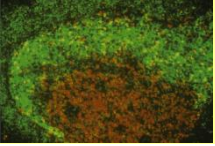
Killing of ingested microbe



Ig Fc Receptors can Activate or Inhibit cells



ITAM and **ITIM** motifs are responsible for activating or inhibitory signaling, respectively.



Immune Injury

The Gell and Coombs Classification

Type I – Allergic- IgE mediated

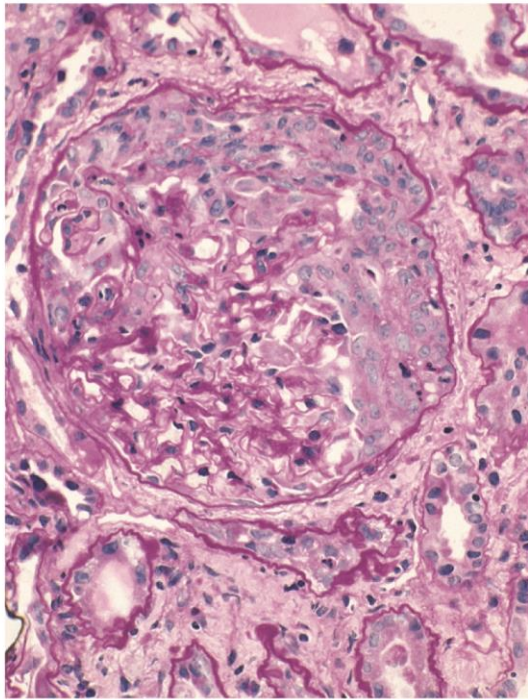
Type II – Antibody mediated

Type III – Immune Complex mediated

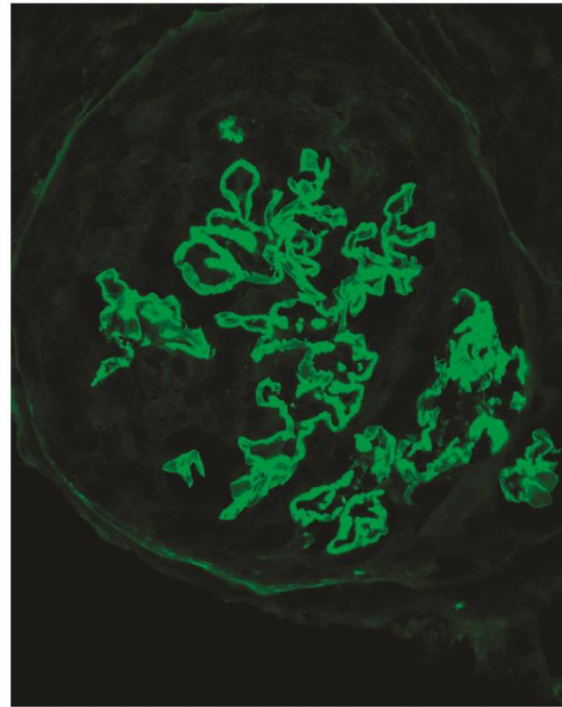
Type IV - T cell mediated Injury

Antibody-mediated Glomerulonephritis (1)

Anti-basement membrane antibody-mediated glomerulonephritis



Light microscopy



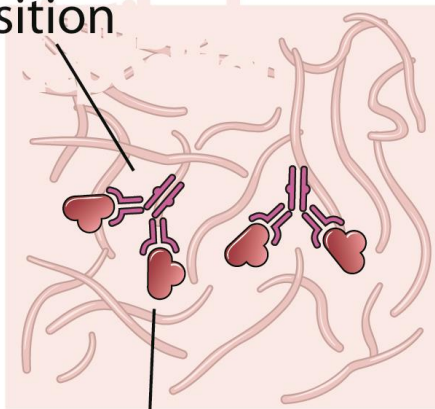
Immunofluorescence

Types of Antibody-Mediated Diseases

Injury caused by anti-tissue antibody

Mechanism of antibody deposition

Antibody deposition



Antigen in extracellular matrix

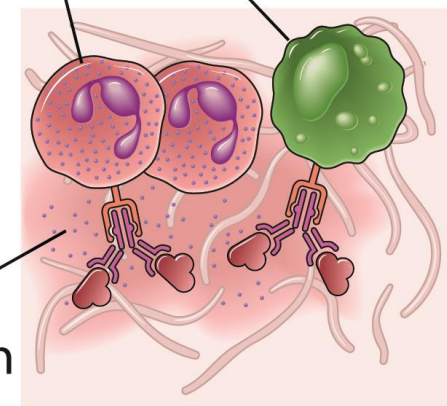
Complement- and Fc receptor-mediated recruitment and activation of inflammatory cells



