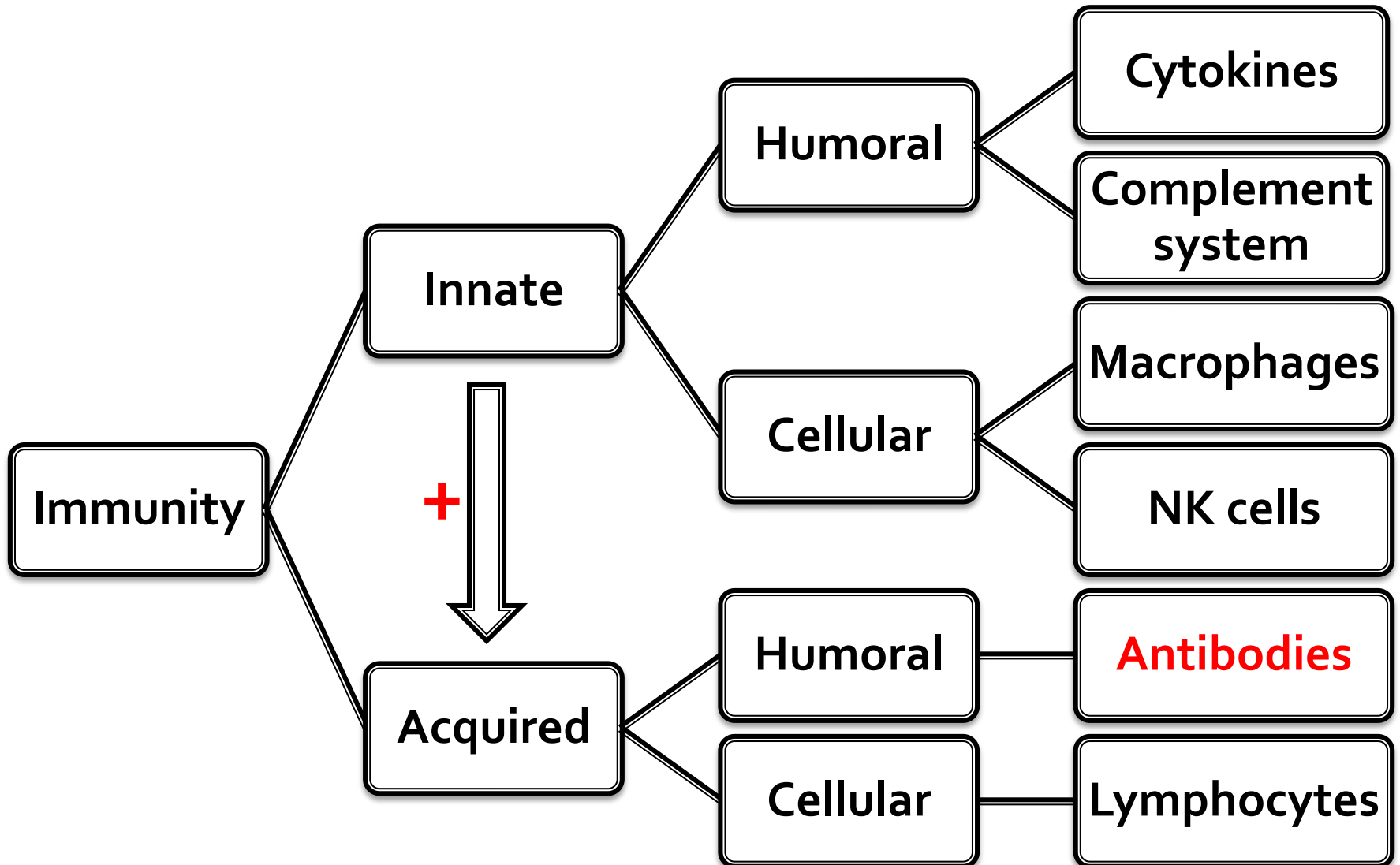


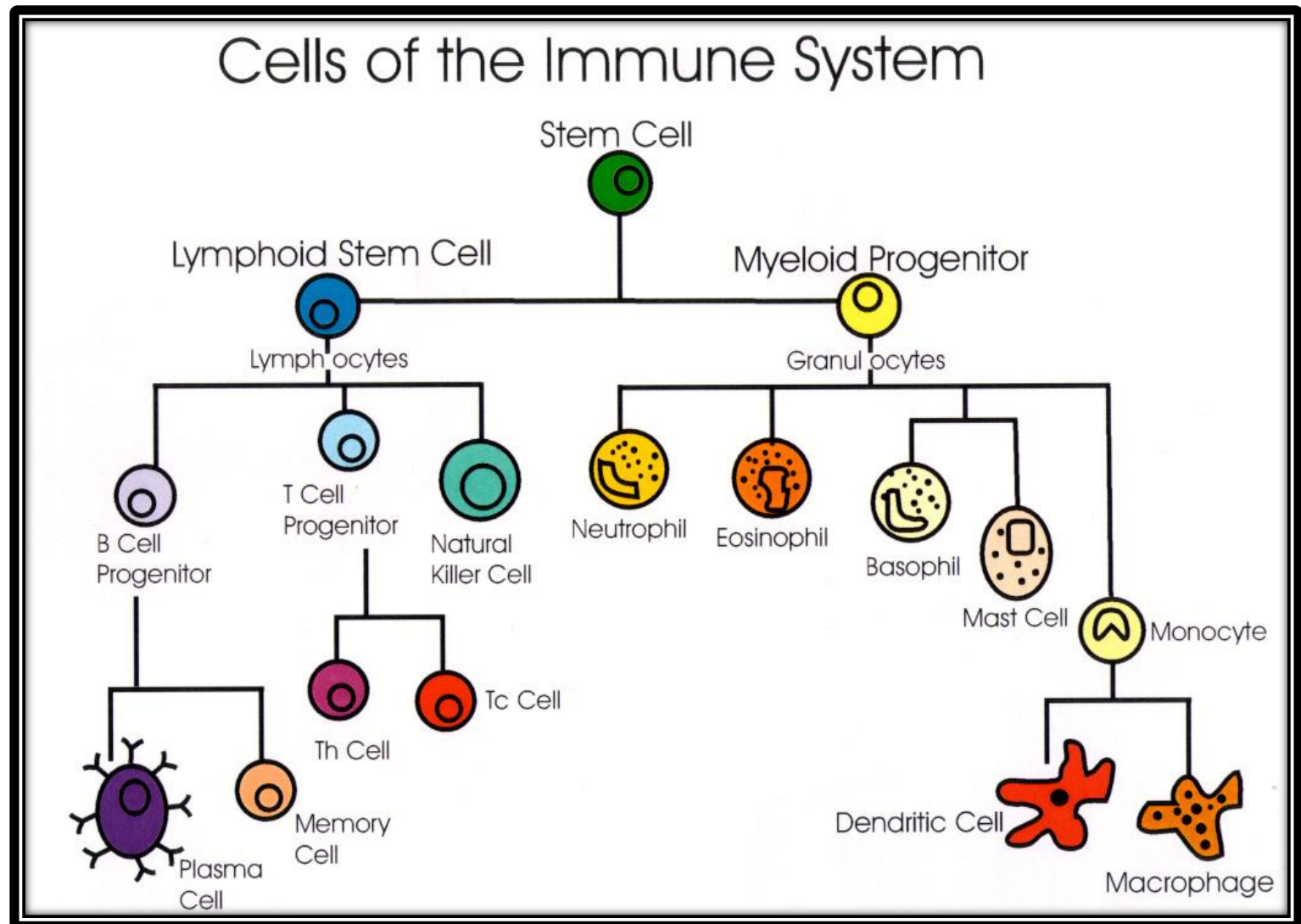
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Immunoglobulins

