بسم الله الرحمن الرحيم

BioChemistry | FINAL 8

Immunoglobulins

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IMMUNOGLOBULINS

It is a synonym name for antibodies and the same as gamma globulins

DEFENSE LINES (SPECIFIC VS. NON-SPECIFIC)

- The immune system plays a major role in the body's defense mechanisms

Non-specific (innate)		Specific (acquired)
First line	Second line	Third line
Barriers ✓ Physical: skin, hair, mucous membranes ✓ Chemical: sweat, tears, saliva, stomach acid, urine	✓ Phagocytic WBCs ✓ Antimicrobial proteins ✓ The inflammatory response	Lymphocytes (**T-lymphocytes** as cell mediated immunity or **B-lymphocytes** which are able to produce antibodies) Antibodies

ACQUIRED (SPECIFIC) IMMUNITY

- Two major components:
  - T lymphocytes (thymus, cell-mediated immunologic processes; graft rejection, hypersensitivity reactions, & defense against malignant cells and many viruses)
  - B lymphocytes (bone marrow, synthesis of circulating, humoral antibodies; Igs) matured and synthesized in bone marrow ,lymph node and spleen.
    - plasma cells: specialized B cells that synthesize and secrete immunoglobulins into the plasma in response to exposure to antigens
- Genetic deficiency is reported (recurrent infections) in both T cells and b cells.
  Cause immune responses by T and B cells not working well which will cause recurrent infections.

IMMUNOGLOBULINS & ANTIGENS

- Antibodies: glyco-proteins synthesized by plasma cells(mature B lymphocytes)& able to bind foreign molecules even if not encountered before (not recognized in our body)
  - High specificity & high affinity
  - Huge number of different kinds (~10^8) of antibodies.
  - Synthesis is stimulated by having an immunogen (introduction of a new molecule to our body **which can set or start a new immune response).**
  - These antibodies after they bind to their immunogen they Induces the "effector functions": Inactivation, degradation, lysis
- Antigen: Foreign molecules to which Igs (immunoglobulins) bind
  - Can elicit antibody formation (immounogen)
  - Immunogen should be macromolecule; Protein, polysaccharide, nucleic acid which are present on the surface of micro organisms.
  - Epitope (antigenic determinant): each epitope is recognized by a different antibody
  - Hapten: small molecule, antigen if attached to a macromolecule

IMMUNOGLOBULINS & ANTIGENS

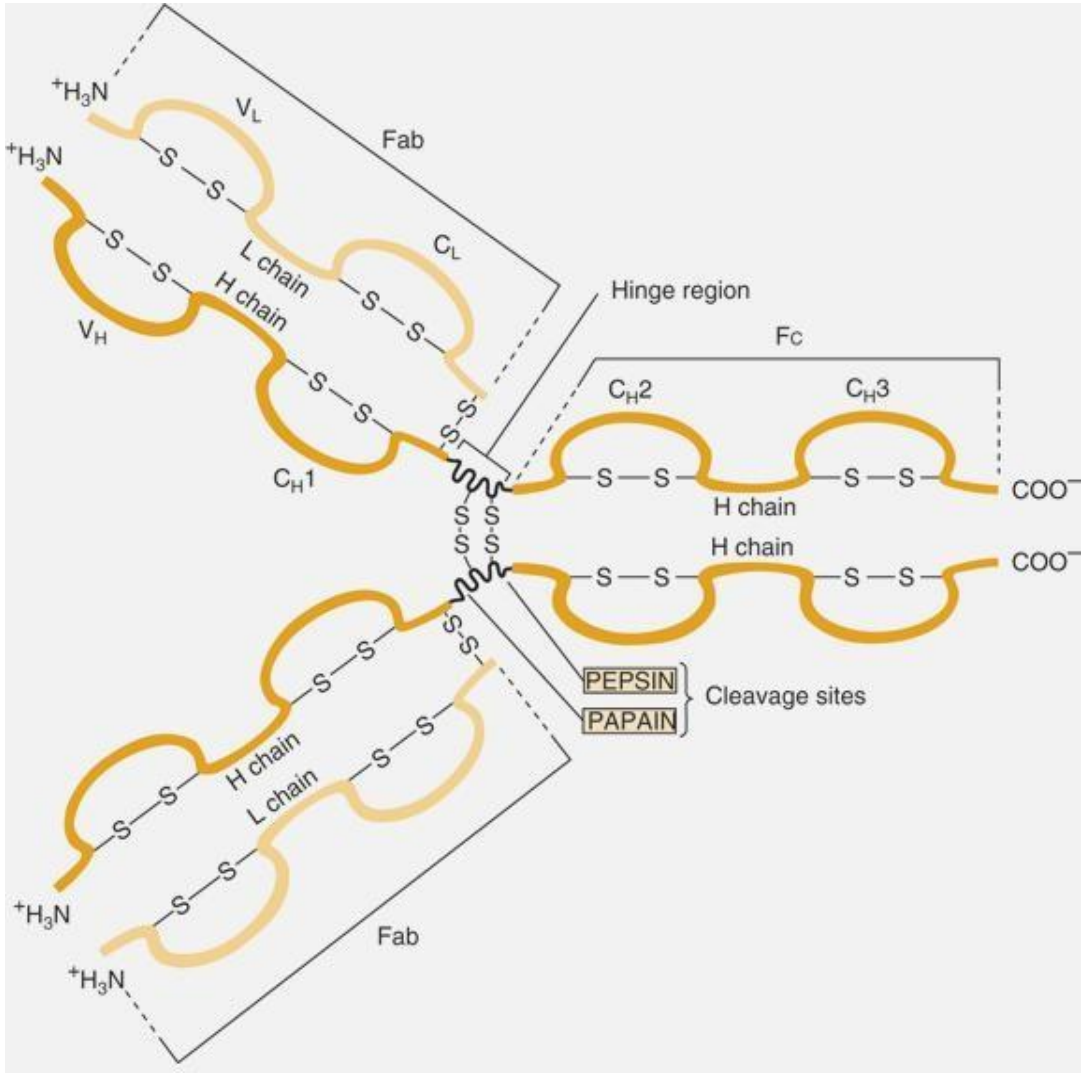
- Epitope (the exact body of the antigen where the antibody bind, antigenic determinant): each epitope is recognized by a different antibody.

➢ At the same bacteria there could be more than one site where the antibody bind **not by quantity but by quality** (different types of antibodies) each place on the surface of a bacteria **is considered an epitope** because recognized by different antibody so the epitope is the antigenic determinant it's the thing on foreign molecules that tells the body : I'm foreign.

❖ **Haptens** (opposite to Immunogen): are small foreign molecules that can bind to antibodies, but they **can't** induce an immune response on their own.

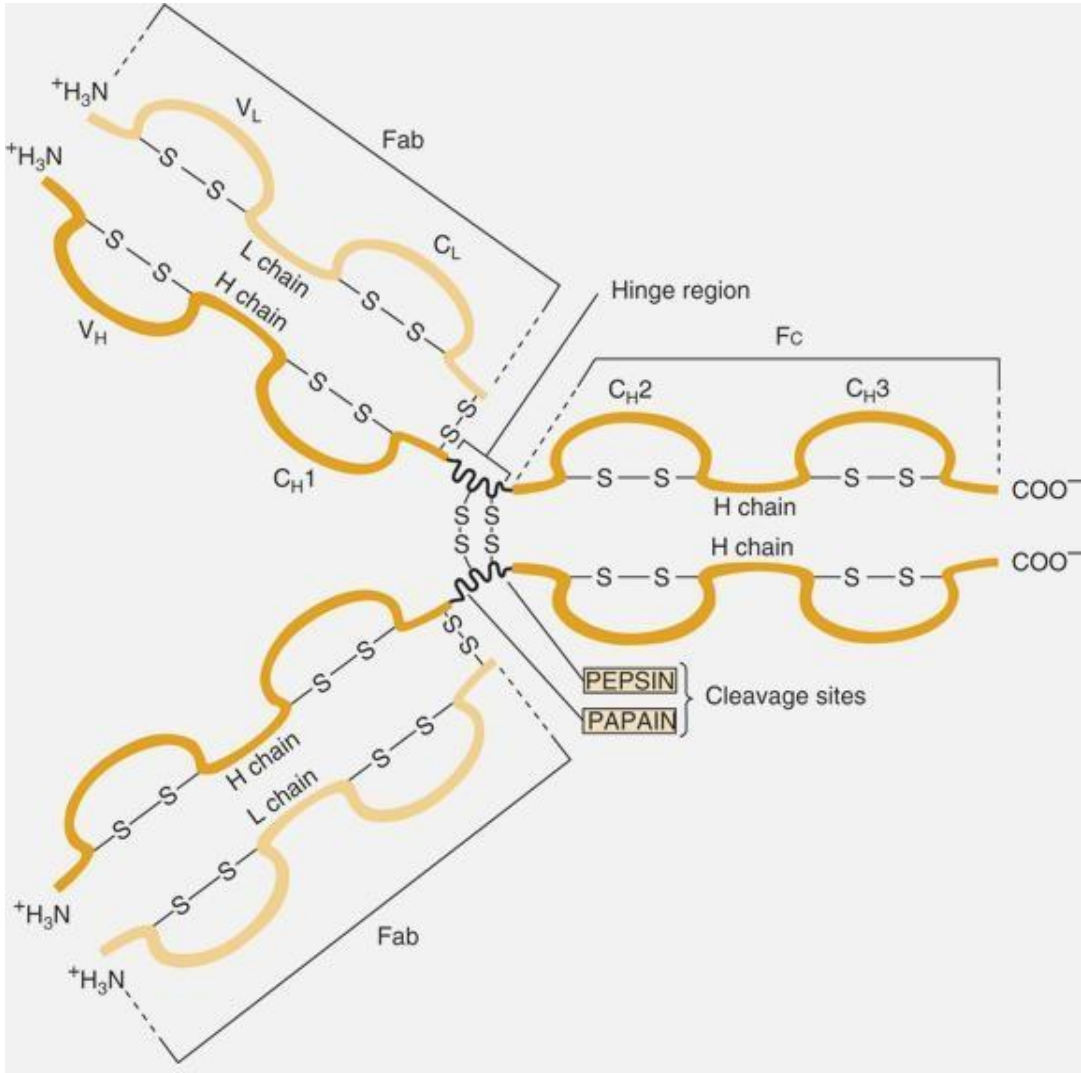
IMMUNOGLOBULINS - STRUCTURE

- All contain a minimum of 2 identical light chains (25 kDa) it adopts its name because it's small & 2 identical heavy chains (50 kDa) so the total molecular weight should be approximately 150 kDa.
- Held together by disulfide bonds
- Y-shaped: binding of antigen at both tips antigen binds the tip of it they bind **both** the light and heavy chain.
- Each chain has specific domains
- L chain: amino half (V_L), carboxylic half (C_L)
- H chain: ¼ amino (V_H), ¾ carboxylic (C_H1, C_H2, C_H3)



IMMUNOGLOBULINS - STRUCTURE

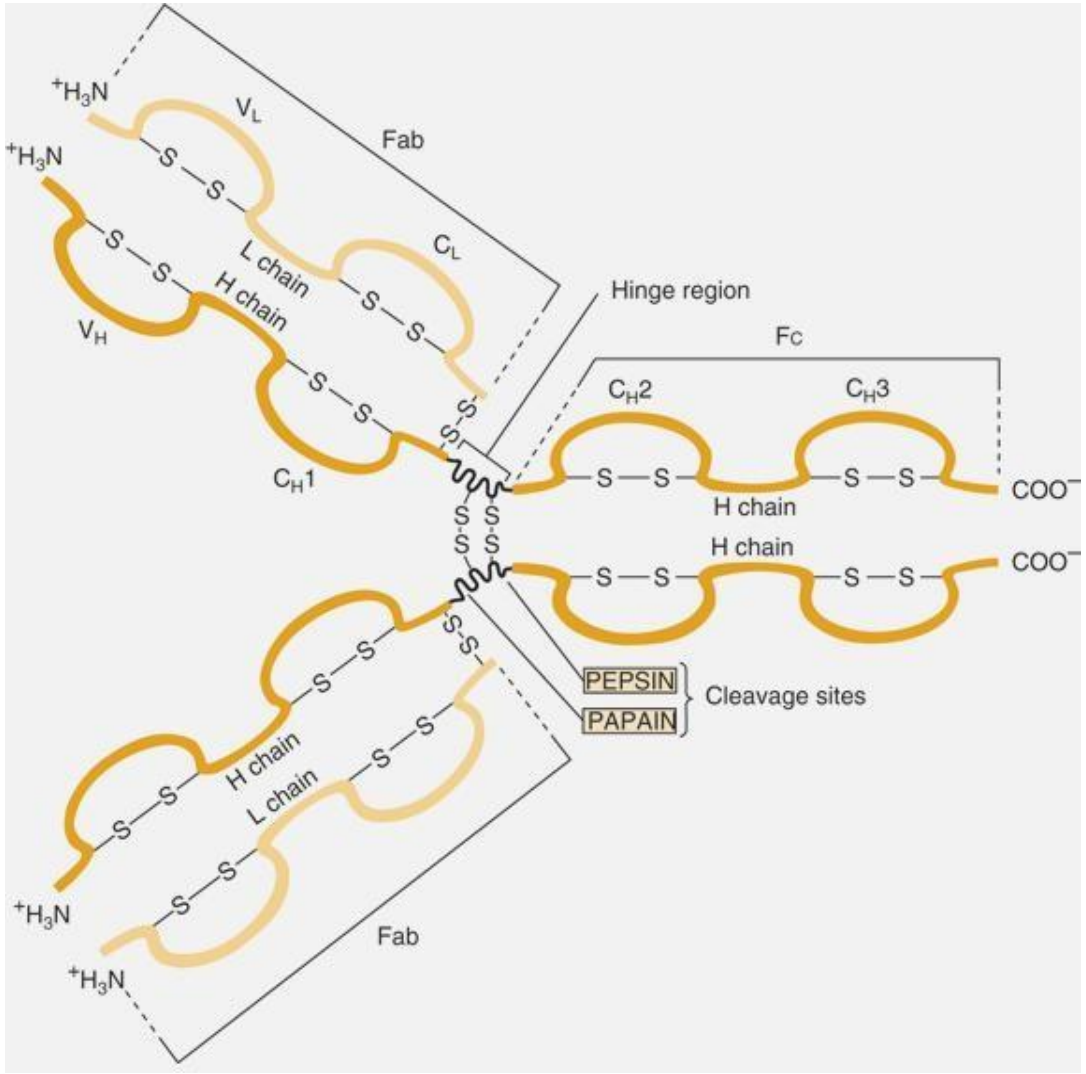
- A special feature of these chains is the presence of disulfide bonds forming the hinge region.
- Each light and heavy chain has a **variable (V)** and a **constant (C) domain.**
- The **heavy** chains are longer, they contain **two additional constant domains (C2 and C3)**, making a total of **four domains in the heavy chain,** <u>three constant and one variable.</u>
- the **light** chain has only **two domains,** <u>one constant and one variable.</u>



IMMUNOGLOBULINS - STRUCTURE

- The **variable** region is called 'variable' because the amino acids in this area **can change** to adapt for binding different antigens.