Enzymes, reactive oxygen intermediates

Effector mechanisms of tissue injury

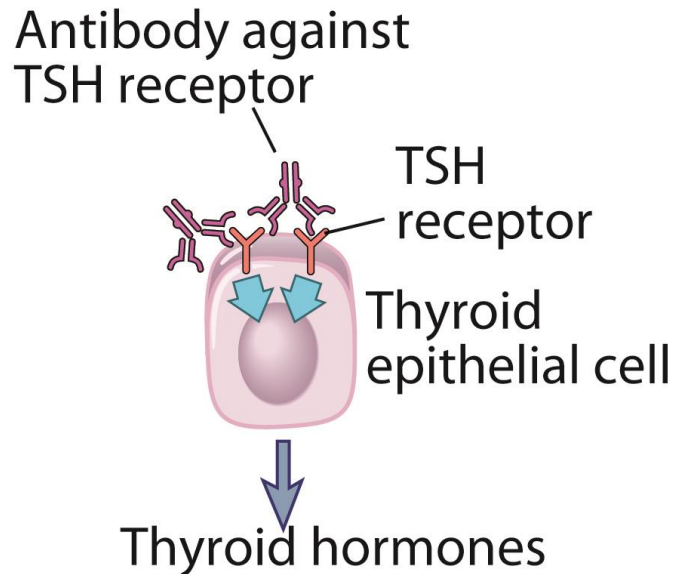
Neutrophils and macrophages



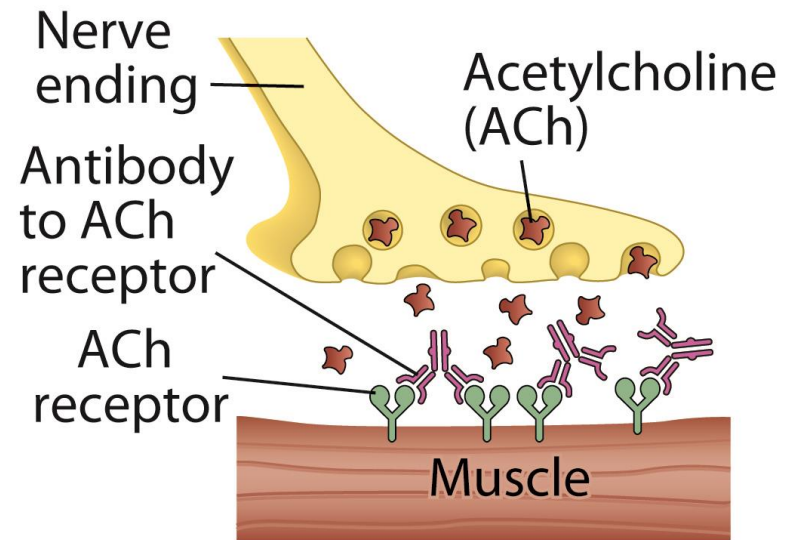
Tissue injury

Mechanisms of Ig-Mediated Disease (3)

Abnormal physiologic responses without cell/tissue injury



Antibody stimulates receptor without ligand

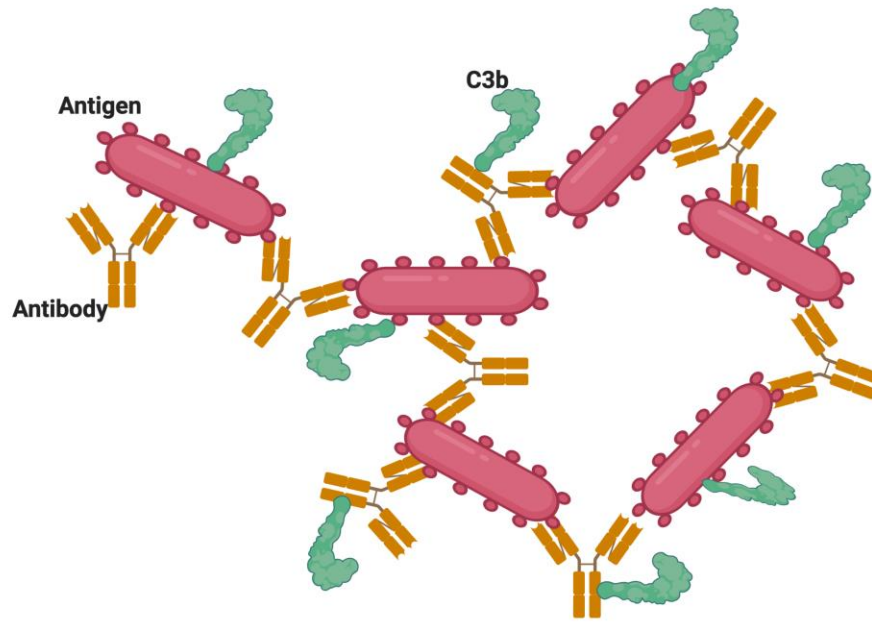


Antibody inhibits binding of ligand to receptor

COMPLEMENT IS ALSO KEY!!!!