Innate vs. Acquired Immunity

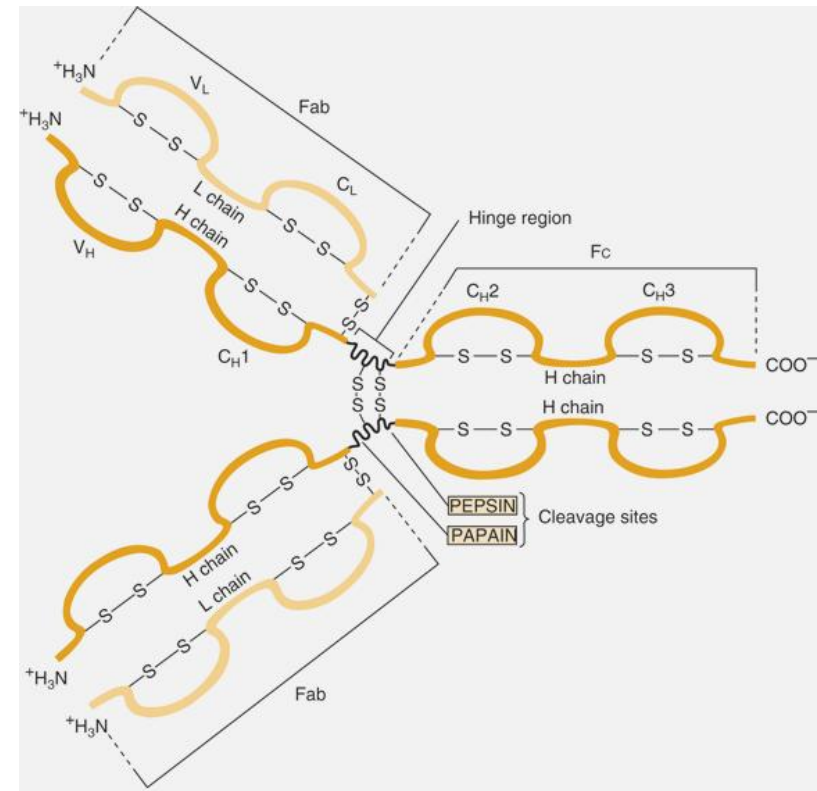


Immune system cells



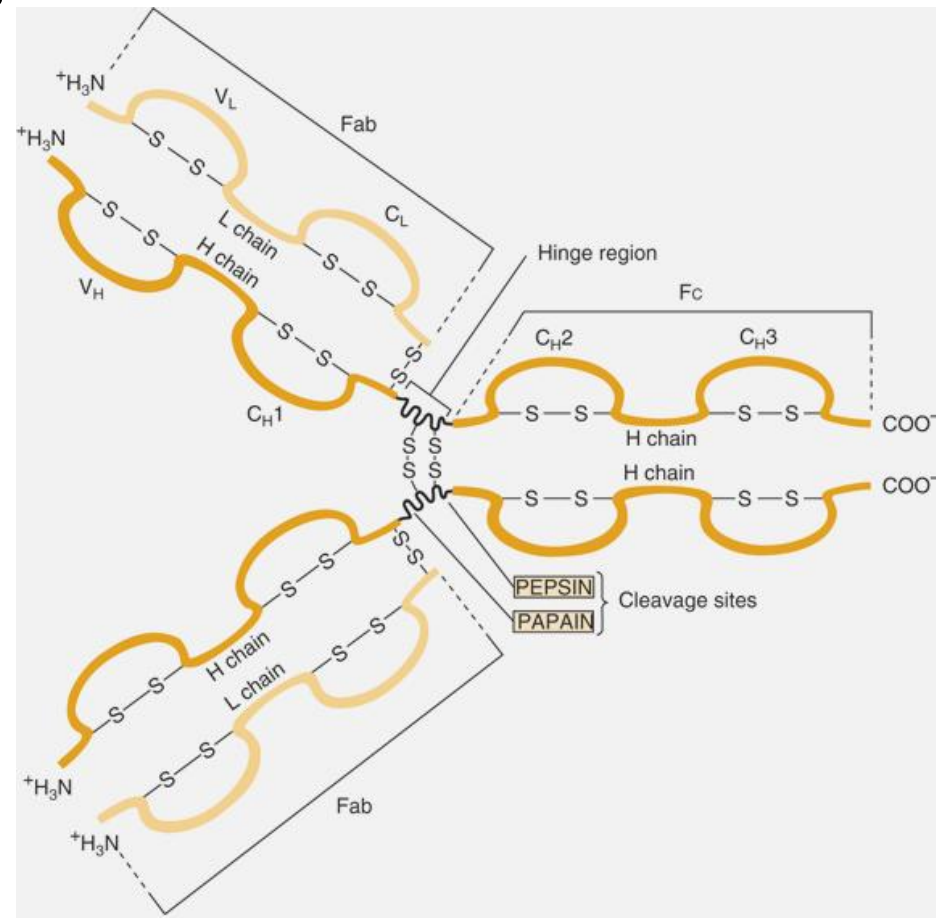
Immunoglobulins - structure

- All contain a minimum of 2 identical light chains (25 kDa) & 2 identical heavy chains (50 kDa)
- Held together by disulfide bonds
- Y-shaped: binding of antigen at both tips
- Each chain has specific domains
- L chain: amino half (V_L), carboxylic half (C_L)
- H chain: $\frac{1}{4}$ amino (V_H), $\frac{3}{4}$ carboxylic (C_{H1} , C_{H2} , C_{H3})



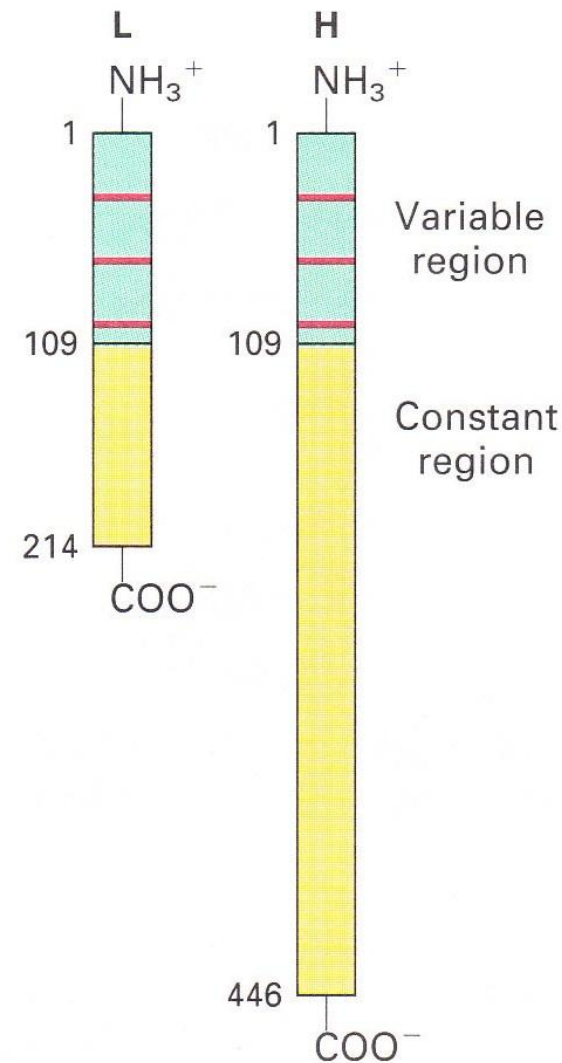
Immunoglobulins - structure

- Antigen binds V_H & V_L domains
- Hinge region: C_H1 & C_H2 domains; flexibility & independent movement
- Fc and hinge regions differ in the different classes of antibodies
- Papain: 2 antigen-binding fragments (Fab) and one crystallizable fragment (Fc)
- Pepsin: one $(Fab)_2$ fragment and one crystallizable fragment (Fc)



Immunoglobulins - structure

- 2 L chains 25 kDa 214 AA
- 2 H chains 50 kDa 446 AA
- Light chain:
 - ✓ 1- 110 variable, 111 – 214 similar
- Heavy chain:
 - ✓ 1- 113 variable, 114 – 446 similar
- 3 stretches (7-12 amino acids) hypervariable