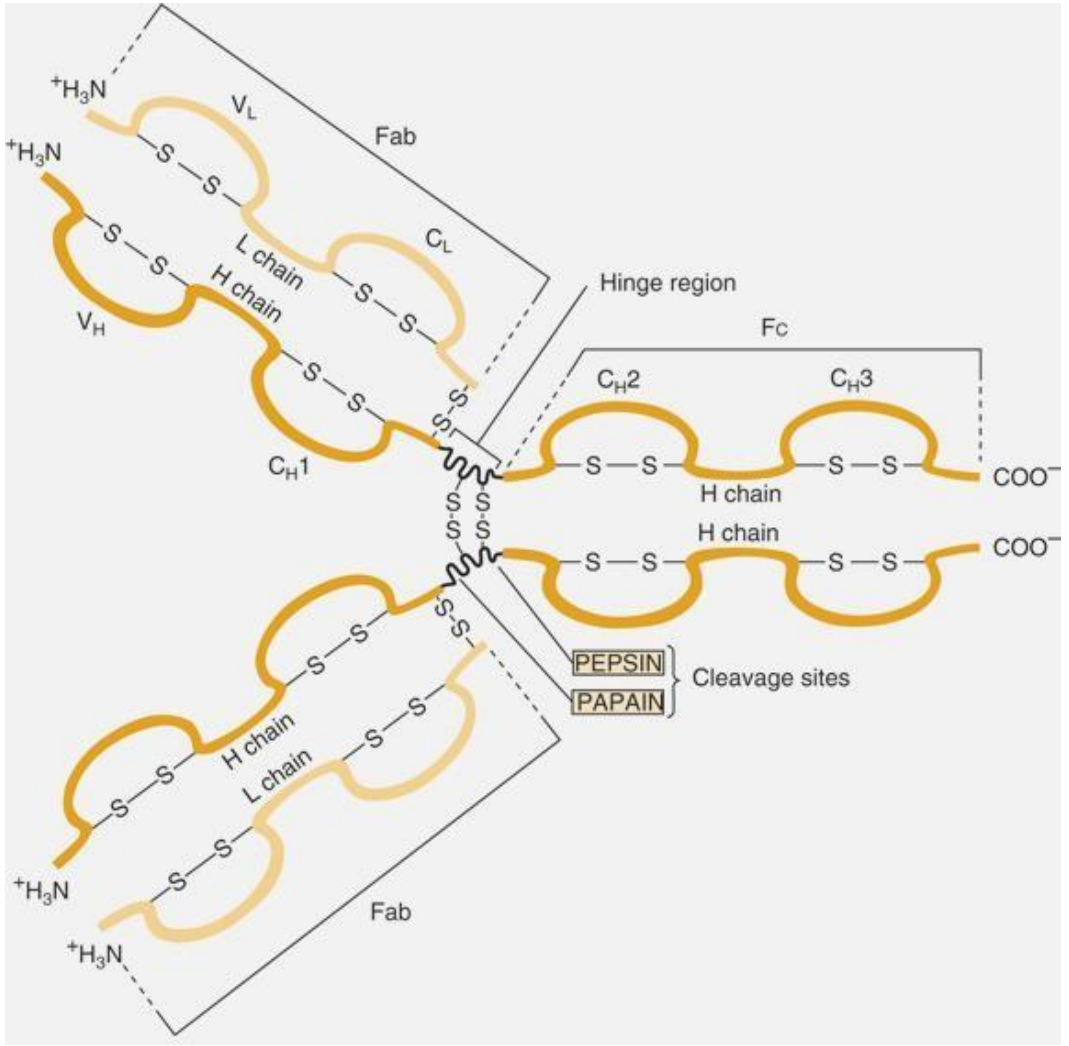
- The **constant** region, on the other hand, is **truly constant** and does not differ between antibodies of the same class.



IMMUNOGLOBULINS - STRUCTURE

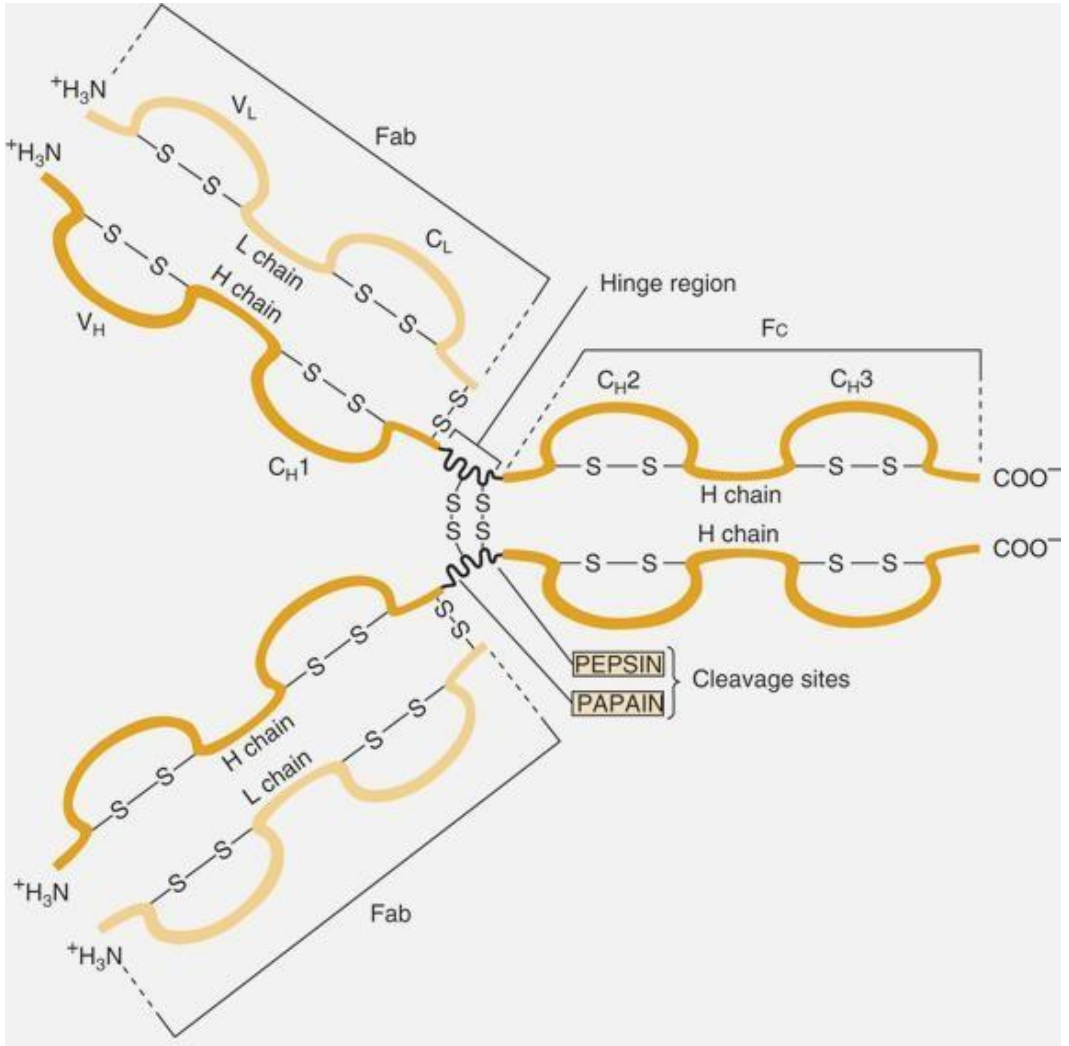
- The term '**Fab**' refers to the **antigen-binding fragment**, Although the actual antigen binding occurs at the **very tips of the Fab region**, the entire region is called the 'antigen-binding fragment' because it functions as a single unit in binding.

- The remaining part is called the '**Fc fragment**' When isolated, the Fc portion tends to **crystallize with other Fc portions**, which is why it is named the 'crystallizable fragment.'"



IMMUNOGLOBULINS - STRUCTURE

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

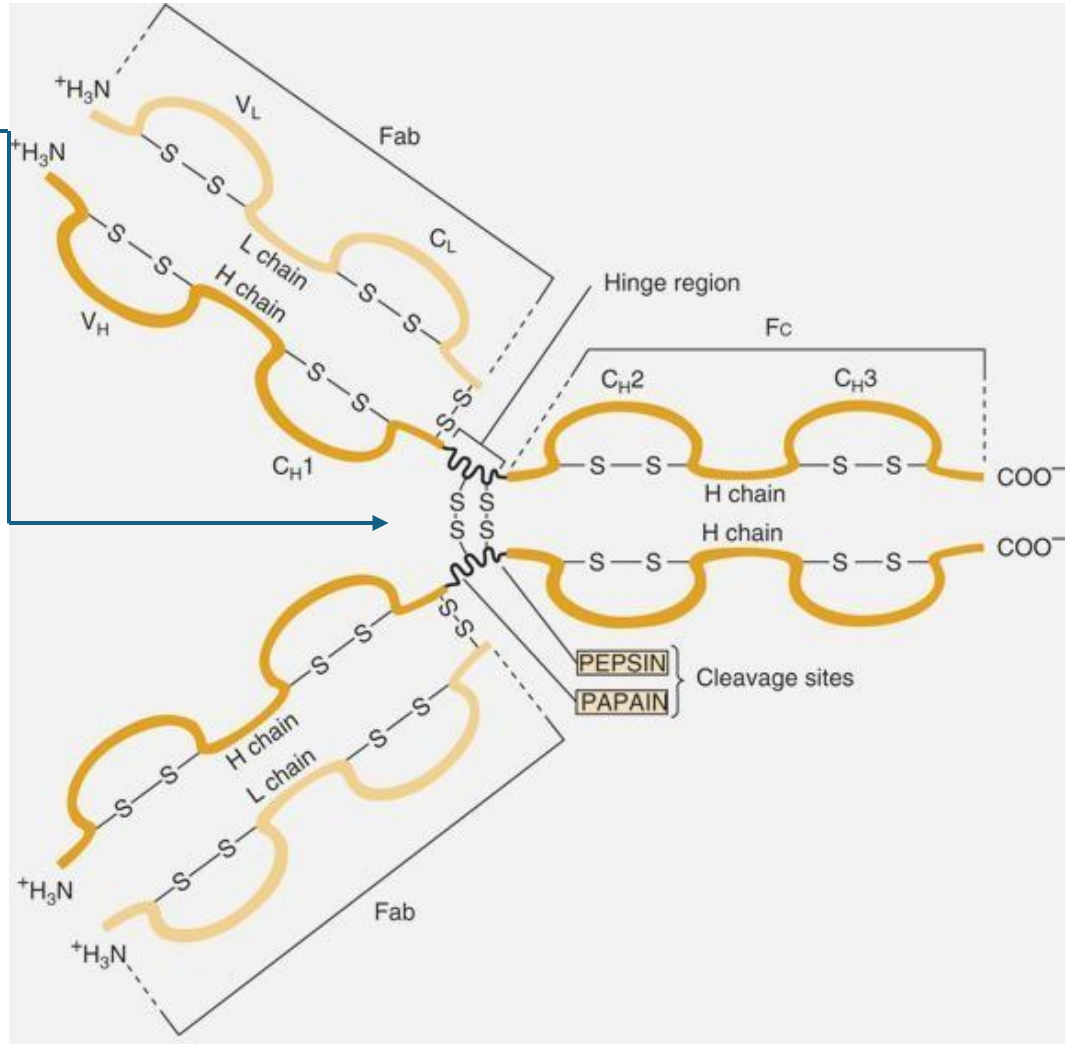


IMMUNOGLOBULINS - STRUCTURE

- **The hinge region** provides **flexibility** to the antibody's convoluted structure.
- This **flexibility** allows the **Fab** arms to move **closer** together if the antigenic determinants on a foreign molecule are close to each other, or to **move farther apart** if the epitopes are widely spaced on the foreign antigen.

- **Immunoglobulins** are proteins that can be cut and hydrolyzed by **proteases**.

- **Pepsin and Papain** were used to **digest immunoglobulins** in the past, and each enzyme cuts at a 2 different site in the hinge region.