Immune complexes

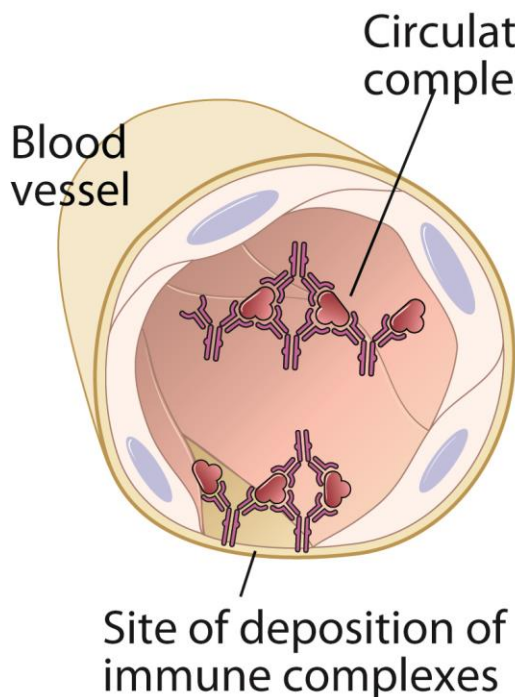
Complexes of antigens, antibodies and complement can deposit in small blood vessels and cause diseases like serum sickness, lupus etc.



Types of Antibody-Mediated Diseases

Immune complex – mediated tissue injury

Mechanism of antibody deposition

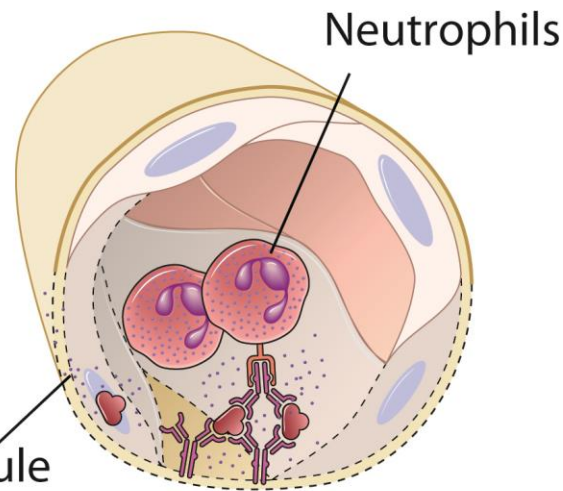


Effector mechanisms of tissue injury

Complement- and Fc receptor – mediated recruitment and activation of inflammatory cells



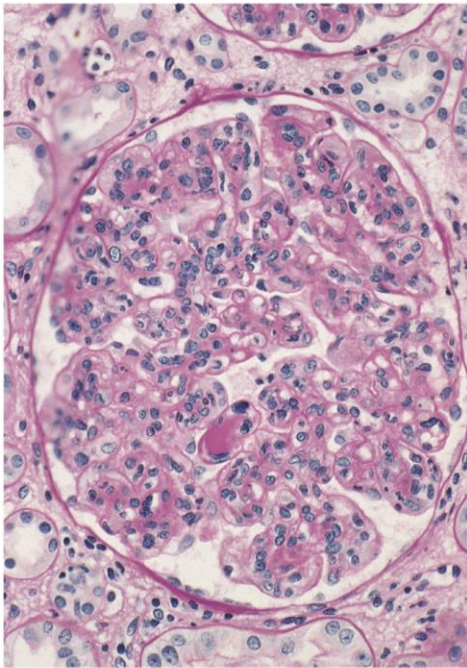
Neutrophil granule enzymes, reactive oxygen intermediates



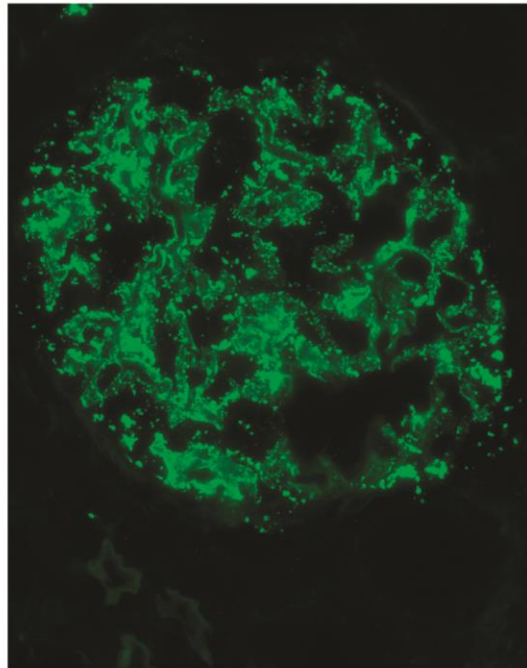
Vasculitis

Antibody-mediated Glomerulonephritis (2)