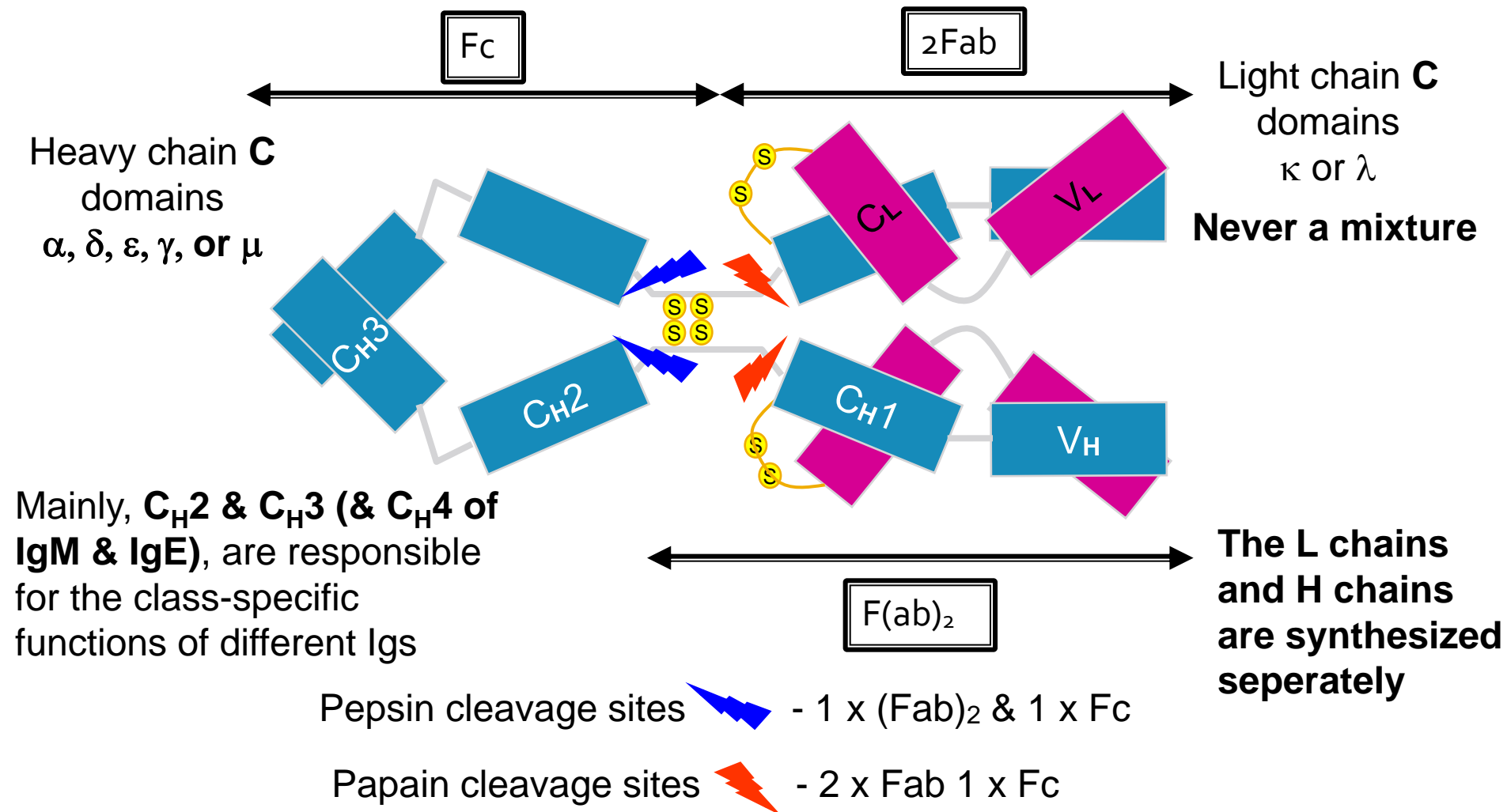


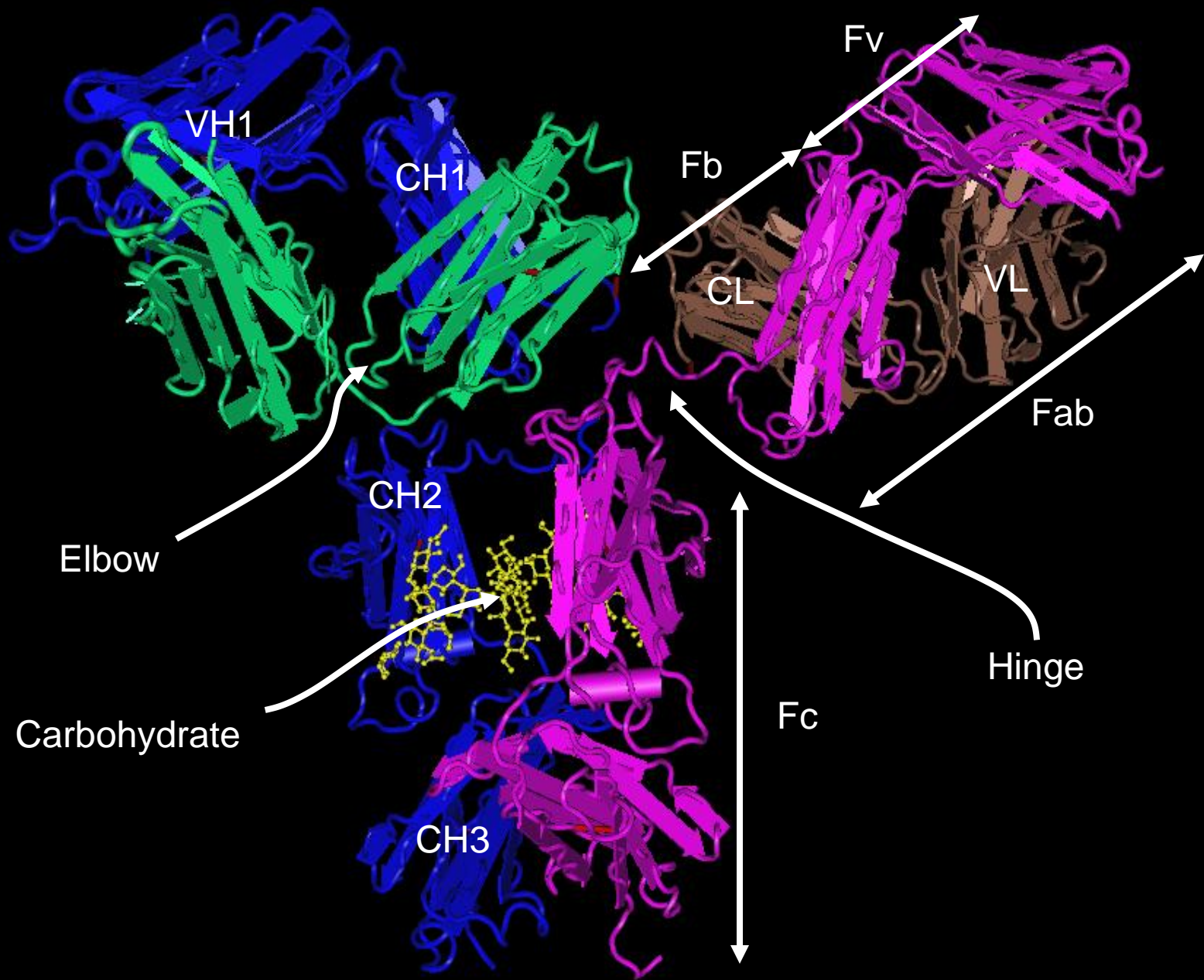
Immunoglobulin - interactions

- With antigen (infinite):
 - ✓ Electrostatic, Hydrogen, Van der Waal's, Hydrophobic
 - The (Fab)₂ fragment CAN:
 - ✓ Detect & bind the antigen
 - ✓ Block the active sites of toxins
 - ✓ Block interactions between host and pathogen
- With other cells and molecules through the Fc portion (finite)
 - The (Fab)₂ fragment CANNOT activate:
 - ✓ Inflammatory functions associated with cells
 - ✓ Inflammatory functions of complement proteins
 - ✓ Intracellular cell signaling molecules

Domain Structural variation of Immunoglobulins – constant region

Domains are folded, compact, protease resistant structures





The Immunoglobulin Fold

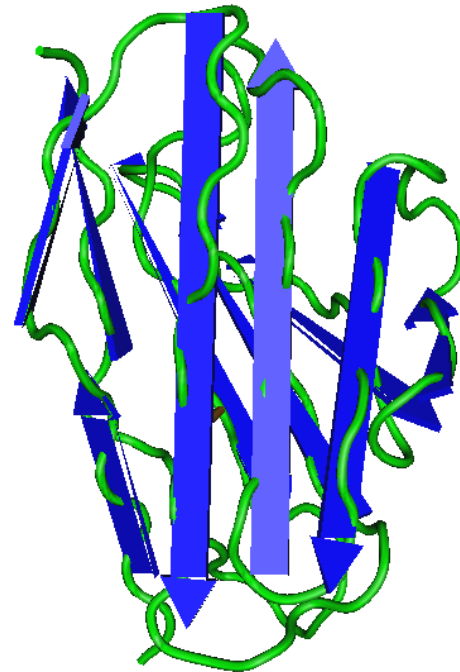
The characteristic structural motif of all Ig domains