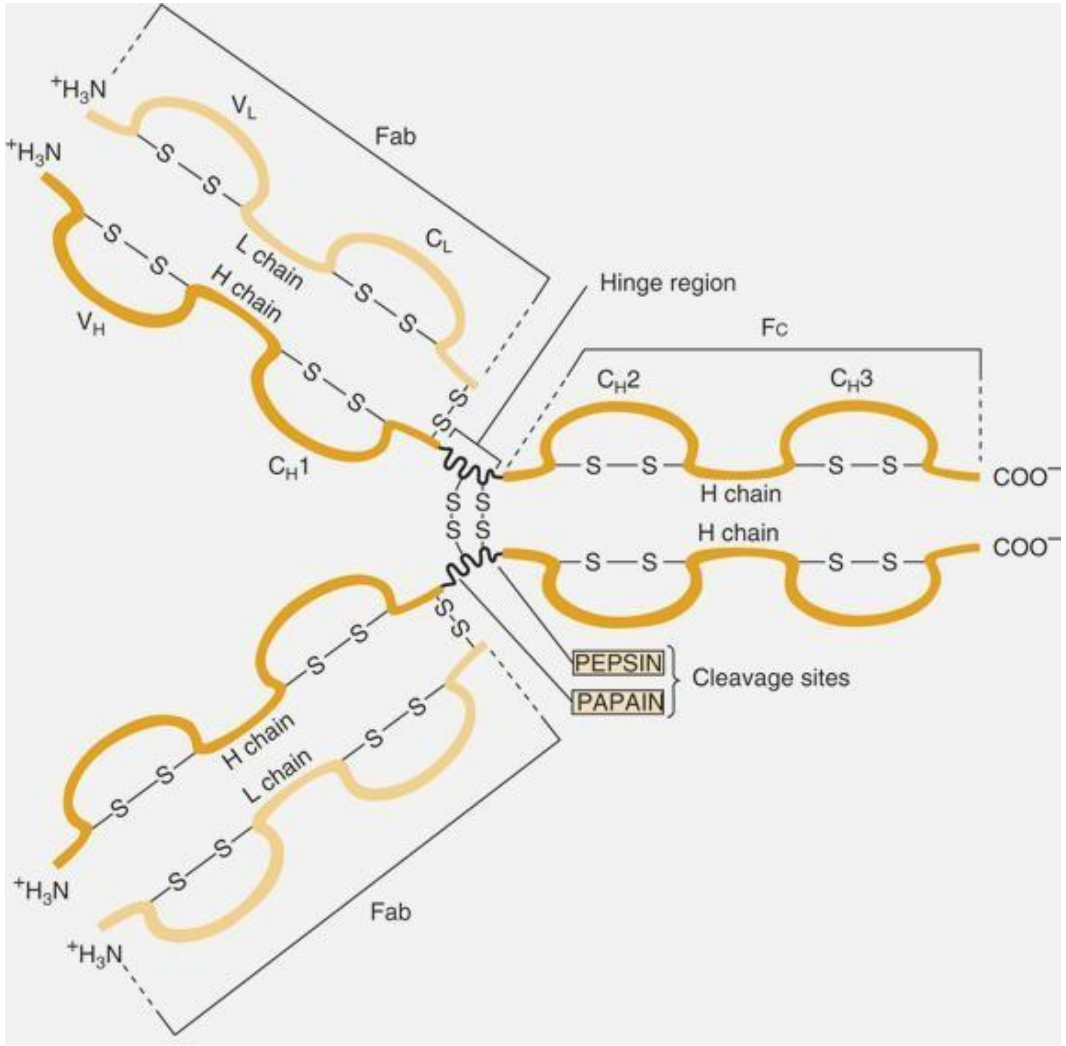


IMMUNOGLOBULINS - STRUCTURE

- Each enzyme (**Pepsin and Papain**) cuts at a 2 different site in the hinge region :

- **Pepsin** cleaves the antibody in the hinge region **toward the Fc fragment**, producing **two fragments**: a connected pair of Fab regions (linked by disulfide bonds) and the Fc fragment (which cristalizes on each other).

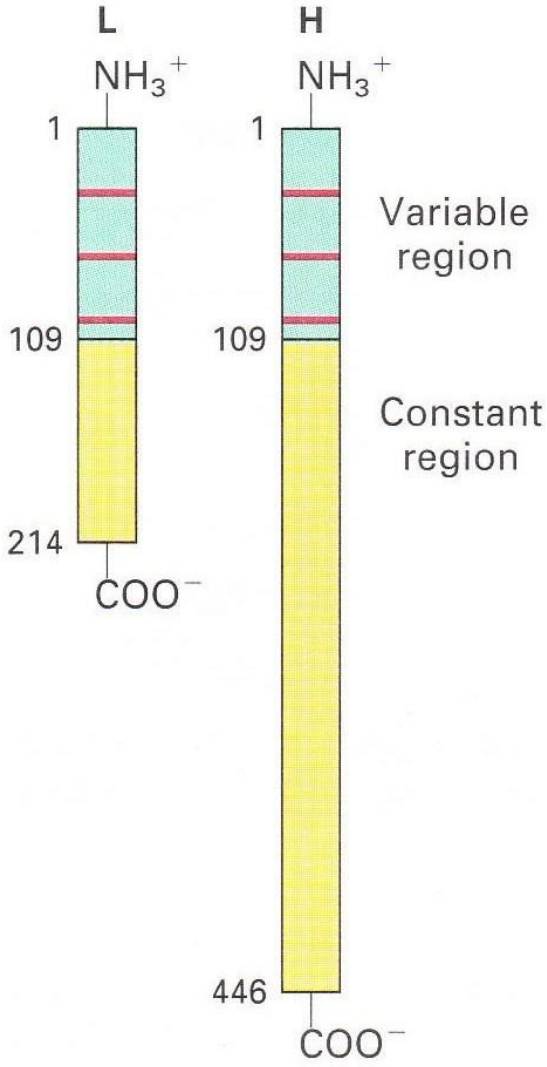
- **Papain** cleaves the hinge region **toward the Fab fragment**, producing **three fragments**: two identical Fab fragments and one Fc fragment.



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

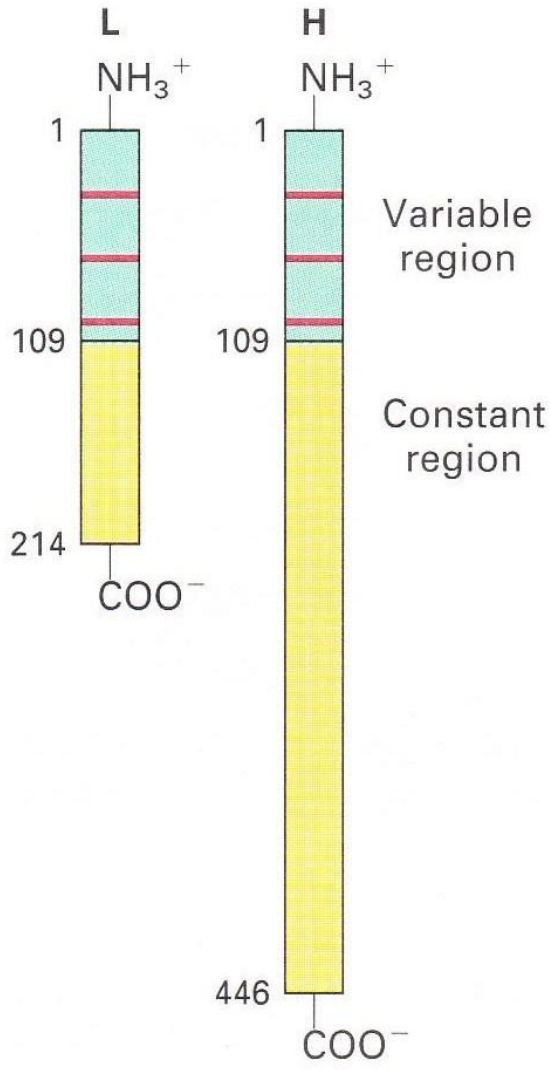
- 3 constant stretches (7-12 amino acids) hyper-variable (In some immunoglobulins it might be four)



IMMUNOGLOBULINS - STRUCTURE

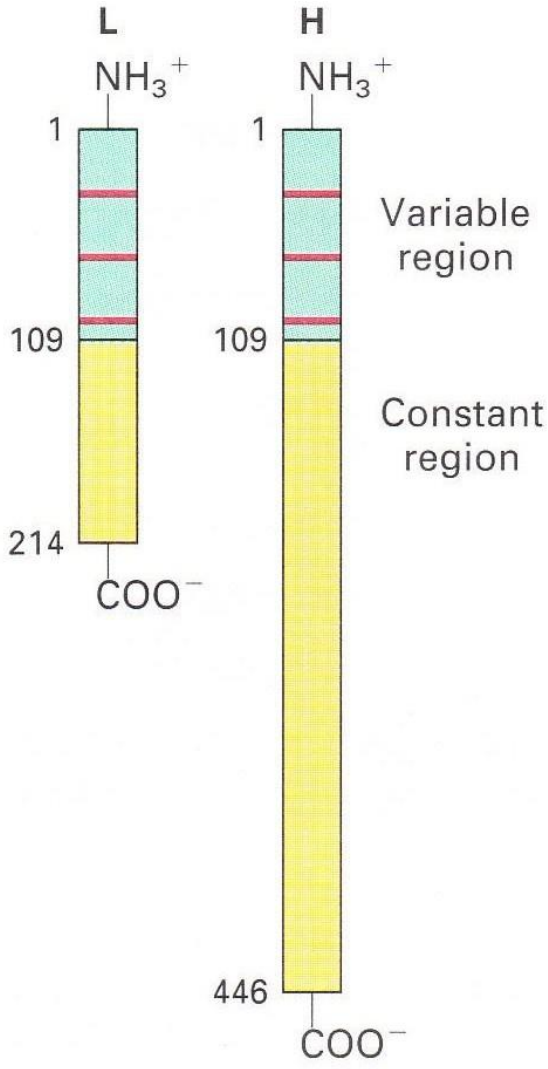
- If we look at the variable region in both the light and heavy chains, we can see pink stretches, **four in the heavy chain** and **three in the light chain.**
- These stretches are **sequences of amino acids** within the protein.

- The variable region is the part that changes when the antibody encounters new antigens. **However**, not all of it changes, the parts that change **the most** are <u>three stretches in the light chain and four in the heavy chain</u>, called **hypervariable regions**.
- The rest of the variable region shows **much less variation** than hypervariable region.



IMMUNOGLOBULINS - STRUCTURE

- The **hypervariable** regions are keep changing to recognize new antigens
- Each hypervariable stretch is **about 7–12 amino acids** long, and these regions keep changing <u>to allow the antibody to recognize new antigens.</u>



IMMUNOGLOBULIN - INTERACTIONS

- With antigen (infinite amount of binding to antigens): we can recognize any antigen which come over our body.
  - Non covalent interactions :Electrostatic, Hydrogen, Van der Waal's, Hydrophobic
  - The (Fab)2 fragment CAN:
    - Detect, bind & precipitate the antigen
    - Block the active sites of toxins (If the foreign material are considered a toxin).
    - Block interactions between host and pathogen
      So the pathogen is gonna go and do whatever it likes inside the body when it binds to antibody it blocks the interaction with the host cell.
- 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.

IMMUNOGLOBULIN - INTERACTIONS

- **The Fab fragment of an immunoglobulin binds to the antigen**, while **other molecules bind through the Fc fragment,** binding to the antigen induces conformational changes in the Fab region, which in **turn cause structural changes in the Fc region.**

- **The Fc region** is responsible for binding to specific components within our body, this is **not unlimited (infinite)**; antibodies bind only to certain targets, through the Fc the antibodie can activate :
  - Inflammatory functions associated with cells.
  - Inflammatory functions of complement proteins.
  - Intracellular cell signaling molecules.
- Ultimately, the Fc fragment binds to immune cells such as B lymphocytes or macrophages, this binding triggers molecular changes in their signaling systems, allowing the immune cells to recognize what is bound to the antibody and then activate the immune system inside our bodies.

DOMAIN STRUCTURAL VARIATION OF IMMUNOGLOBULINS – CONSTANT REGION

Five different types of immunoglobulin
- IgA, IgD, IgE, IgG, IgM

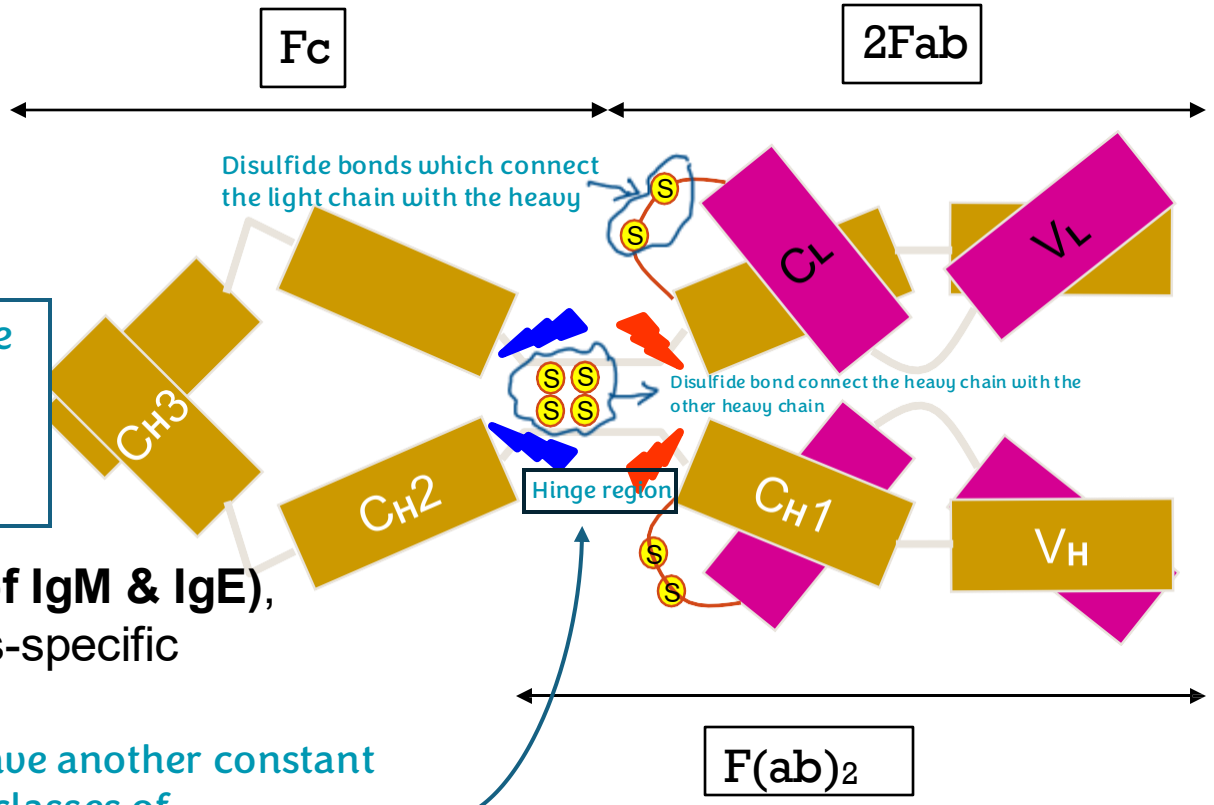
Five different genes that constitute the heavy chains which are