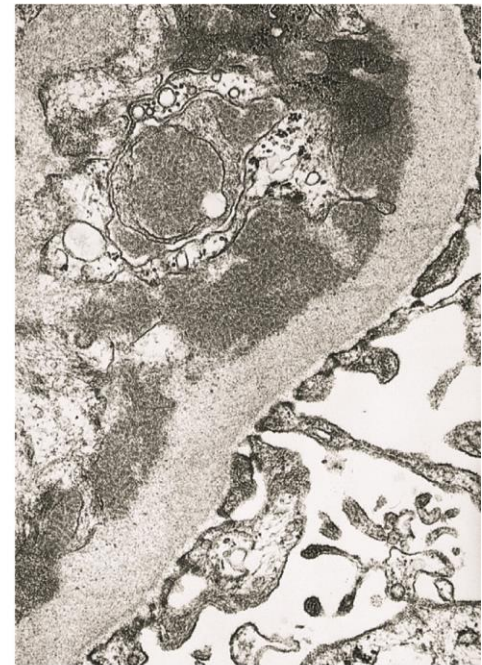
Immune complex-mediated
glomerulonephritis



Light microscopy



Immunofluorescence



Electron microscopy

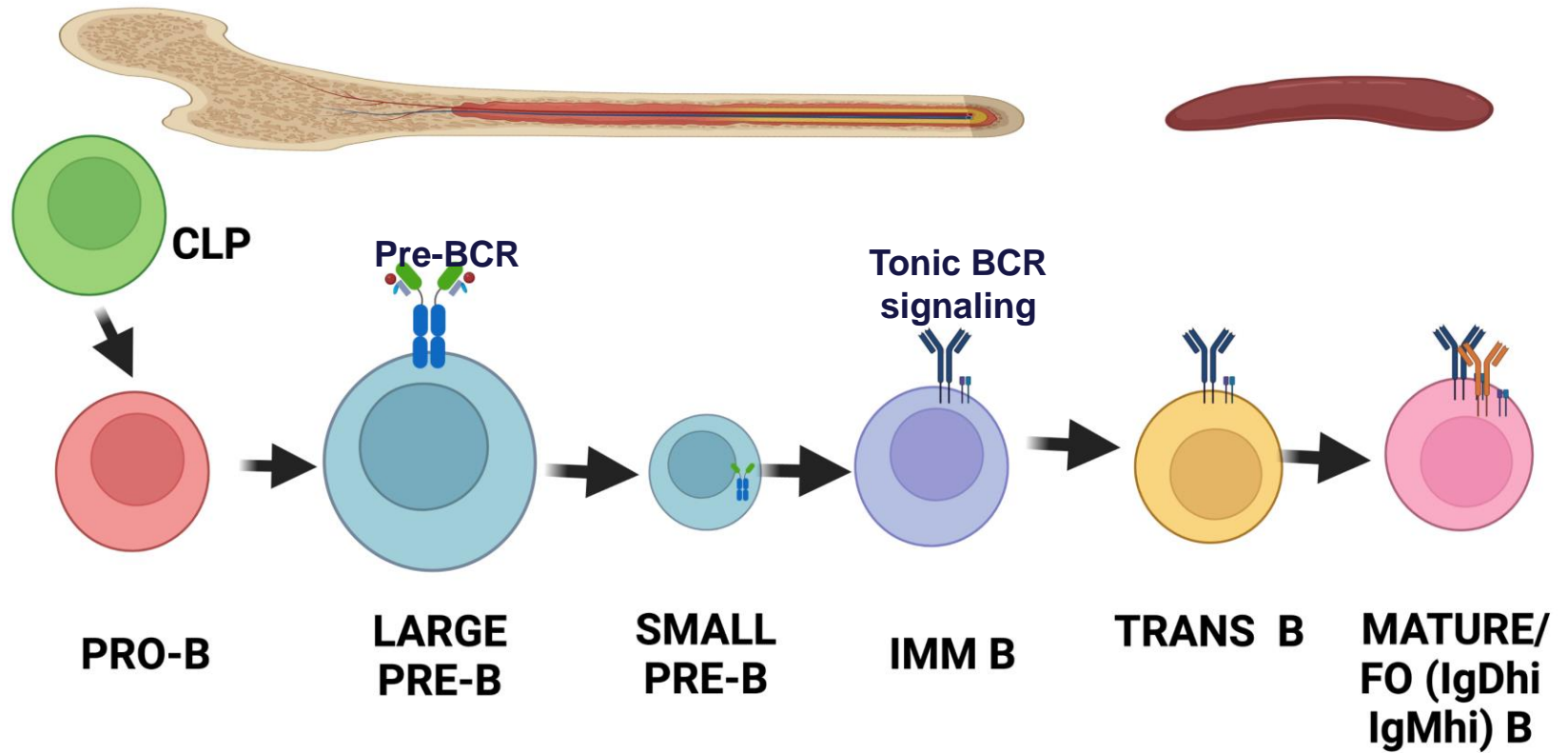