A β barrel of 7 (C_L) or 8 (V_L) polypeptide strands connected by loops and arranged to enclose a hydrophobic interior

A barrel

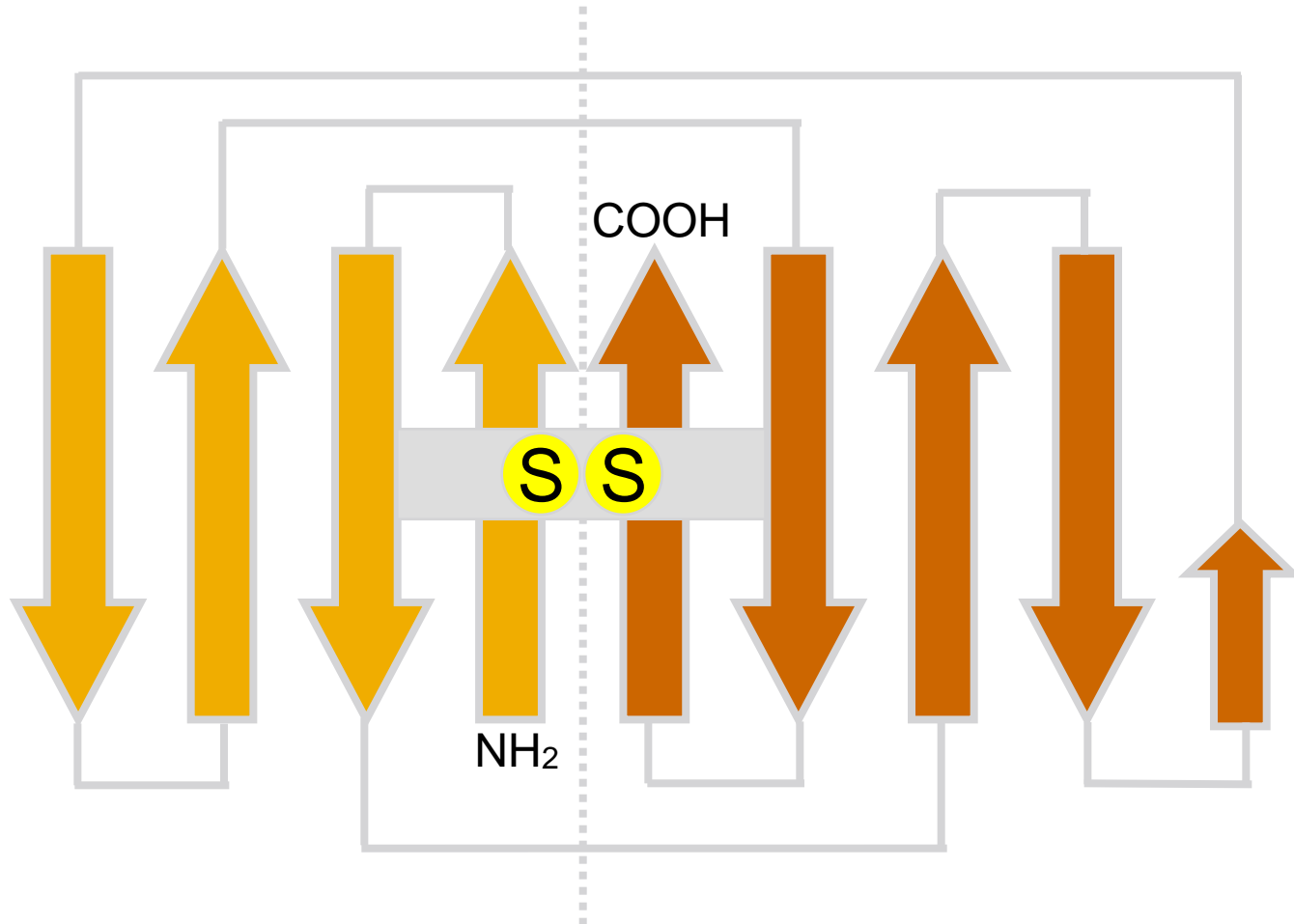


Barrel under construction



Single V_L domain

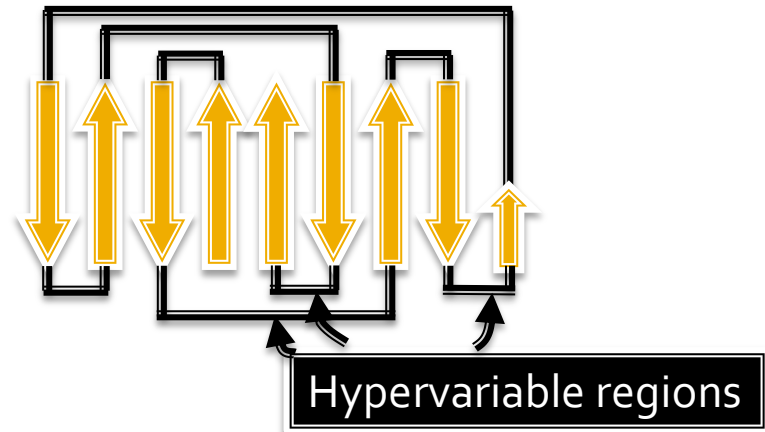
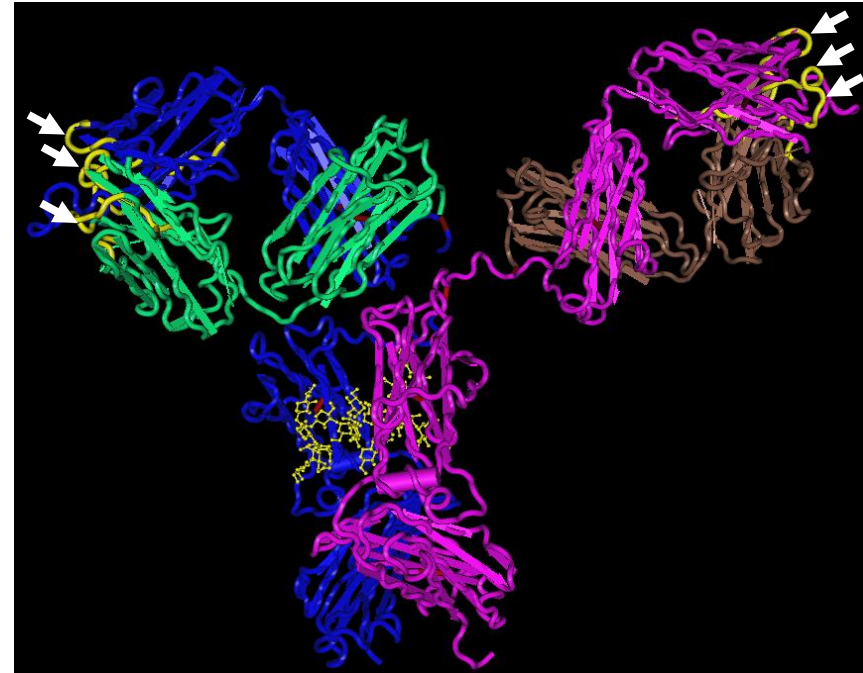
The Immunoglobulin Fold