Heavy chain **C** domains

→ **α, δ, ε, γ, or μ**

We have variable domain in the heavy chain and constant 1,2,3
We need a gene to make these protein

Domains are folded, compact, protease resistant structures



Light chain **C** domains

Either of two types κ or λ

Which is also encoded genetically

Never a mixture

(we can't have them in the same immunoglobulin)

The L chains and H chains are synthesized seperately

Since they are products of different genes then they are associated together to make the whole protein

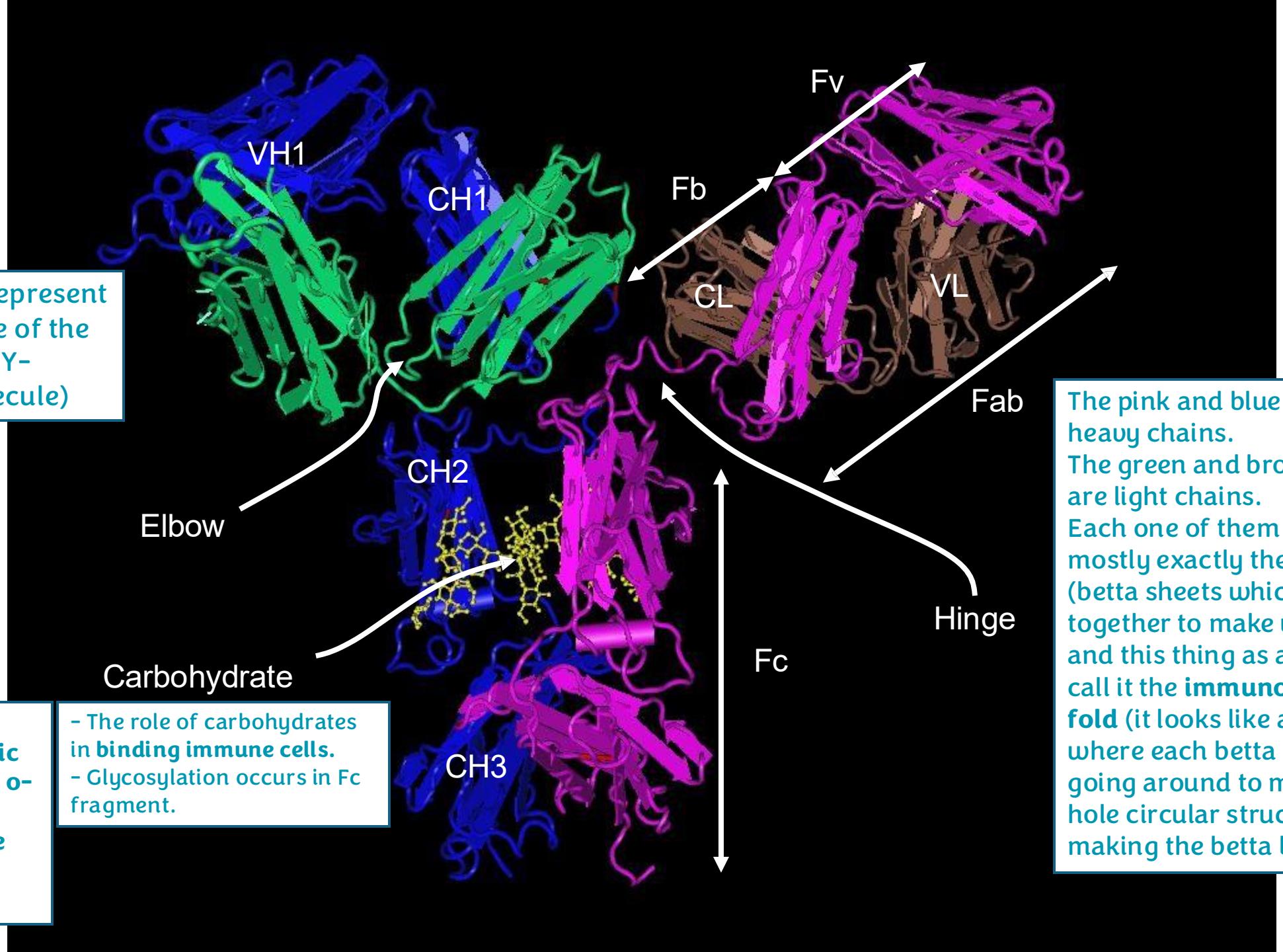
Mainly, **C_H2 & C_H3 (& C_H4 of IgM & IgE)**, are responsible for the class-specific functions of different Igs

In some immunoglobulin we have another constant domain in hinge region in two classes of immunoglobulins, IgM and IgE, the heavy chain contains an extra constant domain.
Instead of having three constant domains (CH1, CH2, CH3) like most antibodies, they have four: CH1, CH2, CH3, and CH4.

Pepsin cleavage sites - 1 x $(Fab)_2$ & 1 x Fc

Papain cleavage sites - 2 x $(Fab)_1$ & 1 x Fc

This photo represent the structure of the anti body (a Y-shaped molecule)



The pink and blue ones are heavy chains.
The green and brown ones are light chains.
Each one of them looks mostly exactly the same (betta sheets which are joined together to make up a circle and this thing as a domain we call it the **immunoglobulin fold** (it looks like a barrel where each betta sheet is going around to make up a hole circular structure making the betta barrel)

- The role of carbohydrates in **binding immune cells.**
- Glycosylation occurs in Fc fragment.

The bond can be both **n-glycosydic for asparagin or o-glycosydic for threonine,serine and sometimes tyrosine**

THE IMMUNOGLOBULIN FOLD

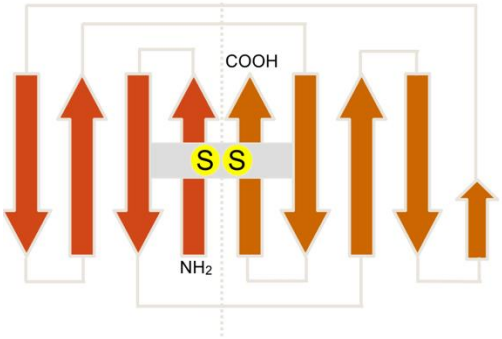
The characteristic structural motif of all Ig domains

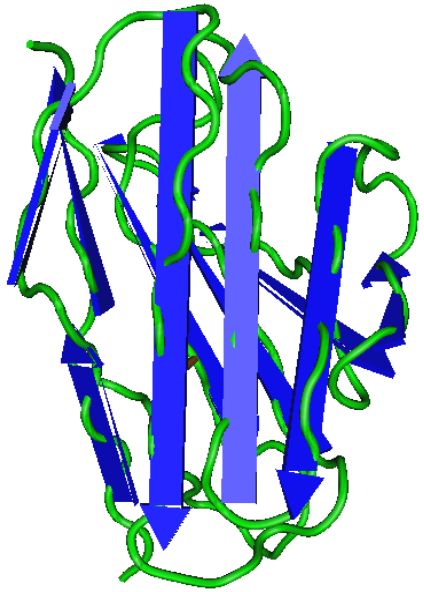
A barrel

Barrel under construction

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

If you come to this barrel and cut it from one side here and you open it you will see how it being formed it will look like this:

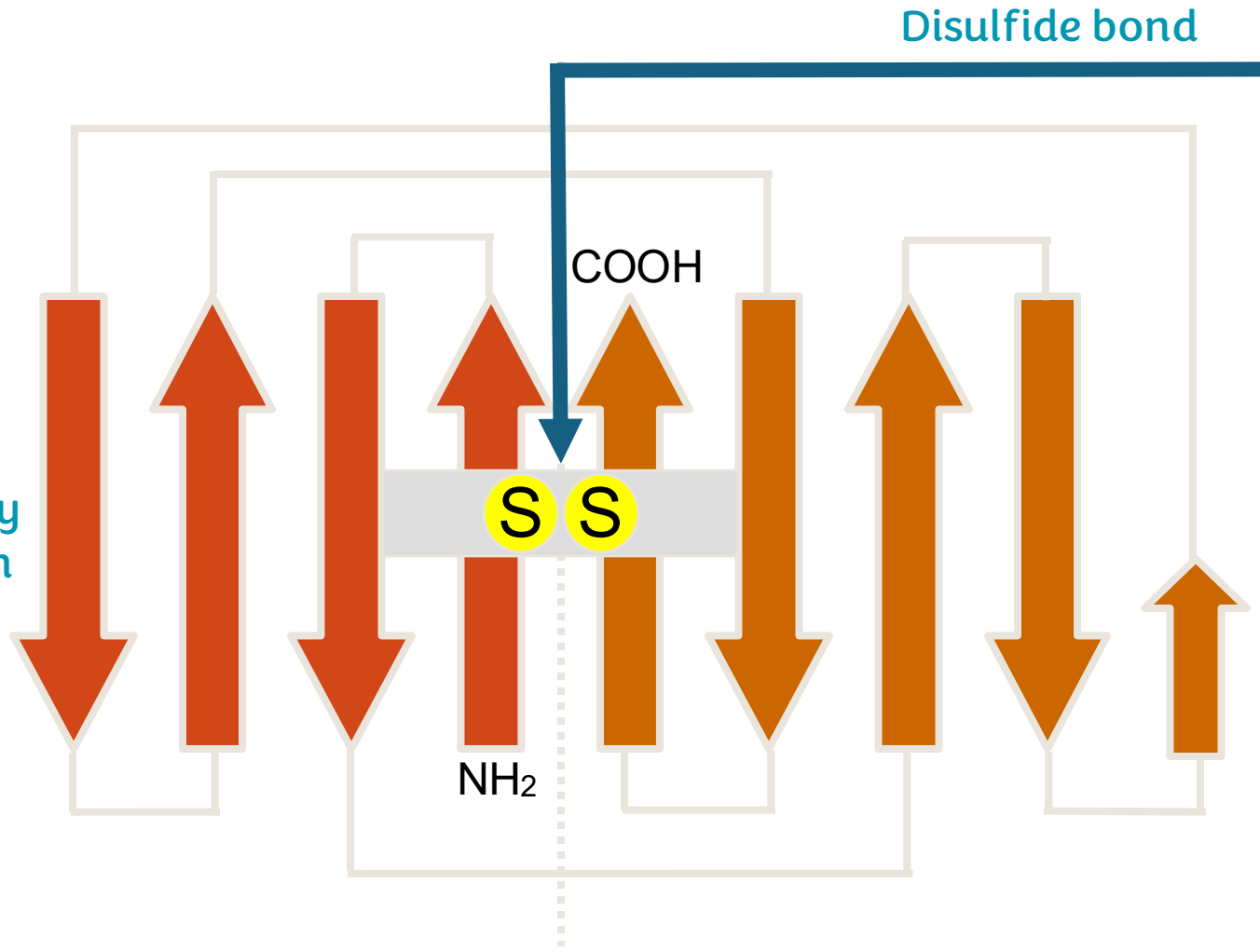


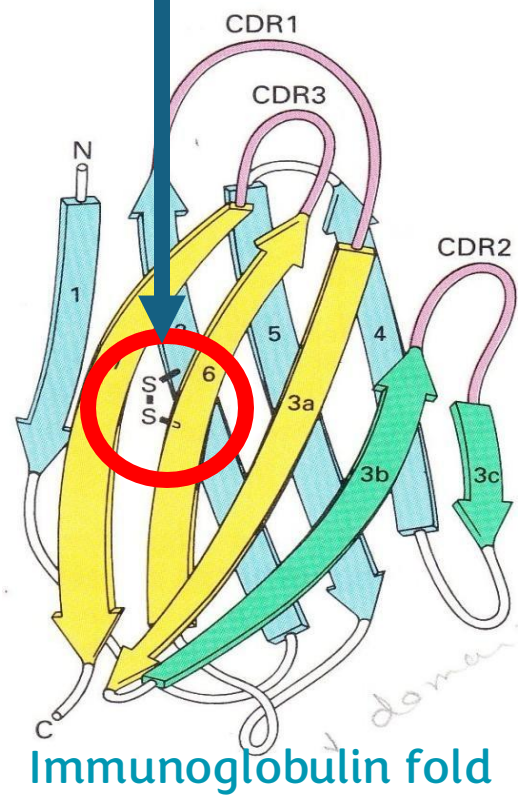


Single V_L domain

THE IMMUNOGLOBULIN FOLD

Each beta barrel ,each immunoglobulin fold is held also from its inside by disulfide bond to keep it in shape





Immunoglobulin fold

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

GENES INVOLVED & DIVERSITY

The "one gene, one protein" concept is not valid

- Immune system can generate > 10^8 antibodies
- Human genome contains ~ 25,000 genes !