B cell tolerance

Receptor Editing - at Immature B cell stage in the bone marrow

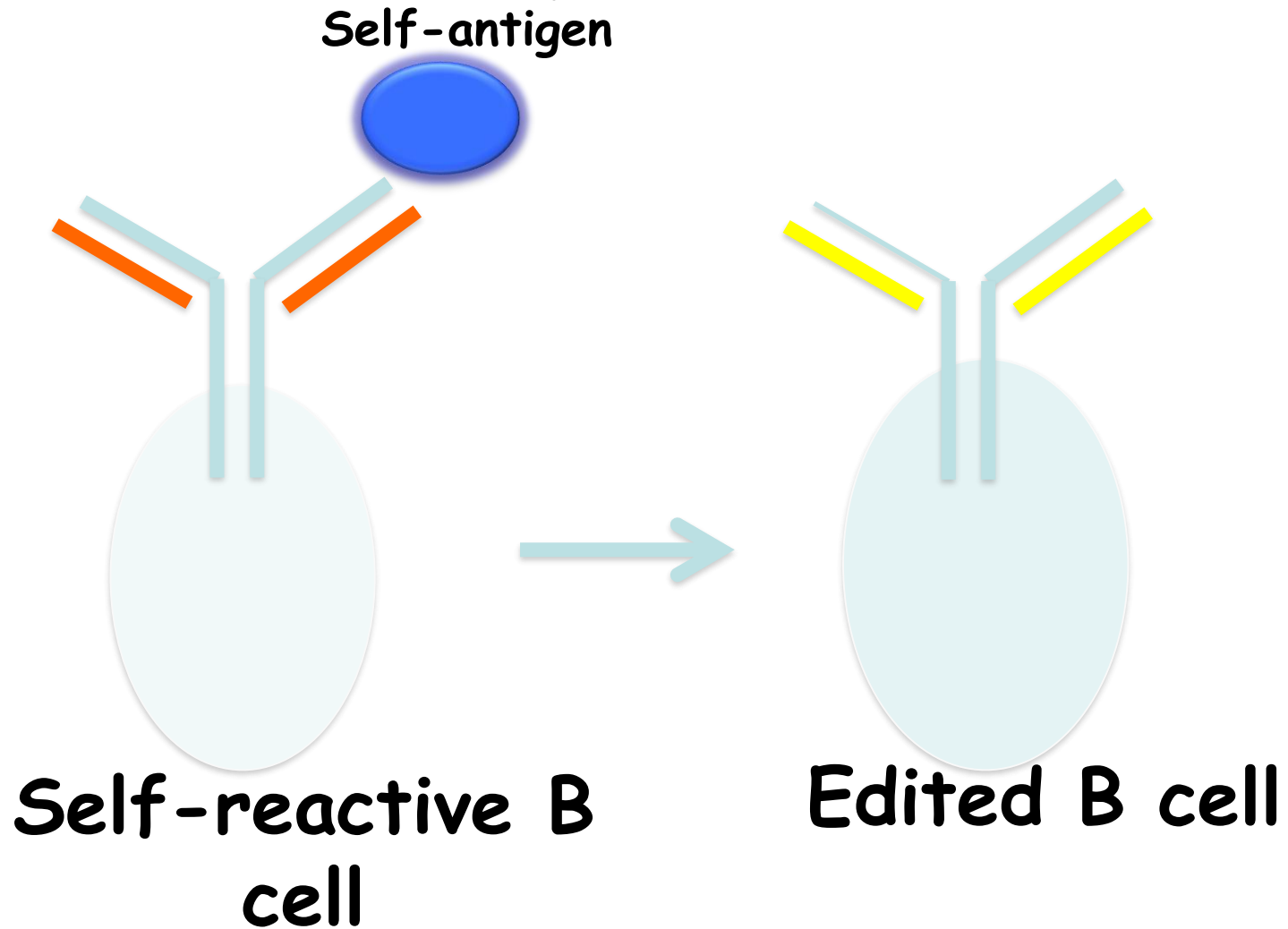
Clonal Deletion – mainly at the Transitional B cell stage in the periphery