Unfolded V_L region showing 8 antiparallel β -pleated sheets connected by loops

Variable Regions

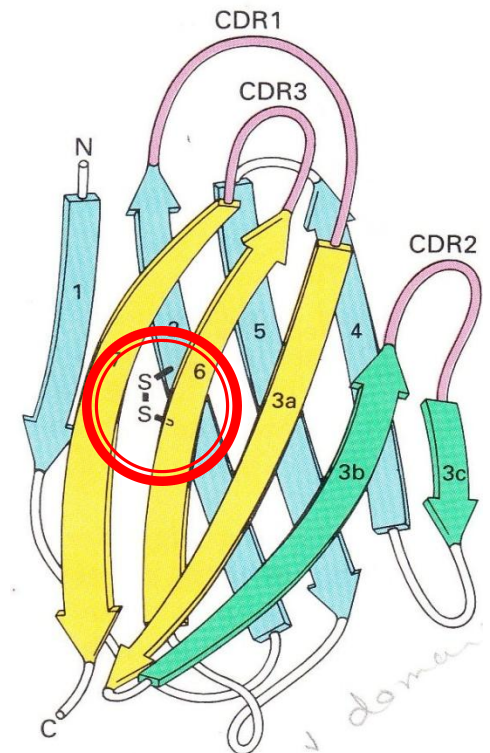
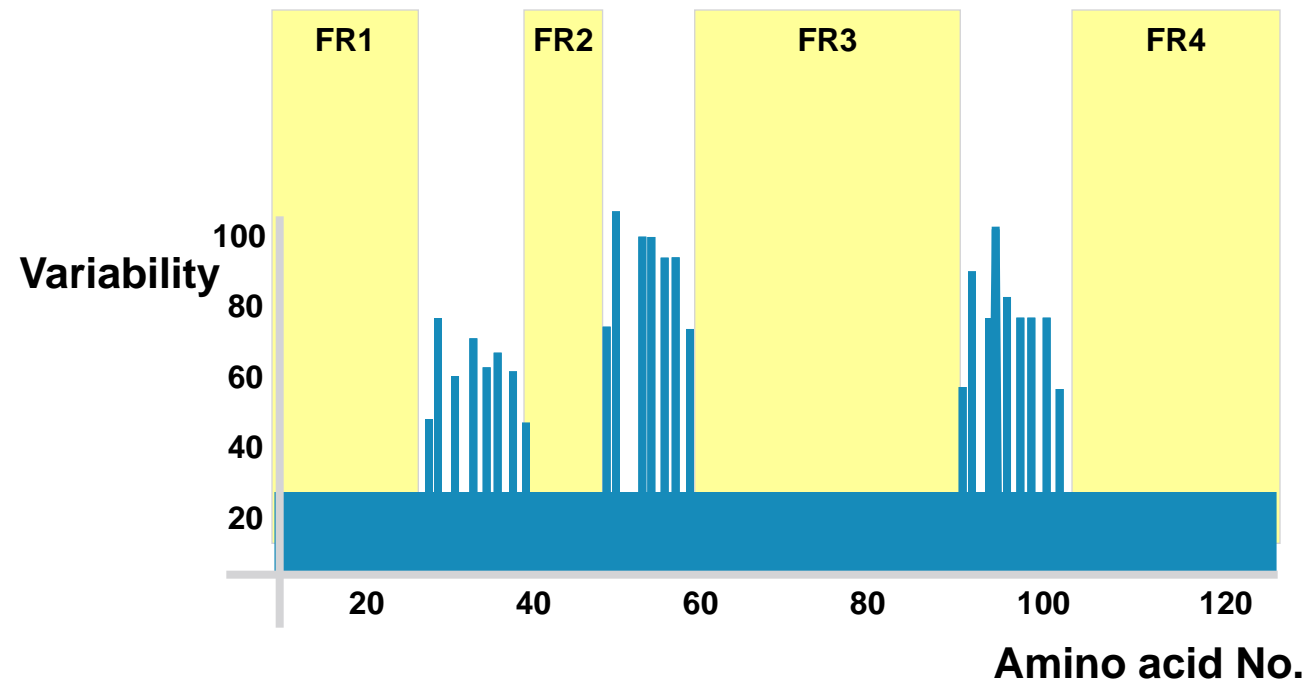
- No two variable regions in different humans are identical
- Relatively invariable regions and other hypervariable regions
- L chains have 3 hypervariable regions (in V_L) and H chains have four (in V_H)
- These hypervariable regions comprise the antigen-binding site
- Dictate the amazing specificity of antibodies



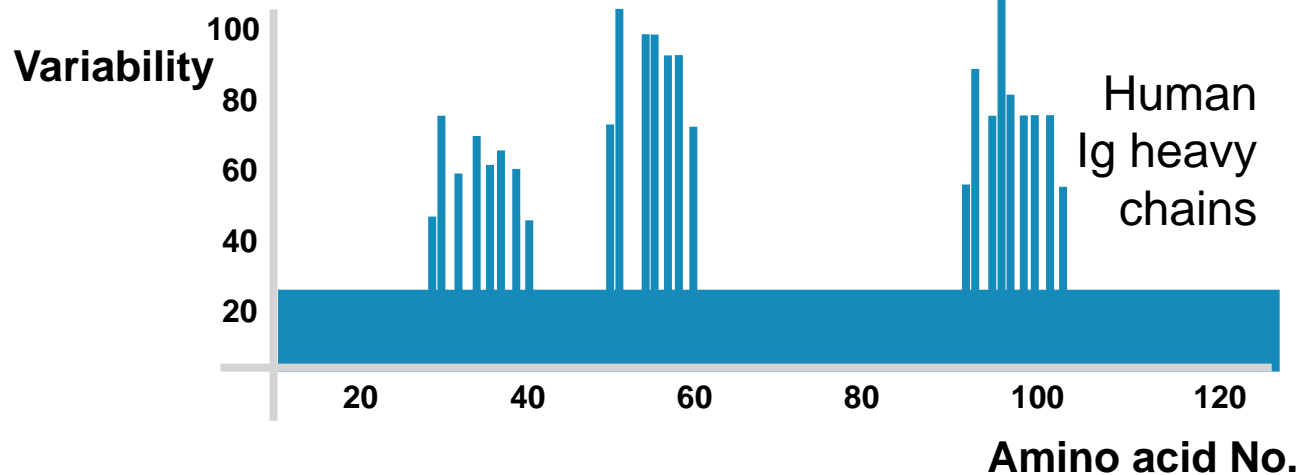
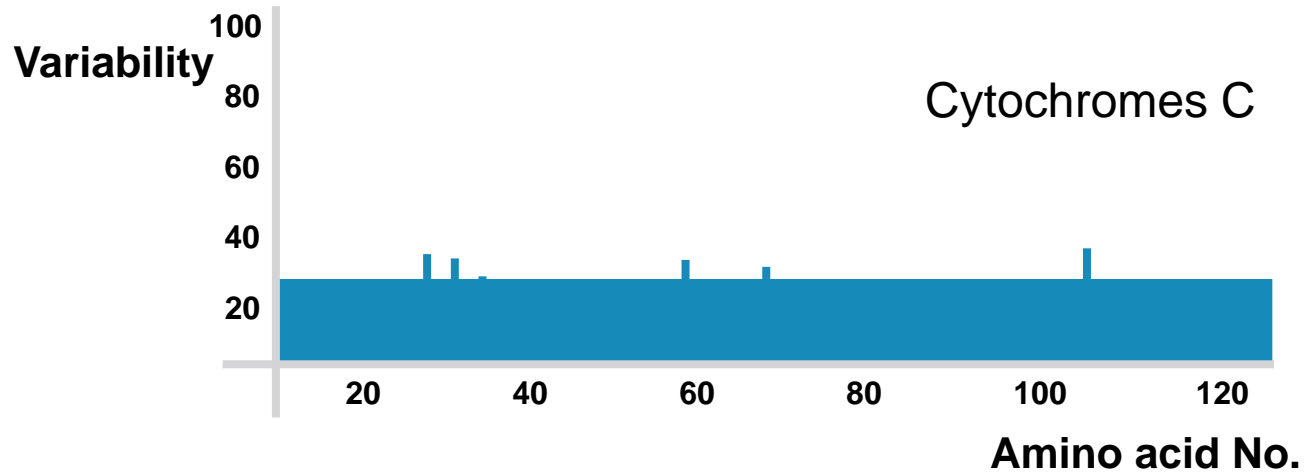
Hypervariable regions

Complementarity-determining regions (CDRs)

- About 7-12 amino acids in each one that contribute to the antigen-binding site
- CDRs are located on small loops of the variable domains
- Framework regions: the surrounding polypeptide regions among the hypervariable regions