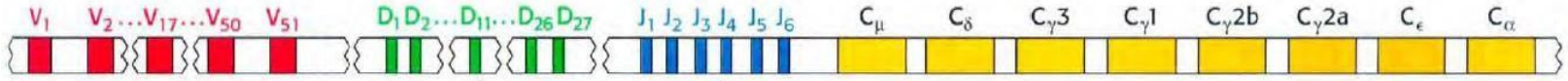
Constant regions are all on one place, so if I keep this region, whatever I did rearrangement in it, one time, I'll couple it with C_H, the other time I'll couple it with Cd so I'll produce C delta, so I'll produce IgD that can recognize an antigen while it first was recognized by an IgM

- Light chain is a product of at least 3 genes:
  - Variable (V_L) gene
  - Joining region (J) gene
  - Constant region (C_L) gene

Light Chain

κ or λ

- Heavy chain is a product of at least 4 genes :
  - Variable region (V_H) gene
  - Diversity region (D) gene
  - Joining region (J) gene
  - Constant region (C_H) gene



Heavy Chain

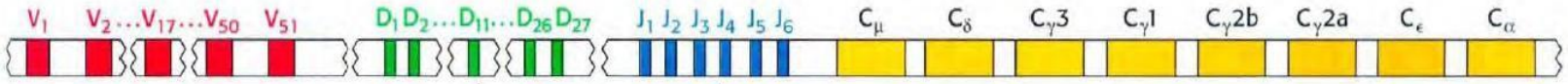
GENES INVOLVED & DIVERSITY

- The concept is that we can generate more than a hundred million antibodies, but we have no more than 25,000 genes. Normally, for every gene there is a protein, so **this concept is not valid at the level of antibodies.**
- This is what was solved in the recombination issue – the genetic variation that exists in light chains and heavy chains.

- Light chains are composed of:
  - Variable region
  - Joining region
  - Constant region

Light Chain

- Heavy chains are composed of:
  - Variable region
  - Diversity region
  - Joining region
  - Constant region



Heavy Chain

GENES INVOLVED & DIVERSITY

- For the light chain, the variable region is composed of 40 variable segments, 5 joining segments, and 1 constant segment (κ or λ).

- For the heavy chain, the variable region is composed of 51 variable segments, 27 diversity segments, 6 joining segments, and the constant regions which determine (Variable region determines) the antibody class:

  - **μ represents IgM.**
  - **δ represents IgD.**
  - **γ (multiple subtypes) represents IgG(All these subtypes of γ are constant regions of the γ chain).**
  - **ε represents IgE.**
  - **α represents IgA.**

GENES INVOLVED & DIVERSITY

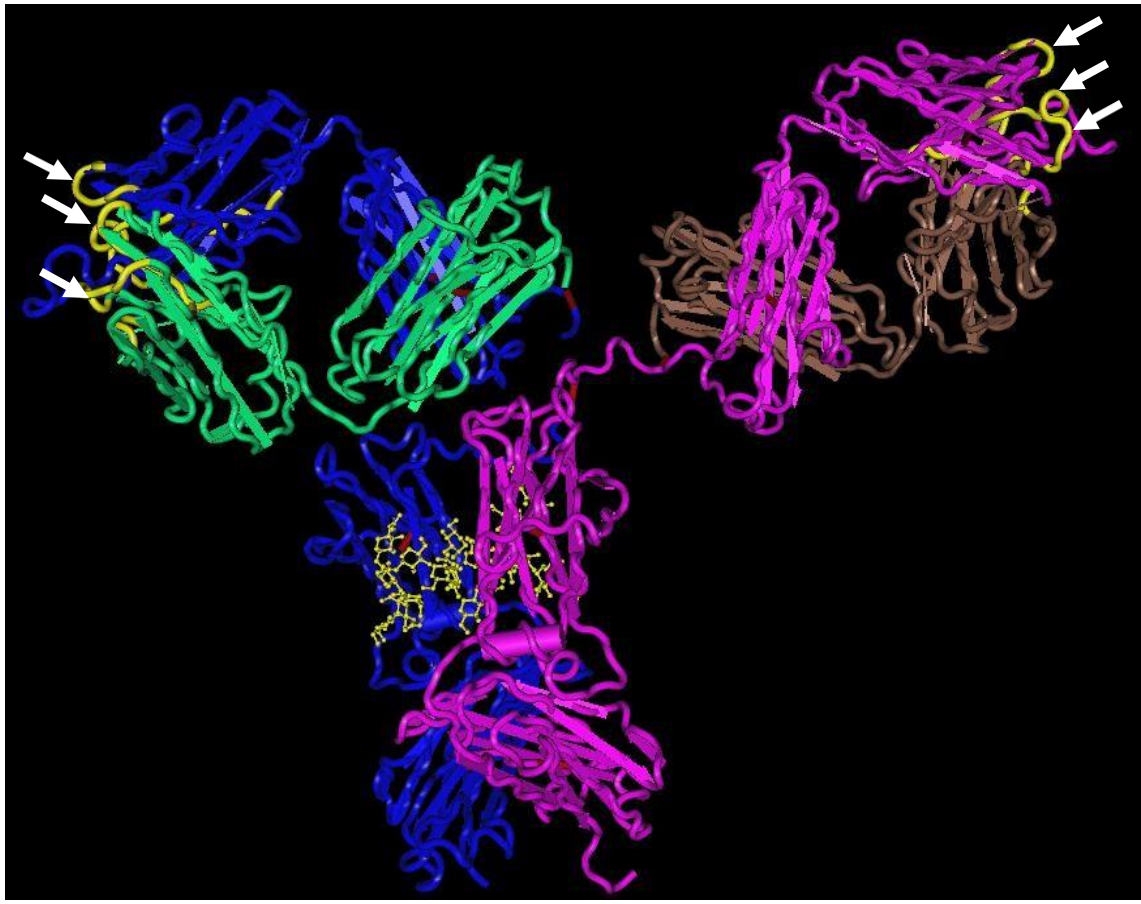
- **How can the body produce so many antibodies for any antigen it might face?**

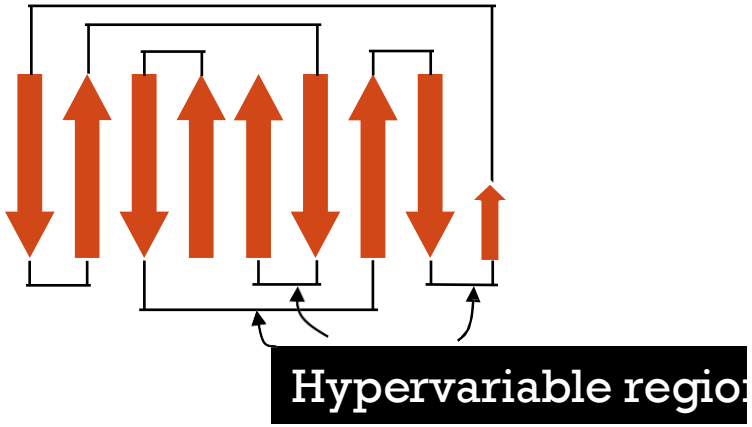
  - What actually happens is that, through **alternative splicing and alternative expression**, the subtypes of these subgroups inside each region are arranged genetically according to what needs to be expressed.

  - **Alternative splicing** of the mRNA that is produced allows for the production of new proteins. With the number of **subregions inside each gene** and recombination between the heavy chain and the light chain, you can generate much more than a hundred million antibodies to respond to any antigen that enters the body.

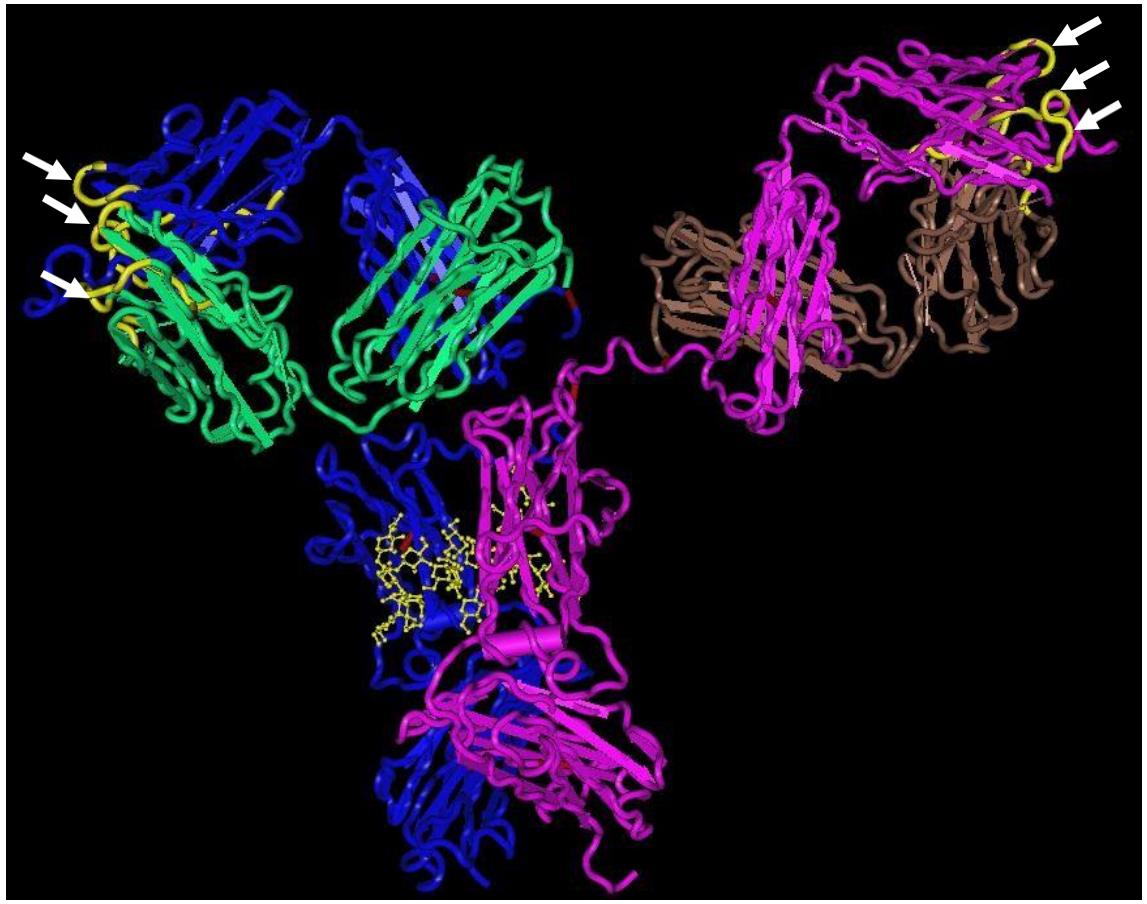
VARIABLE REGIONS

- 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





VARIABLE REGIONS



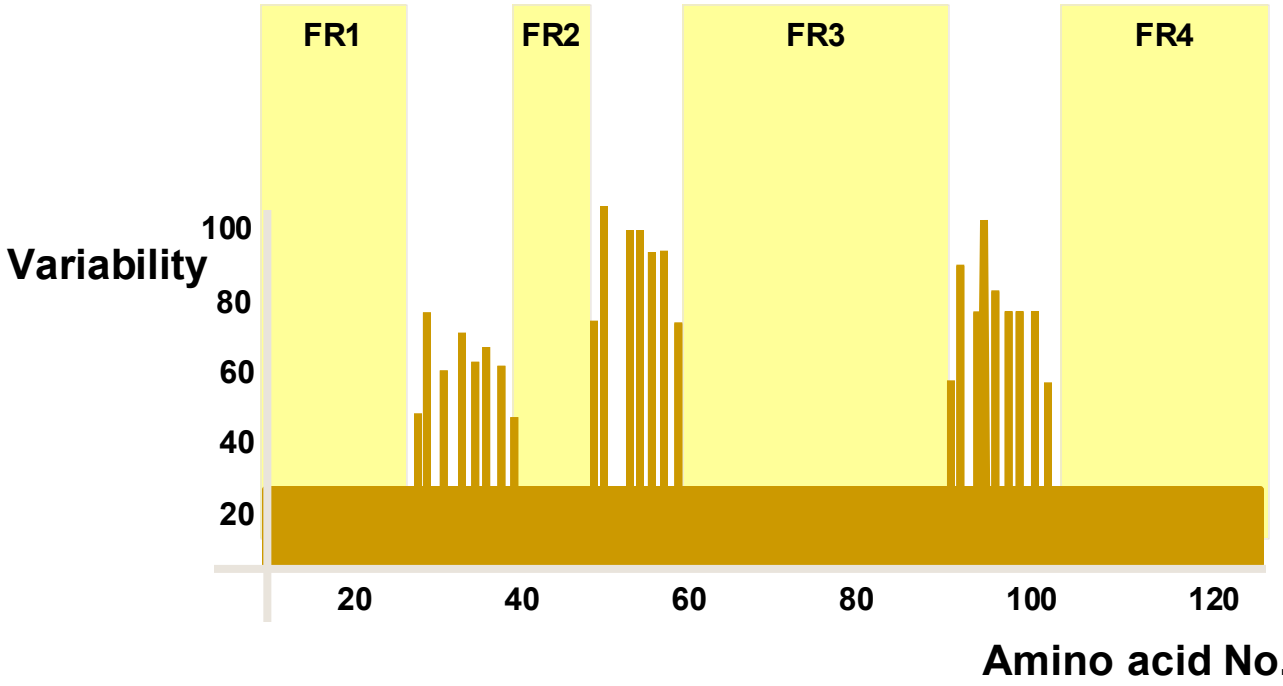
Yellow: hypervariable region.
Green: light chains.

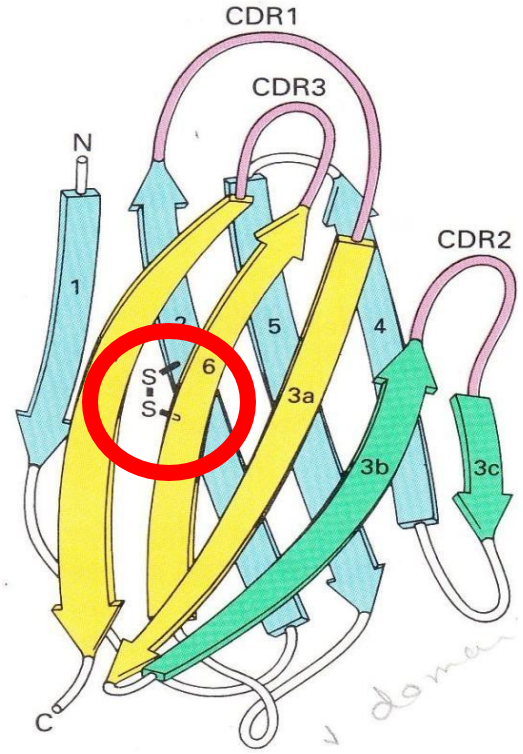
Pink + yellow (on the right side)/ blue: heavy region.