Anergy- in mature Follicular B cells

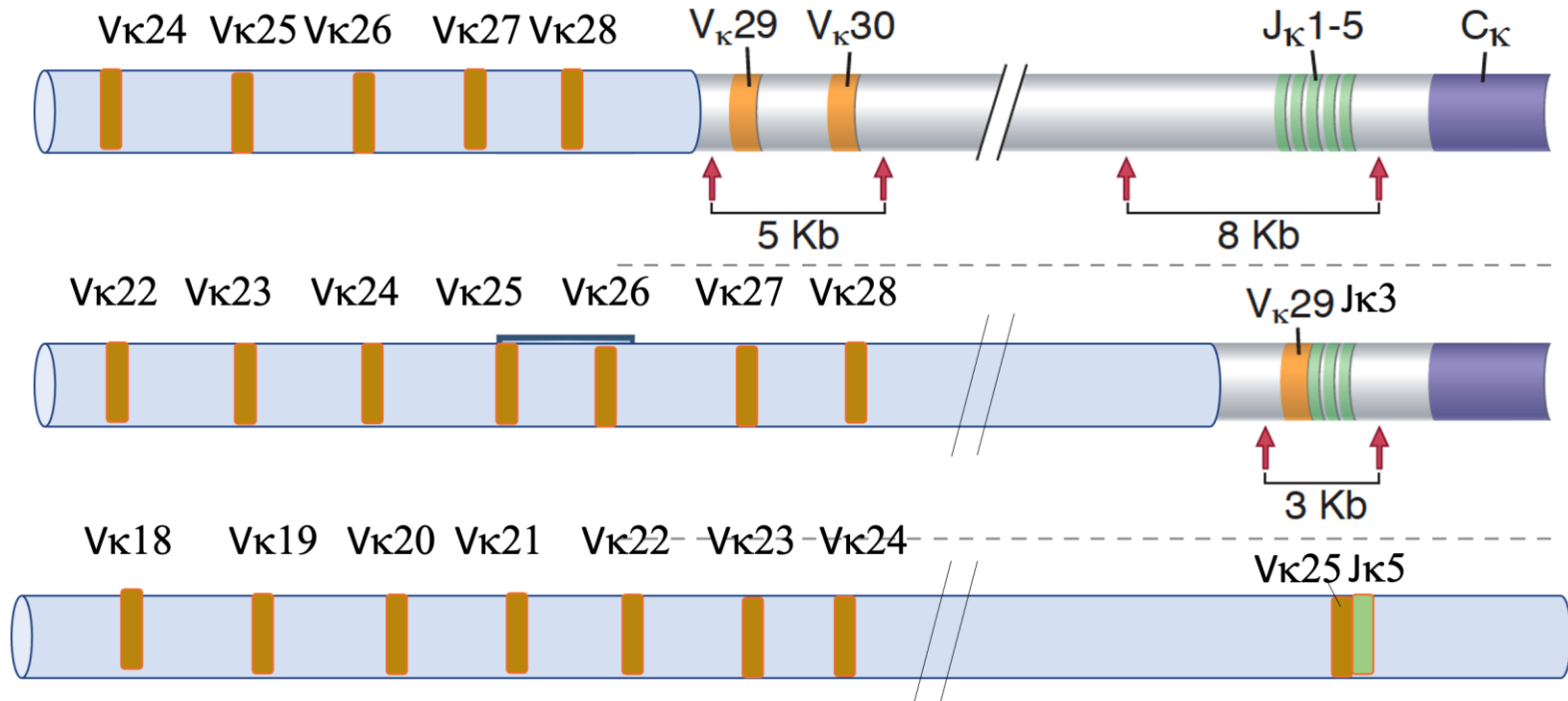
B CELL DEVELOPMENT



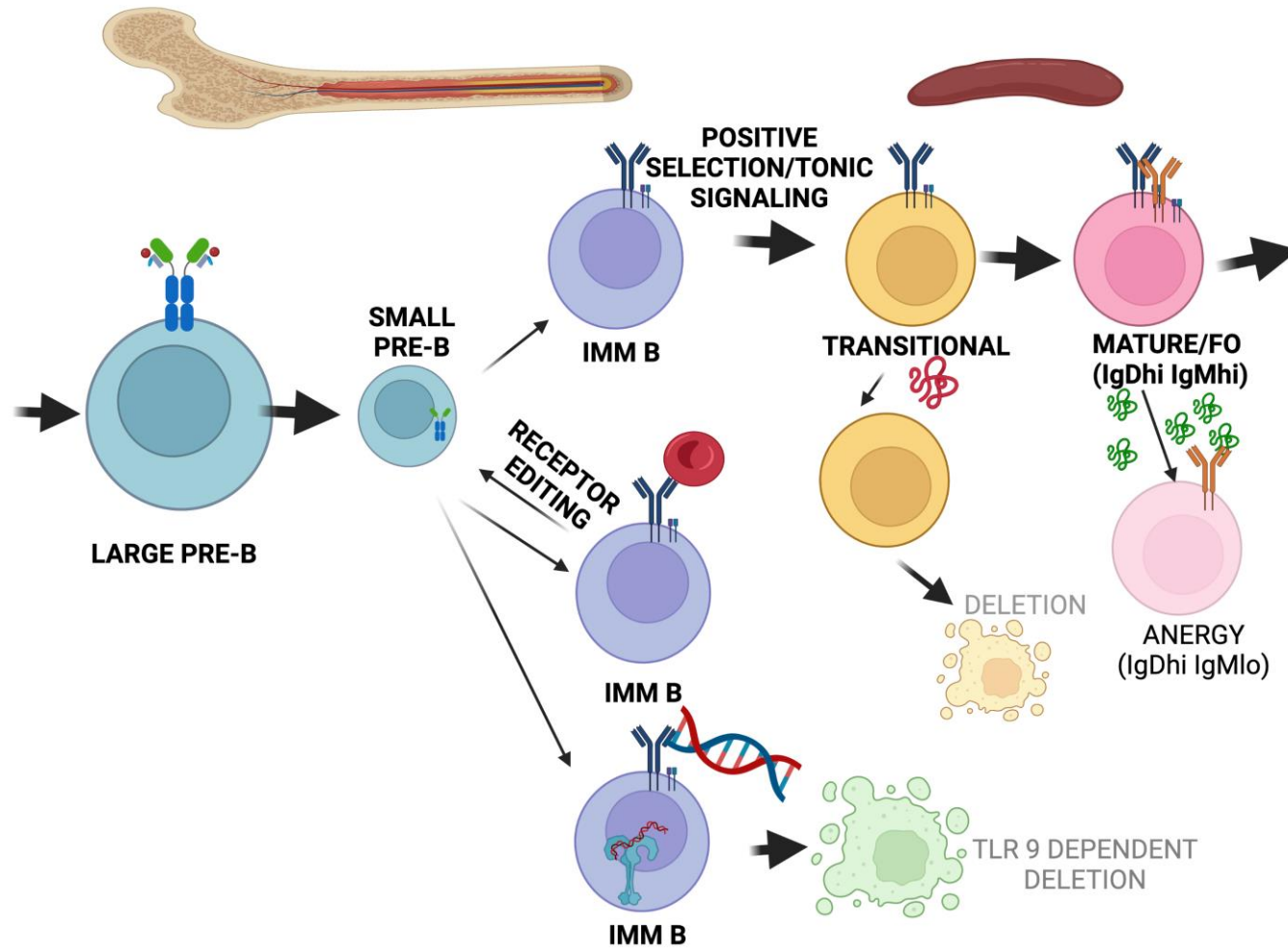