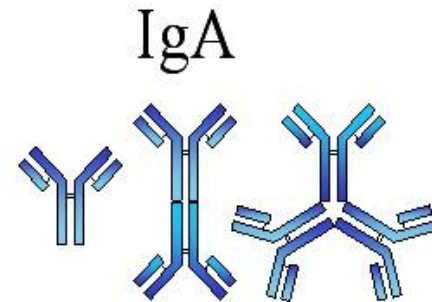


Variability in other proteins



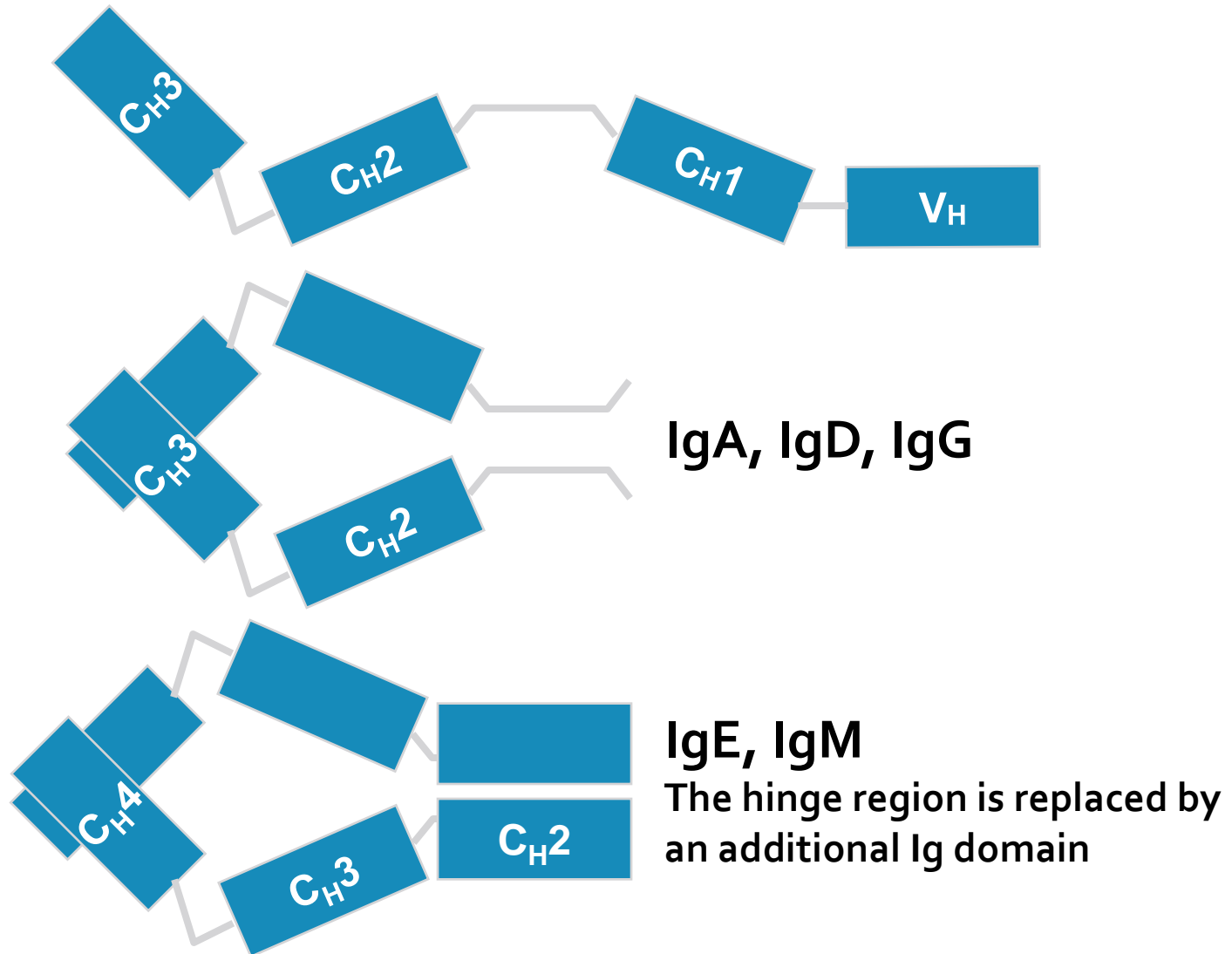
Immunoglobulin classes - overview

- Igs are classified based on the nature of their heavy chain



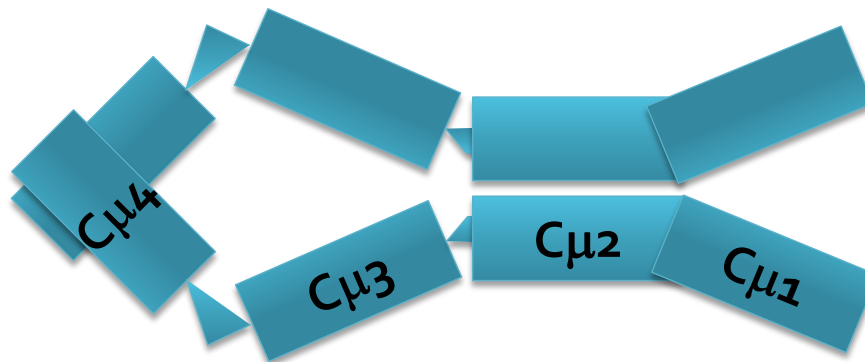
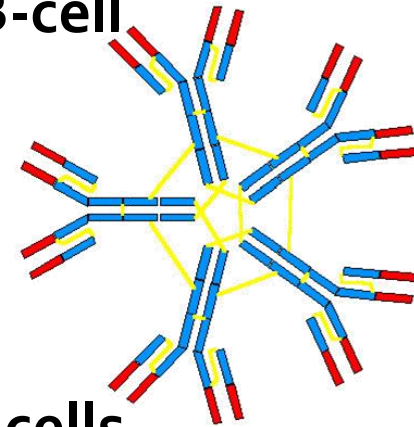
Class	Heavy chain	Chains structure	% in serum	T _{1/2} (days)	Comp. fixation	Placental crossing
IgM	μ	Mono-, penta-, & hexa	5-10	5-10	++++	No
IgG	γ	Monomer	80	23	++	Yes
IgA	α	Mono-, di-, or tri	10-15	6	-	No
IgD	δ	Monomer	0.2-1	3	-	No
IgE	ε	Monomer	0.002	2	-	No

Domains in different classes (H-chain)