The tips of the Y-shaped antibody molecule are responsible for binding to antigens.
These specific binding sites are located within regions known as **hypervariable regions (HVRs)**.
Each binding site is composed of **three stretches** of amino acids, and each stretch **is typically 7 to 12 amino acids** in length.
These hypervariable regions are found on both the heavy and light chains of the antibody and are the parts that directly interact with the antigen.
Because they are the only parts of the molecule that need to change to bind to different antigens, their amino acid sequences are highly variable, **allowing for a unique binding site to be created for each specific antigen.**

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

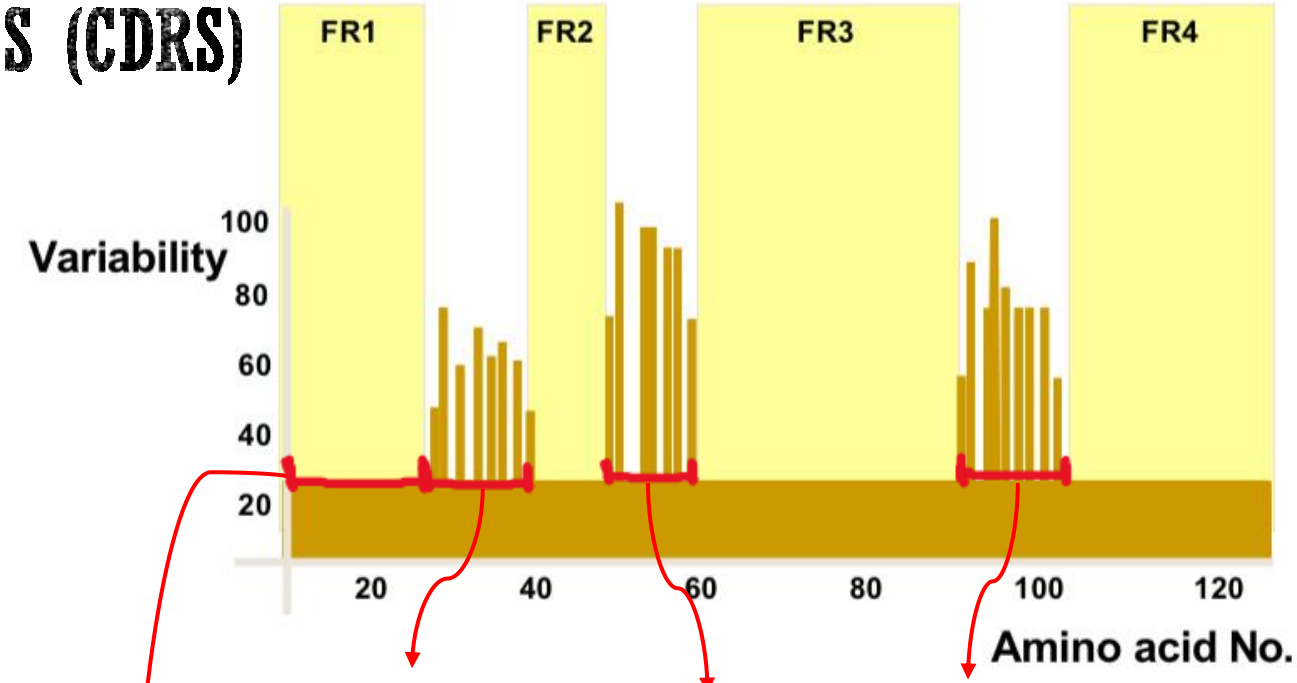




HYPERVARIABLE REGIONS

COMPLEMENTARITY-DETERMINING REGIONS (CDRS)

We have **three stretches** of amino acids. When we examine their variability across different immunoglobulins, we find that these **three stretches** are **highly variable** (marked with red on the chart), whereas the variability of amino acids in **other regions** of the immunoglobulins is **relatively low**. The threshold we use to define variability is **30%**. Therefore, if the variability is **less than 30%**, it is **considered not highly variable**; but if it is **greater than 30%, it is considered highly variable.**

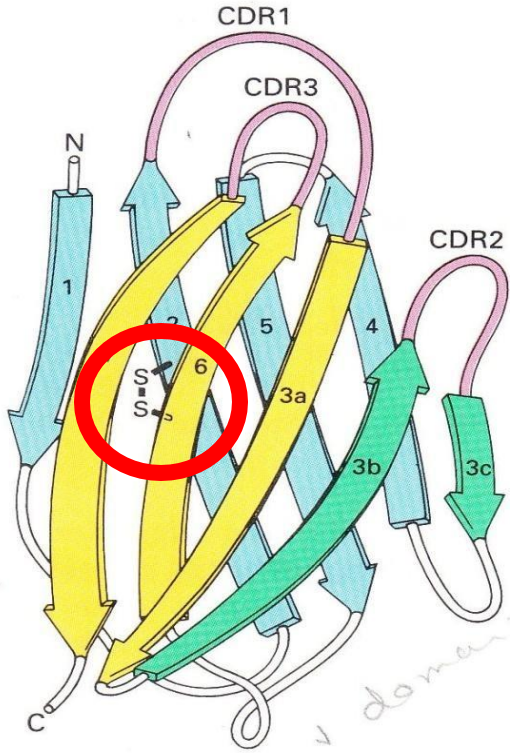


Framework regions (as the name implies framework it is the thing that **preserves the shape of the domain**)

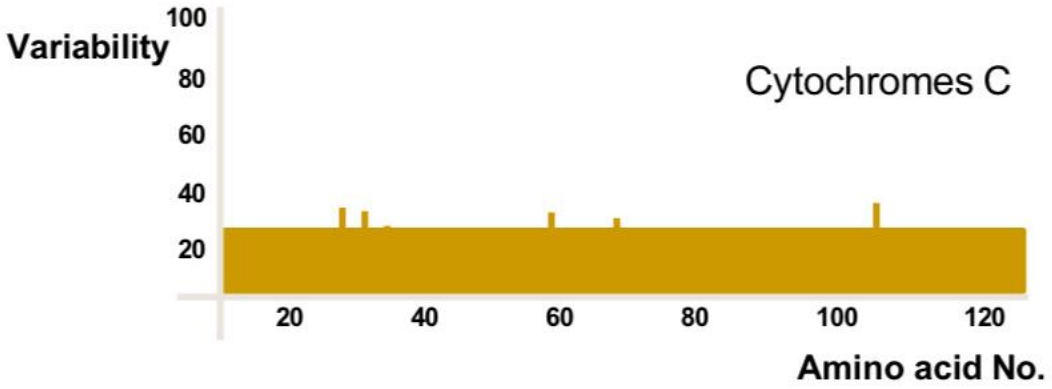
HYPERVARIABLE REGIONS
COMPLEMENTARITY-DETERMINING REGIONS (CDRS)

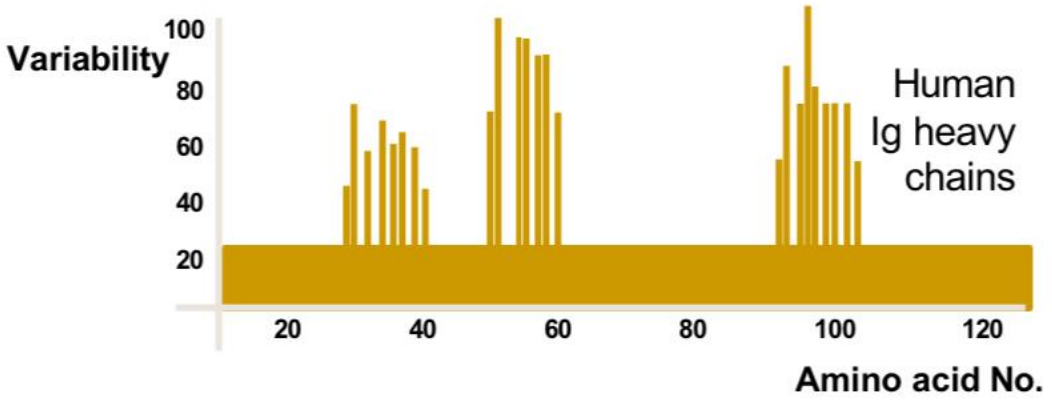
- About 7-12 amino acids in each one that contribute to the antigen-binding site
- CDRs are located on small loops of the variable domains
- Framework regions: the surrounding polypeptide regions among the hypervariable regions

We call the **highly variable regions: complementarity-determining regions (CDRs)**, they are the ones that complement, they bind complementary to the antigen that comes to the body, this is why they call them CDR1, CDR2, CDR3, etc...
CDRs' structure: they adopt a loop structure.



VARIABILITY IN OTHER PROTEINS



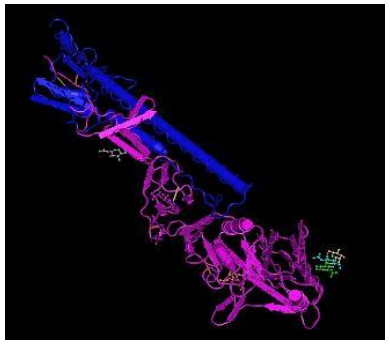


We have a really variable group of proteins that we call Cytochromes C, a lot of proteins that include heme C in their structures, collectively we call them Cytochromes C

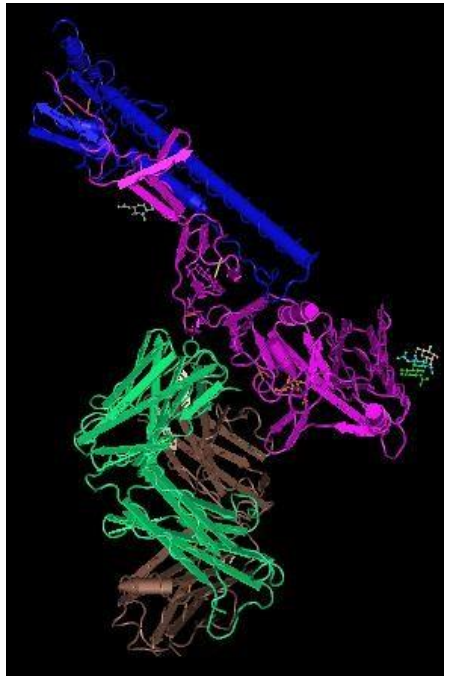
Comparison between Cytochromes C & Immunoglobulins structures:
Cytochromes C aren't highly variable in comparison to immunoglobulins

CDRS INTERACTION WITH ANTIGENS

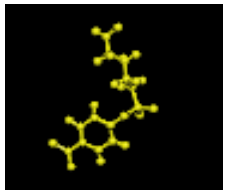
- Antigen-antibody interactions is based on mutual complementarity between surfaces
- Large antigens: interact with all of the CDRs of an antibody
- Small antigens: interact with only one or a few CDRs that form a pocket or groove in the antibody molecule



Protein:
Influenza
haemagglutinin

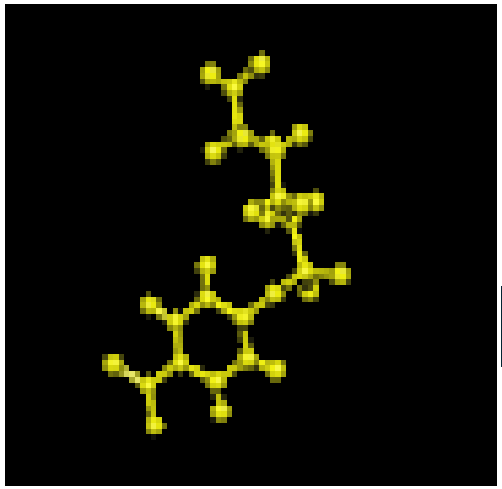


Hapten: 5-(para-nitrophenyl phosphonate)-pentanoic acid



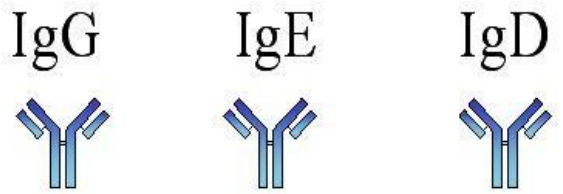
CDRS INTERACTION WITH ANTIGENS

The complementarity-determining regions (CDRs) interact with their specific antigens through mutual surface complementarity. If the antigen is **sufficiently large**, it can induce conformational changes in the CDR domains. These structural changes are then transmitted to the Fc fragment of the antibody, which in turn conveys the signal to the cell through the receptor in the cell membrane that binds the antibody.

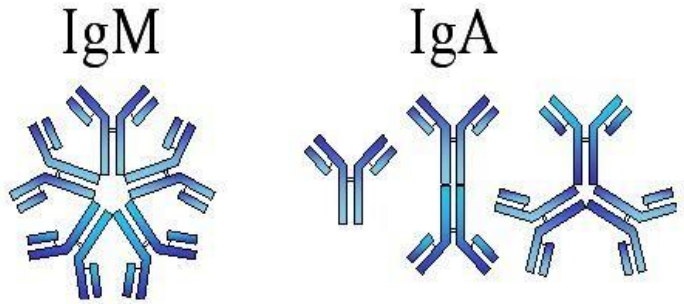


If the structure is small enough -this is what we defined at the beginning as haptens- it won't induce that change and accordingly it won't result in any immune response.