Receptor editing occurs in the bone marrow



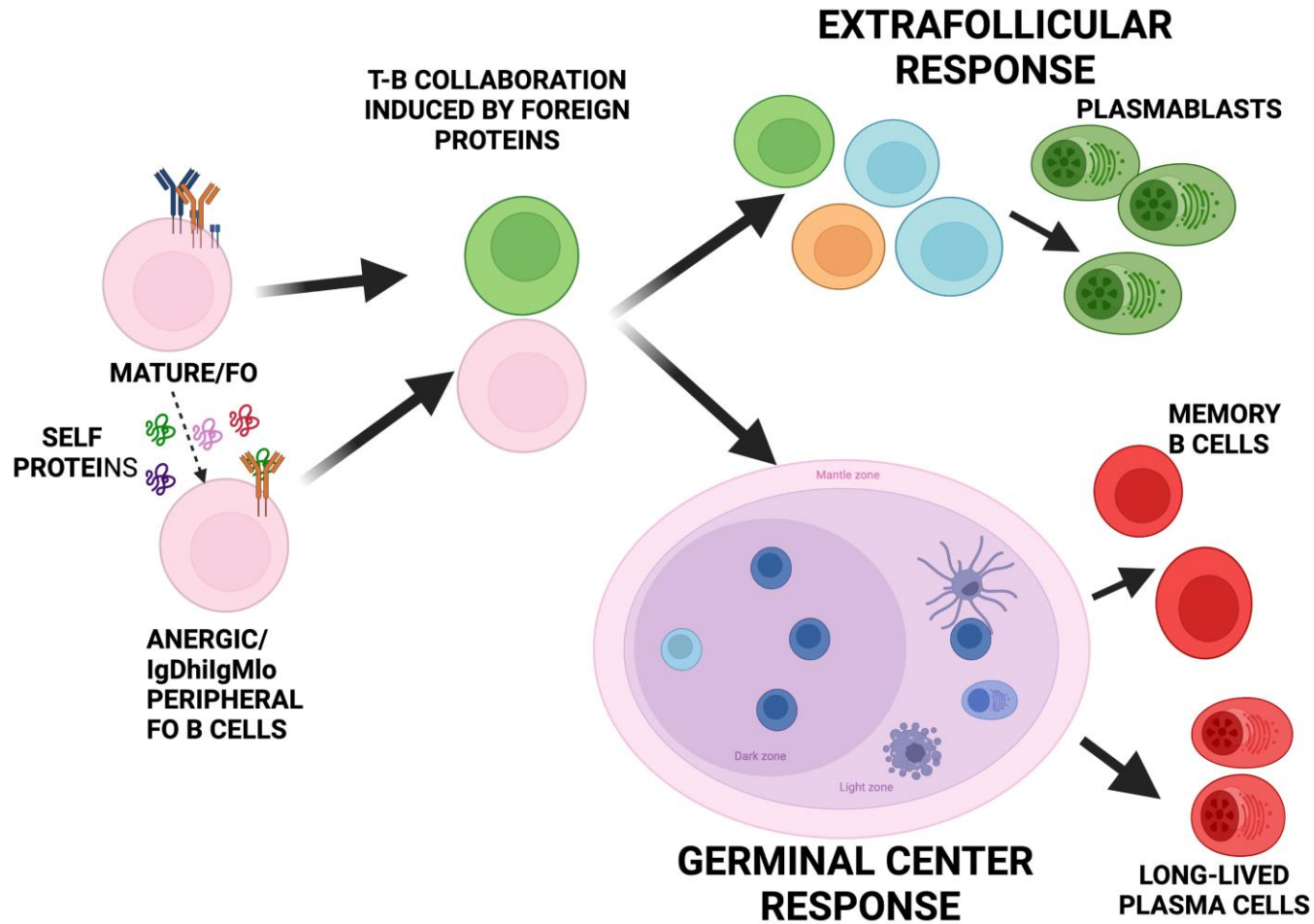
KAPPA GENE REARRANGEMENTS DURING RECEPTOR EDITING