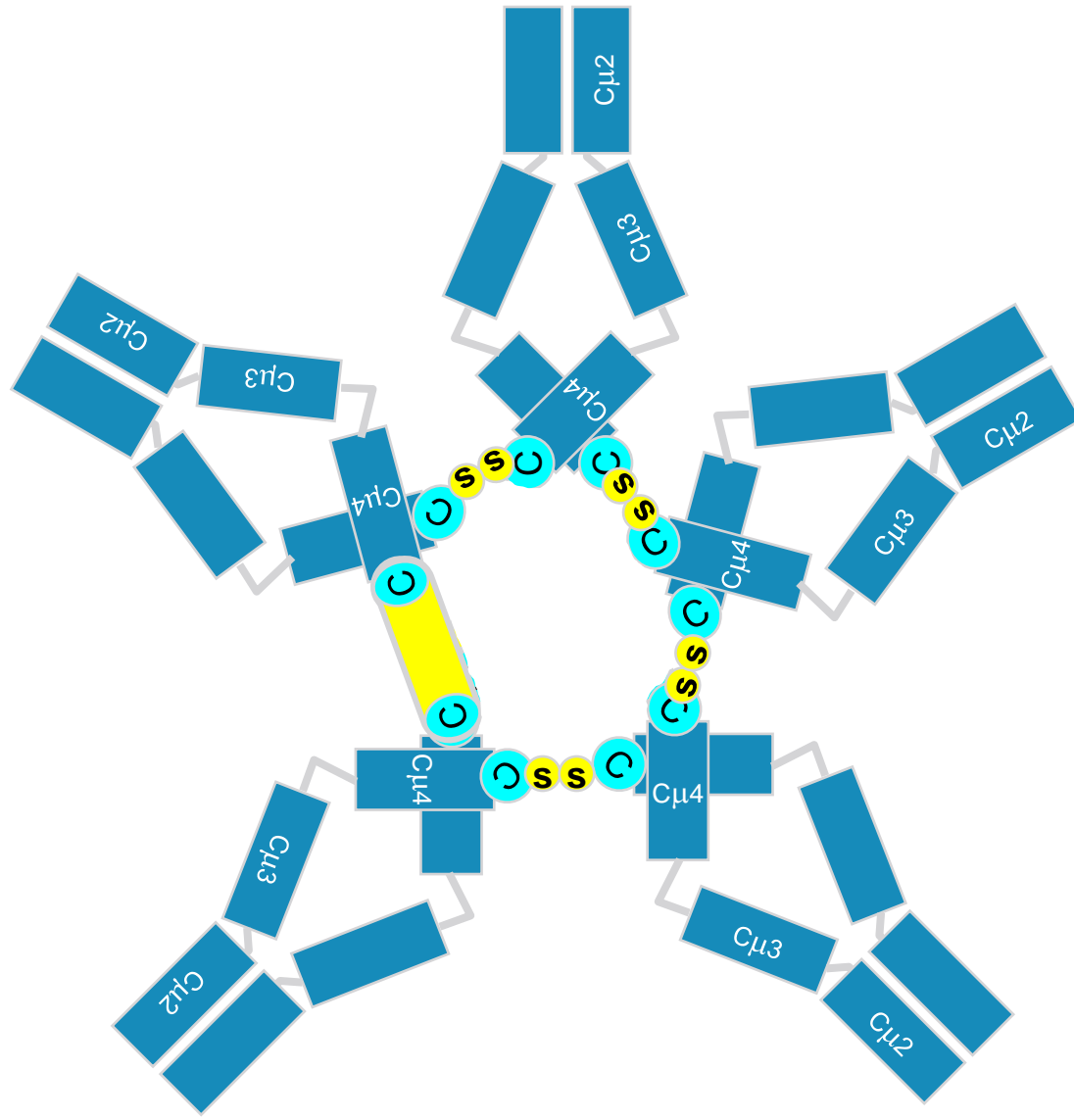


IgM Class

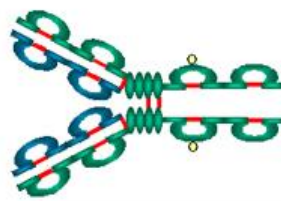
- Location: Mainly intravascular (blood & lymph), B-cell surface (monomer)
- Known Functions:
 - ✓ Primary immune response (1st produced)
 - ✓ Primary role in antigen agglutination (ex. ABO)
- IgM only exists as a monomer on the surface of B cells
- Monomeric IgM has a very low affinity for antigen
- A J-chain is involved in the process of multimerization
- C μ 4 mediates multimerisation (C μ 3 may also be involved)



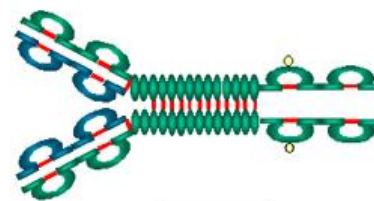
The process of IgM Multimerisation



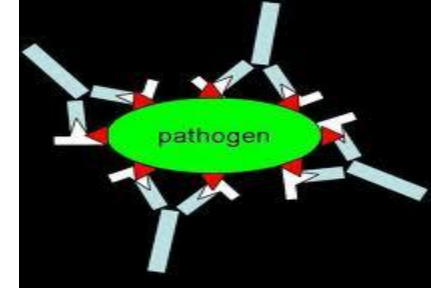
IgG Class



IgG1, IgG2 and IgG4



IgG3



- Location: Blood, lymph, intestine
- Produced in response to a wide variety of antigens, (ex. bacteria, viruses)

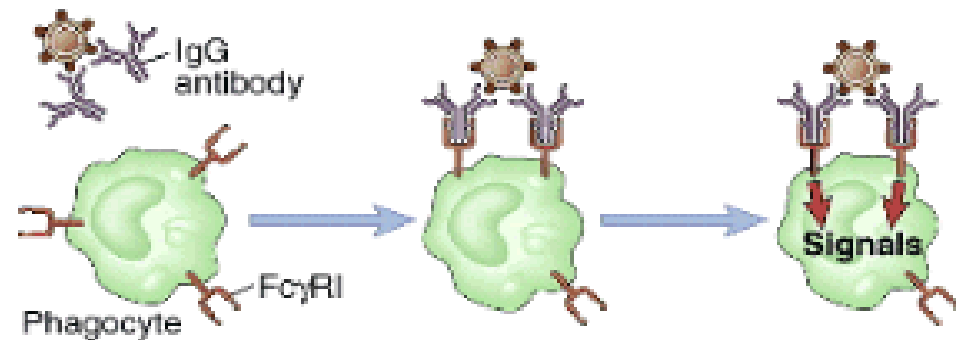
➤ Known Functions

- ✓ The predominant antibody produced in the 2^o immune response
- ✓ Provides the major line of defense for the fetus & during first few weeks of newborns
- ✓ Coats organisms to enhance phagocytosis by neutrophils and macrophages (opsonization)

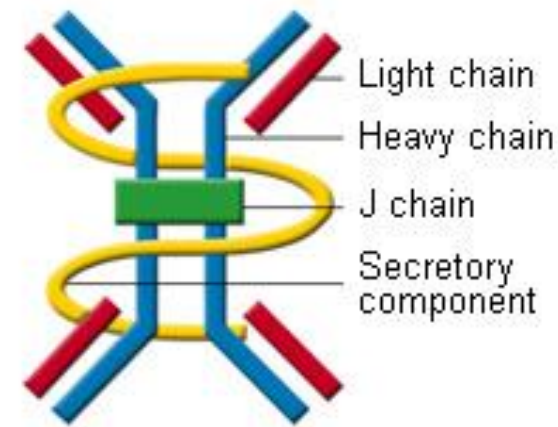
Opsonization of microbe by IgG

Binding of opsonized microbes to phagocyte Fc receptors (FcγRI)