IMMUNOGLOBULIN CLASSES - OVERVIEW



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

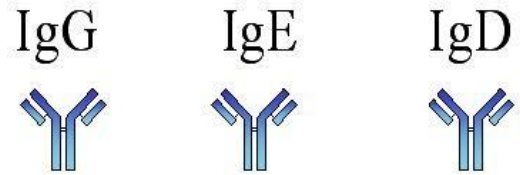


Gene that produces it

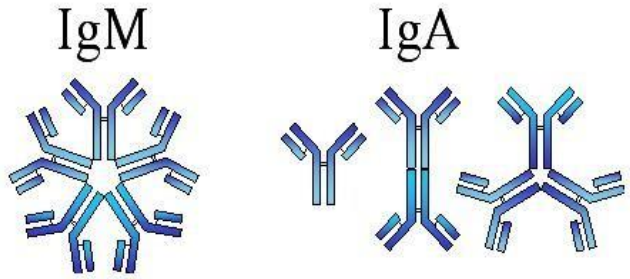
IgM: the most common and prevalent type to find as a **pentamer**
IgA: most common to find it as a **dimer**

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**

IMMUNOGLOBULIN CLASSES - OVERVIEW



The **most prevalent one is IgG** followed by **IgM** inside the serum (the rest should be with **lower amounts** but what can make it higher is the **presence** of **IgA inside secretions**).



We call the ability to bind certain proteins in the body: **the complement system proteins** which are parts of the immune system.

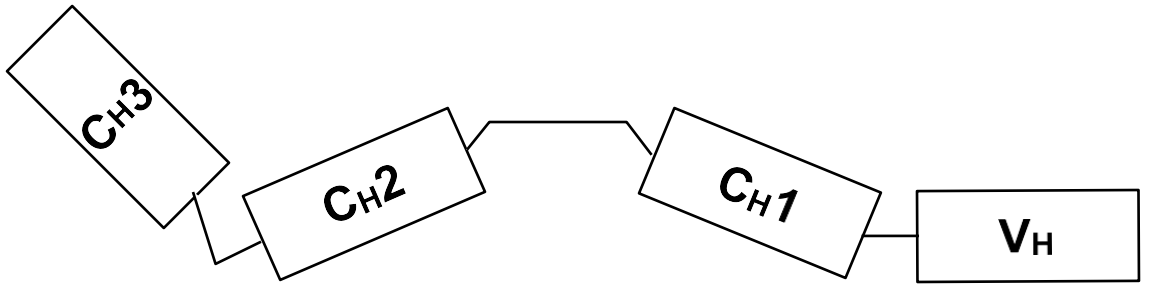
IgM & IgG are the ones that **can bind complement system proteins and induce an immune response through fixing them**, the other three types can't.

IgG is the one with the **highest half life** followed by **IgM.**

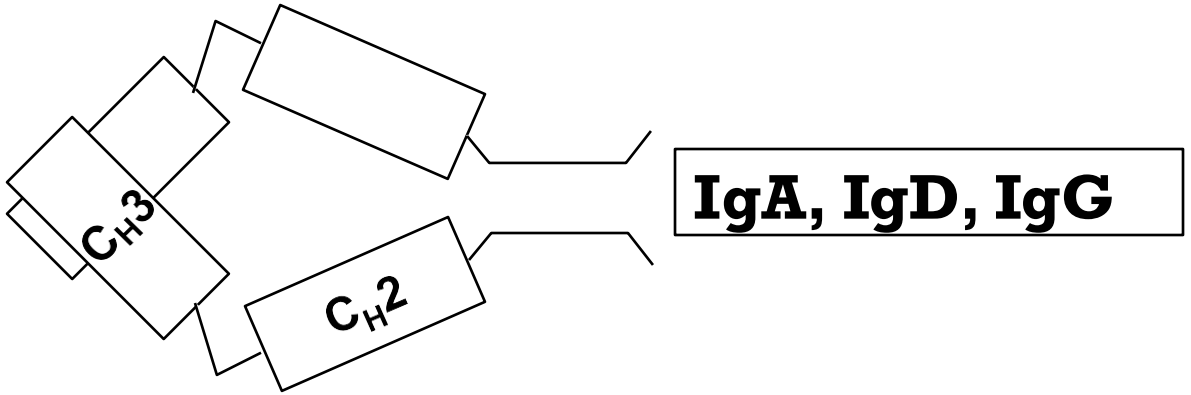
IgG is the only one that can cross the placenta and it's the only one which can **provide immunity** to the **fetus** inside the uterus through his mother's IgG.

DOMAINS IN DIFFERENT CLASSES (H-CHAIN)

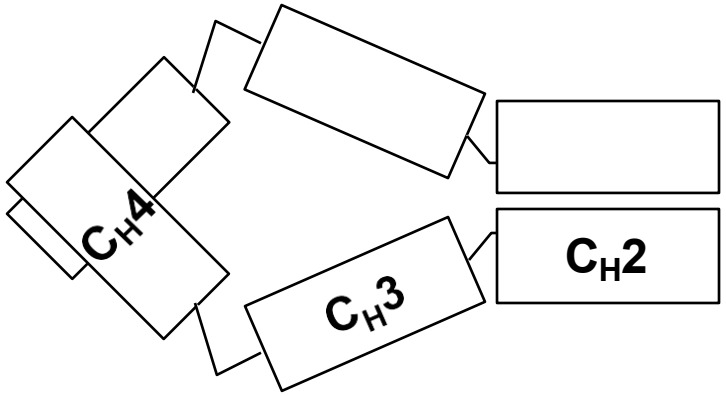
Domains in the heavy chains, variable-> V_H
constant-> C_H1, C_H2, C_H3



What's different about IgM & IgE that they have **fourth domain** in the constant region which is present **inside the hinge region** more or less.
Hinge regions have **flexibility**, however, it's **more limited** compared to these three immunoglobulins.



IgA, IgD, IgG



IgE, IgM
The hinge region is replaced by an additional Ig domain

اللهم full mark
من حيث لا
نحتسب

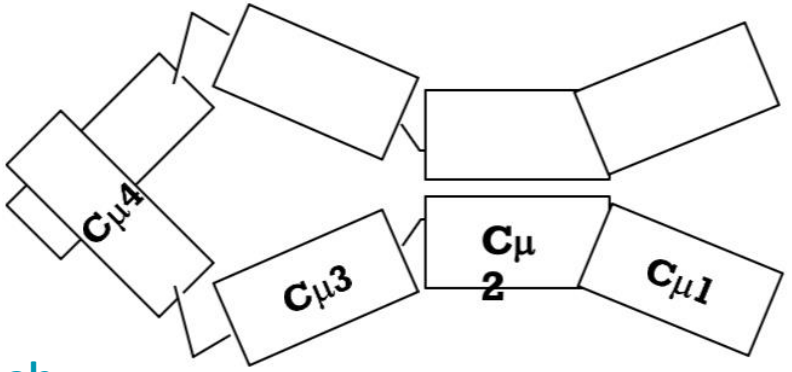
IgM CLASS

- 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 multemerization
- Cμ4 mediates multimerization (Cμ3 may also be involved)

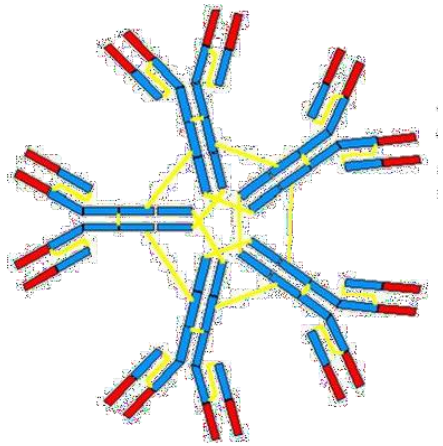
Any antibody should be a monomer when it binds the B cells because the binding occurs through the Fc region (Fc fragment).

It's the first immunoglobulin that faces antigens.

If you give a different blood group to a patient, what is responsible about the immune response is the IgM.



The reason which makes it really with very high affinity to antigens is their presence as multimeric proteins.



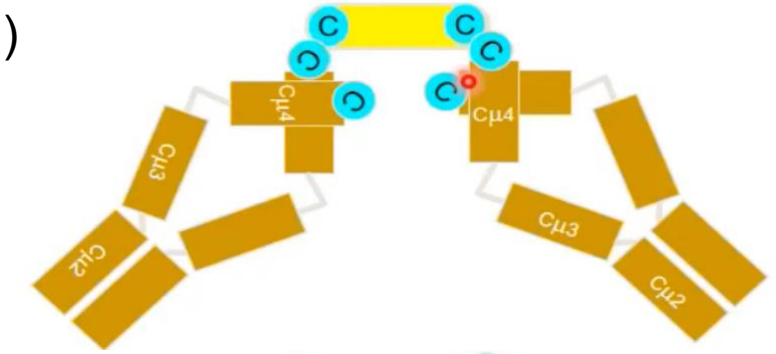
THE PROCESS OF IgM MULTIMERISATION

Initially, IgM contains an additional constant region in its hinge region, along with C_H3 and C_H4 domains. In addition, it possesses two cysteine residues (and in general, immunoglobulins contain many cysteines, which explains their numerous disulfide bridges).

1) another identical IgM molecule associates with the first one, and a joining (J) chain links them together.

2) The J chain brings the molecules into close proximity, which allows the formation of disulfide bridges between the terminal constant domains of two different immunoglobulins, **and this process continues to connect additional molecules (as shown in the next slide).**

1)



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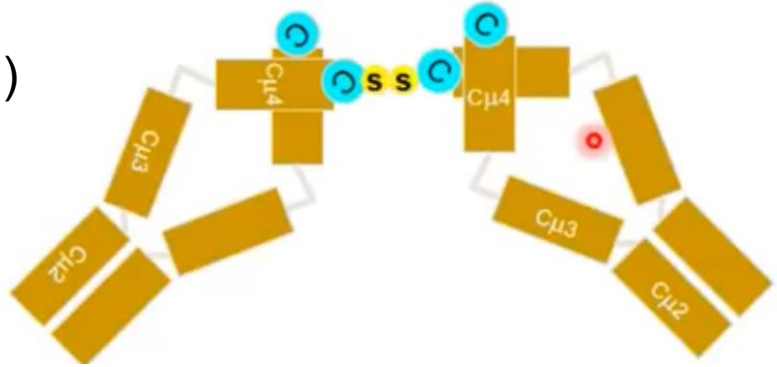
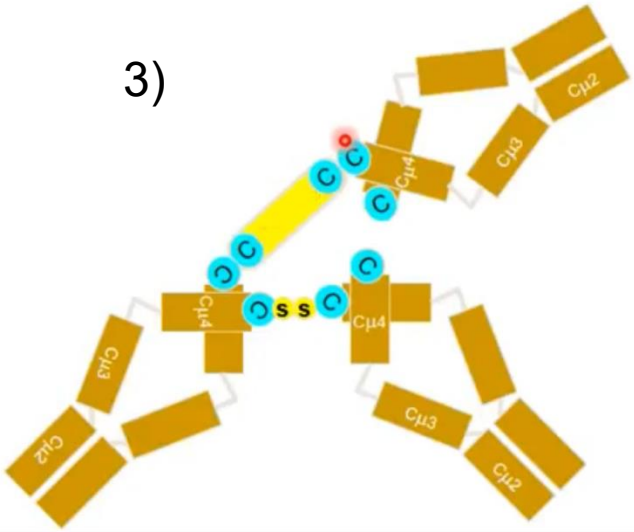


THE PROCESS OF IgM MULTIMERISATION

3)



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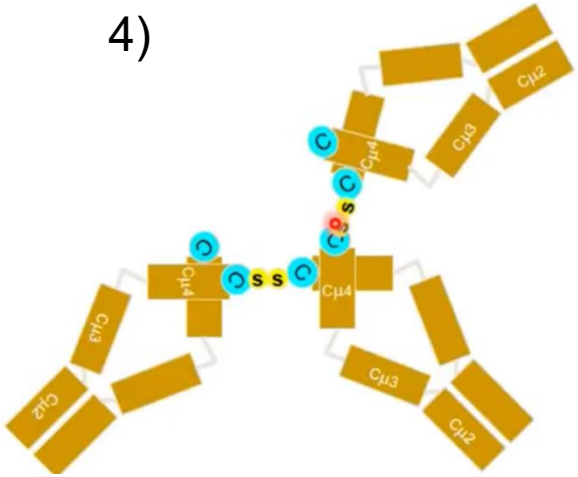

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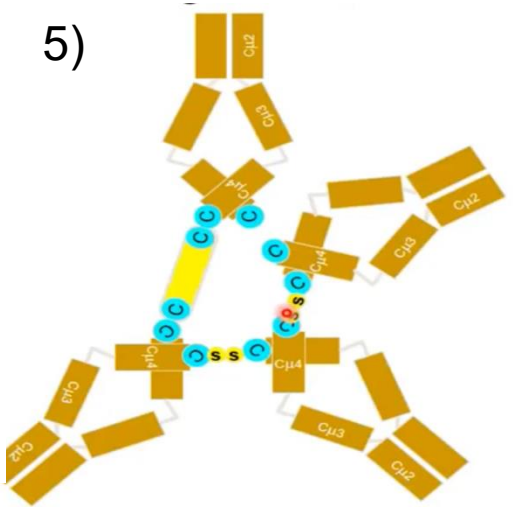

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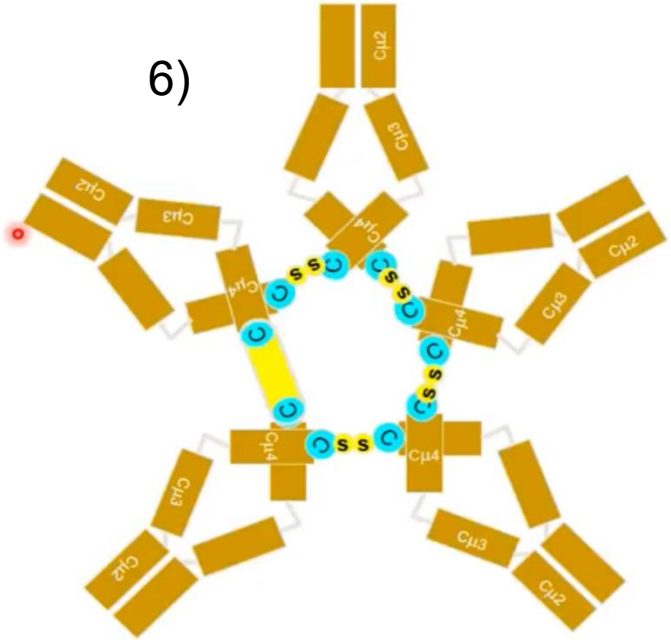