SOME B CELL TOLERANCE CHECKPOINTS



TOLERANCE CAN BREAK EXTRAFOLLICULARLY OR IN THE GERMINAL CENTER



B regs, Homeostasis and Disease

In some disease models – IL-10 secreting B cells inhibit disease process – now called B regs

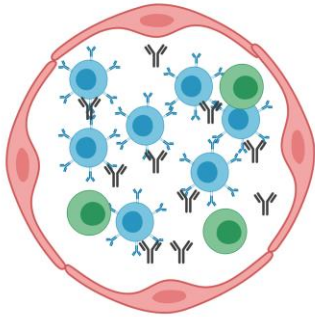
Can be thought of as “maintainers of homeostasis”

Cell types with different phenotypes might function as Bregs, many express TIM-1

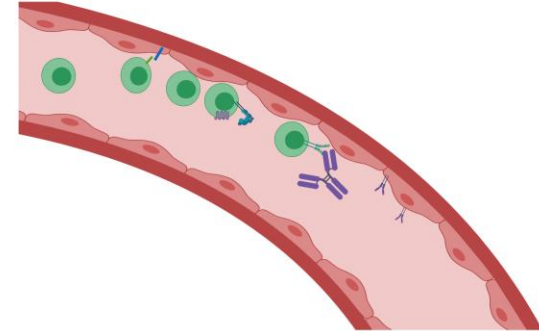
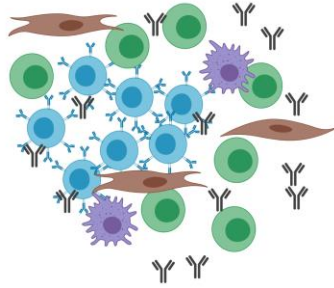
Triggering of CD40 and of TIM-1 (by apoptotic cells) in many different B cells can induce IL-10

Field murky, still evolving

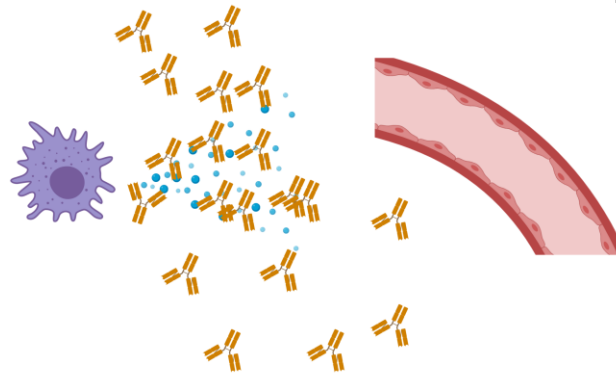
ANTIBODIES AS THERAPEUTICS



**DEplete
CELLS**



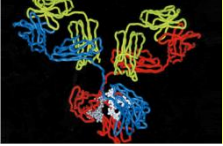
**BLOCK
MIGRATION**



**BLOCK CYTOKINES OR RECEPTORS
OR COMPLEMENT**

Therapeutic strategies targeting B cells and antibodies

- Plasmapheresis (in severe cases of autoimmunity)
- B cell depletion: anti-CD20 antibody (Rituxan)
- CAR-T CELLS (CD19, BCMA, TACI, CD37)
- IVIg
- BAFF antagonists such as Benlysta
- BCR signaling inhibitors- Btk and Syk antagonists



The Lymphocyte Rap