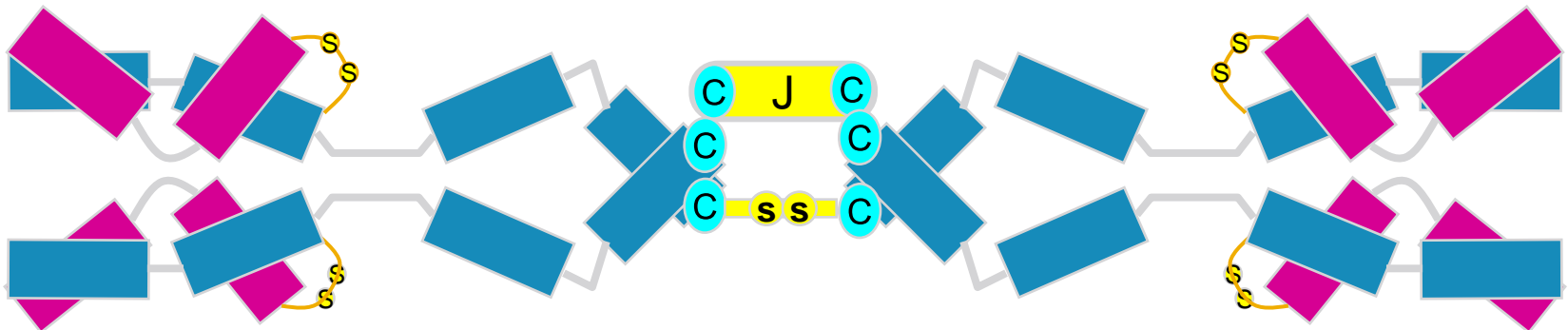
Fc receptor signals activate phagocyte



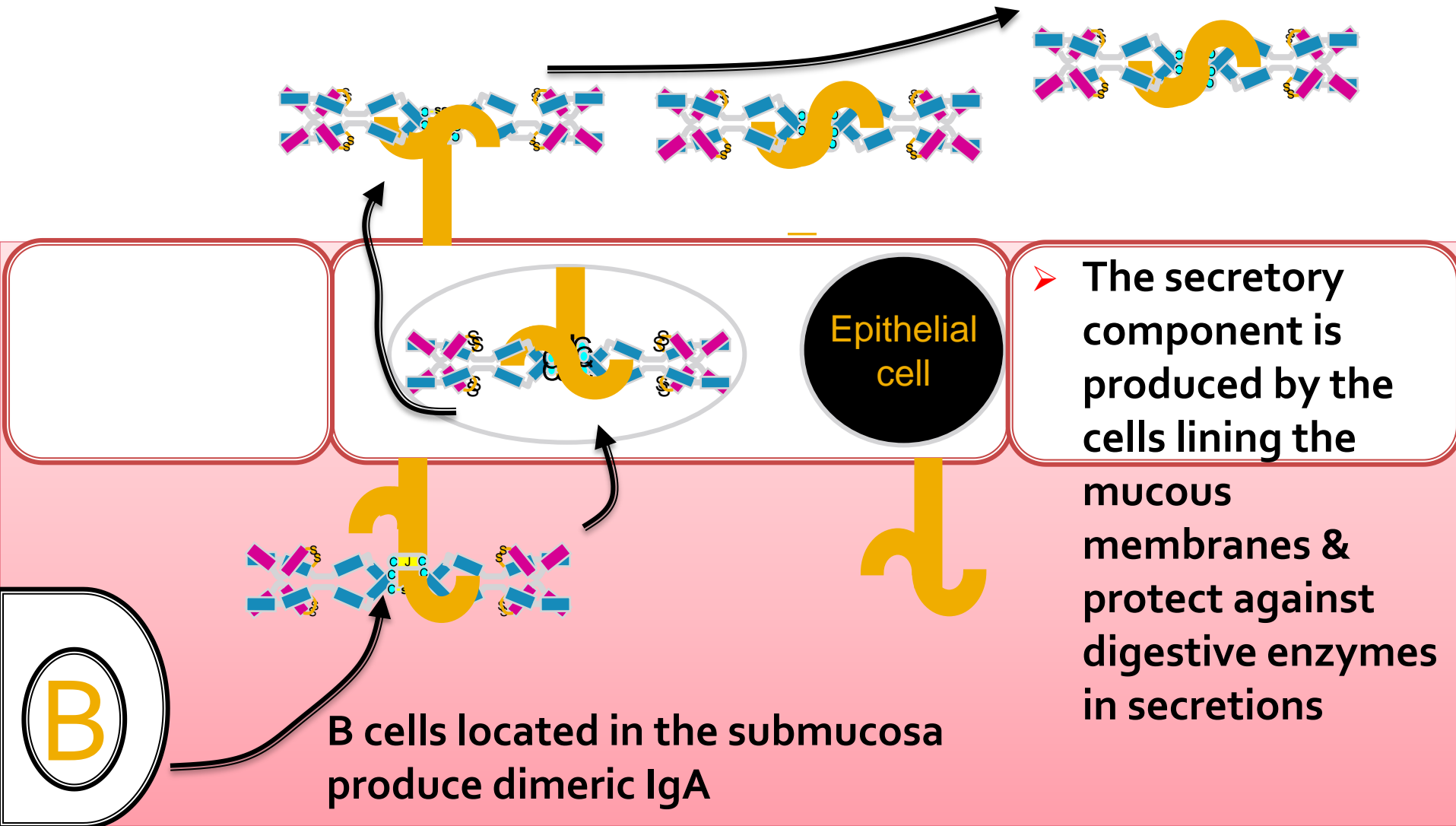
IgA class



- Structure & location:
- ✓ Plasma → monomer, dimer, or trimer
- ✓ Secretions (tears, saliva, intestines, milk, bronchial secretion, urine)
→ dimer attached to “secretory component”
- Known Functions:
- Localized protection (respiratory, urinary tract and bowel infections)
- Provides immunity to infant’s digestive tract & body (translocated)
- The process of dimerization

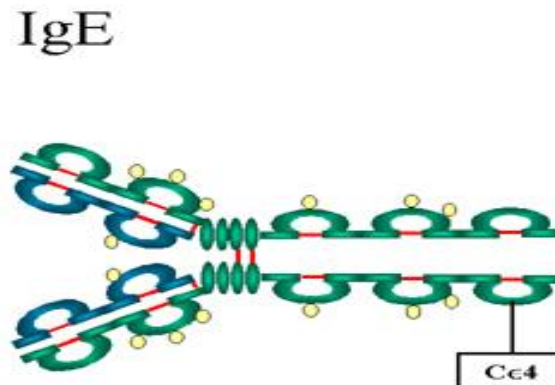


IgA & transcytosis

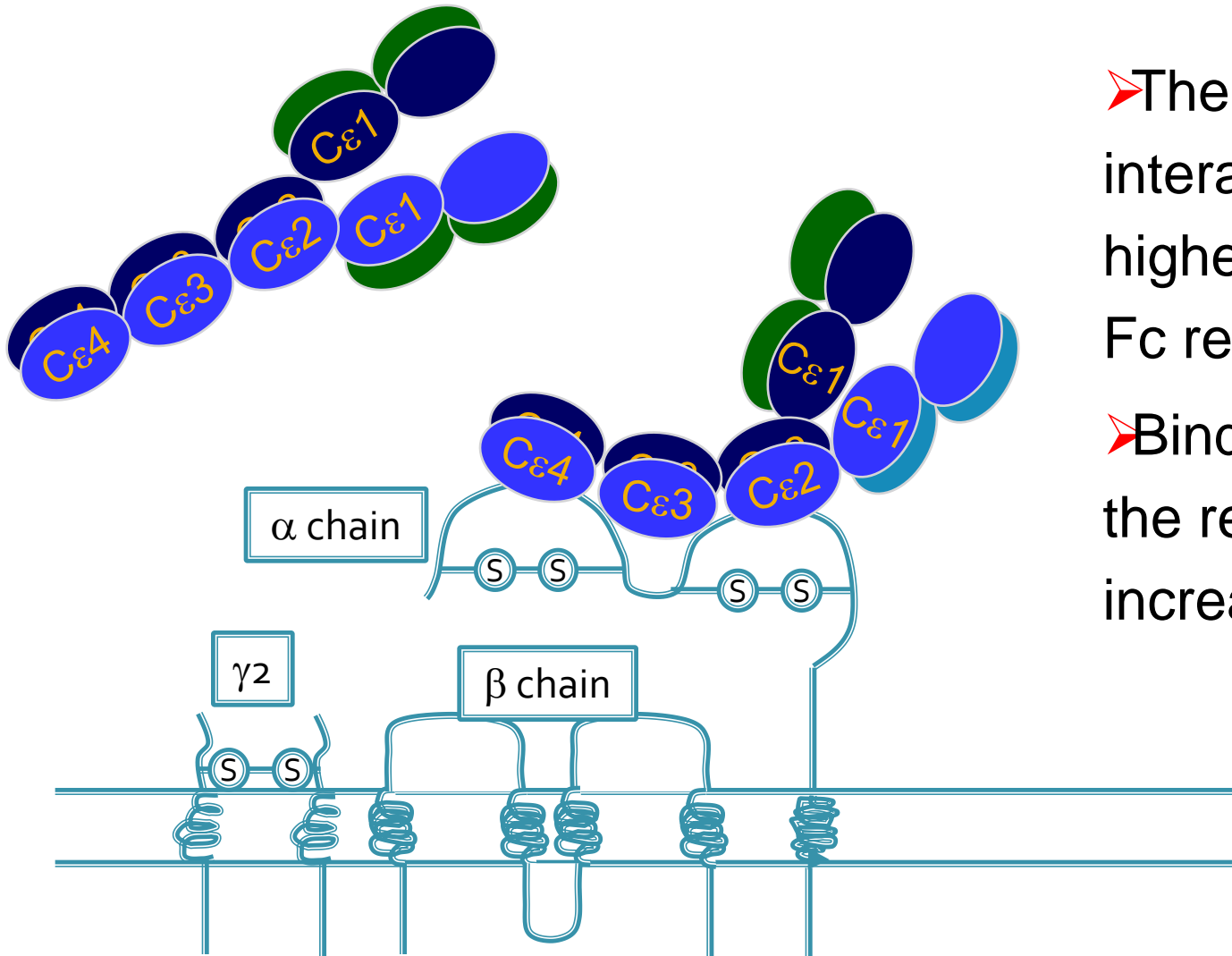


IgE class

- Location: Blood & Bound to mast cells and basophils throughout body
- Known Functions:
 - Allergic reactions (histamines and heparin): increased vascular permeability, skin rashes, respiratory tract constriction (wheezing), and increased secretions from epithelium (watery eyes, runny nose)



IgE-receptor affinity



➤ The IgE–receptor interaction is the highest affinity of any Fc receptor

➤ Binding of IgE to the receptor increases the half life

Diseases

- **Myelomas: increased production**
- **Multiple myeloma: a neoplastic condition, increase in one class, or a particular light chain (Bence Jones protein)**
- **Decreased production may be restricted to a single class or may involve underproduction of all classes (ex. agammaglobulinemia)**