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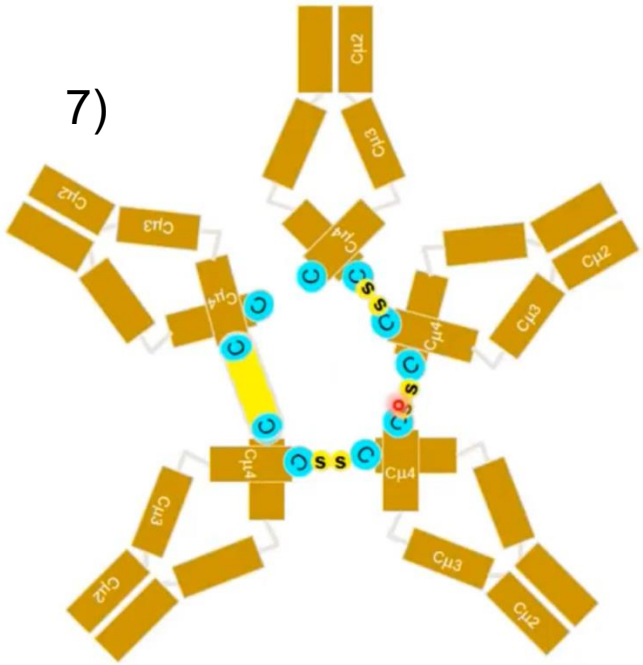
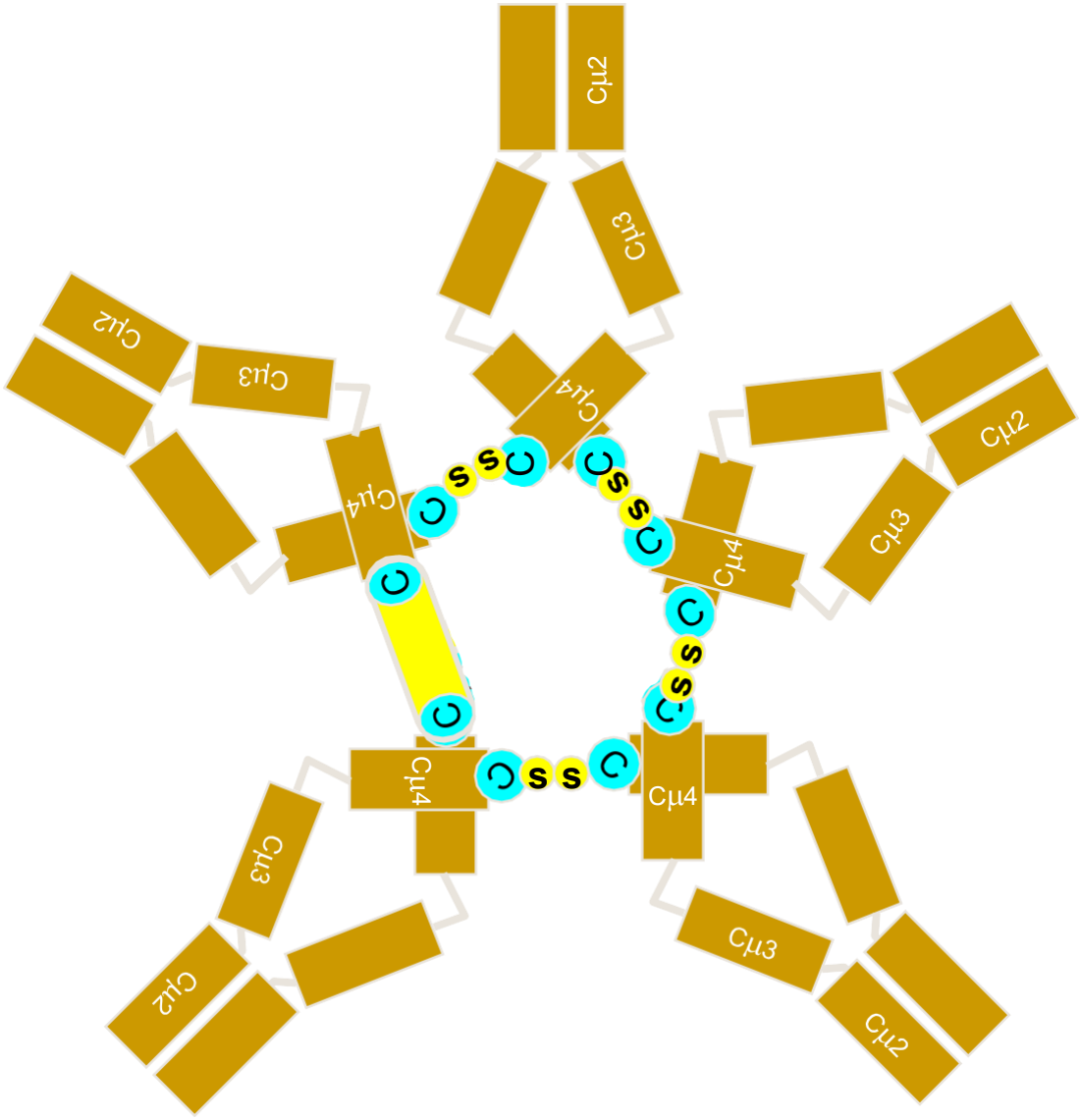
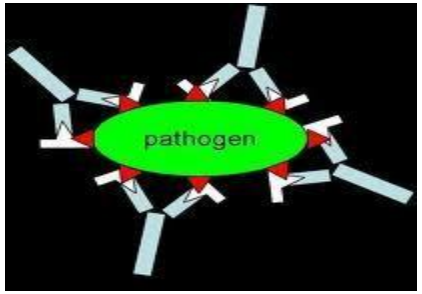


Since each IgM monomer can bind two antigens, a pentameric IgM structure is able to bind up to ten antigens.

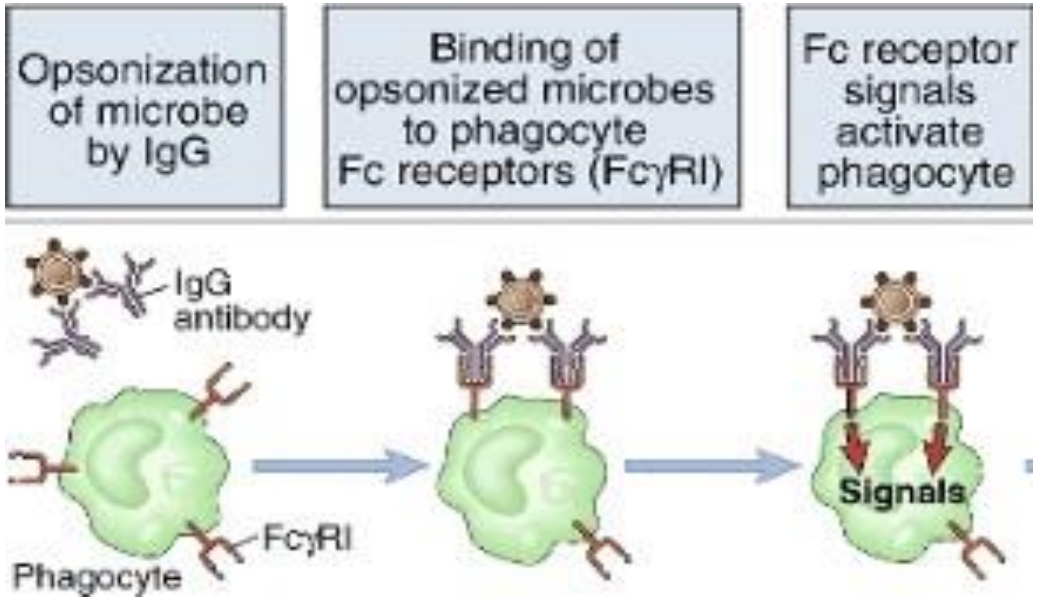
THE PROCESS OF IgM MULTIMERISATION

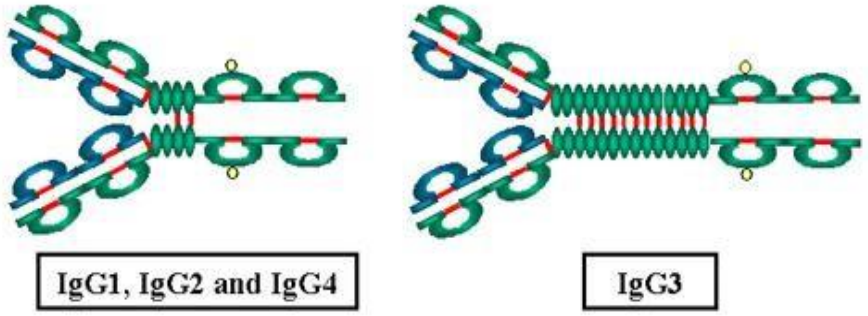


IgG CLASS



- Location: Blood, lymph, intestine
  - Produced in response to a wide variety of antigens, (ex. bacteria, viruses)
  - Known Functions
    - ✓ The predominant antibody produced in the 2^0 immune response
    - ✓ Provides the major line of defense for the fetus & during first few weeks of newborns
      Because other immunoglobulins can't cross the placenta
    - ✓ Coats organisms to enhance phagocytosis by neutrophils and macrophages (opsonization)





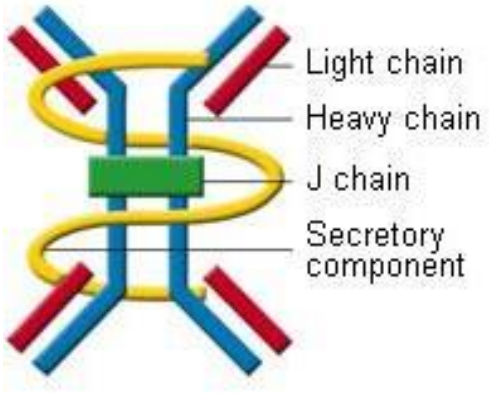
IgG CLASS

- Location: Blood, lymph, intestine
  - Produced in response to a wide variety of antigens, (ex. bacteria, viruses)
  - Known Functions
    - ✓ The predominant antibody produced in the 2^0 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)

IgG is the antibody responsible for the secondary immune response, and it also mediates agglutination, although it is a weaker agglutinator compared to IgM. When a **pathogen is present**, IgG antibodies bind to and surround the pathogen from all sides (opsonization). This process **facilitates the presentation of the pathogen to immune system cells**, including neutrophils and macrophages.

IgA CLASS

(The only one which is present in **secretions**) Any secretion from your body includes IgA, it provides the first line of defense before the pathogen gets into the body.

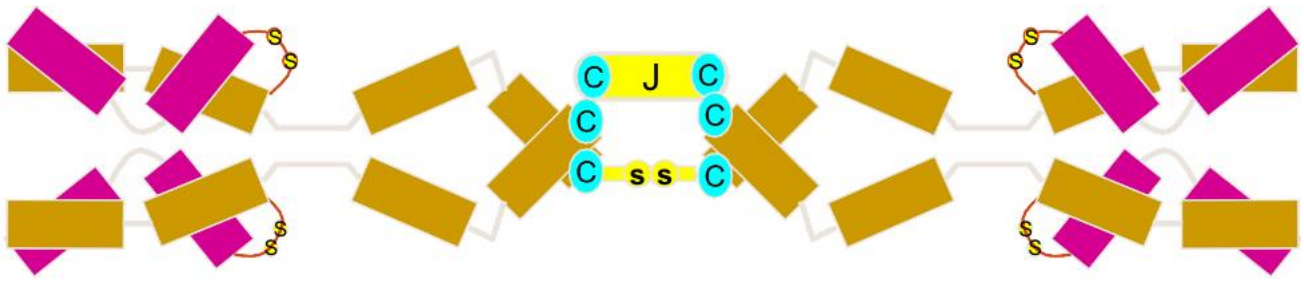


- Structure & location:
  - ✓ Plasma → monomer, dimer, or trimer
  - ✓ Secretions (tears, saliva, intestines, milk, bronchial secretion, urine)
    → dimer attached to "secretory component"

In secretions it is always present as a dimer.

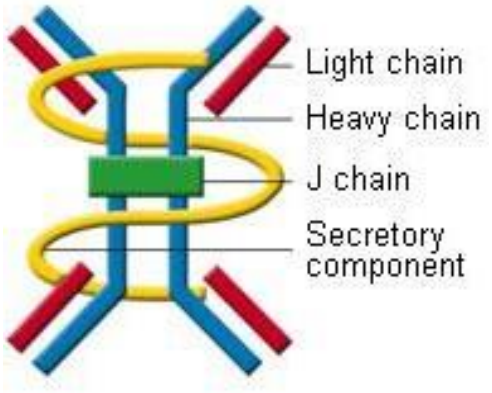
- Known Functions:
  - Localized protection (respiratory, urinary tract and bowel infections)
  - Provides immunity to infant's digestive tract & body (translocated)
  - The process of dimerization

Localized also in mammary glands



In the figure of the IgA dimer, there is one joining (J) chain. What about the number of joining chains in the case of an IgM pentamer or hexamer? There is also only one. This is because the J chain functions to bring two antibodies close to each other; once it brings them together and the disulfide bond is formed, it can detach and help bring another antibody molecule into position. In contrast, in the IgA dimer there are no additional antibody molecules to be recruited, so the J chain remains attached and becomes a permanent component of the structure.

IgA CLASS

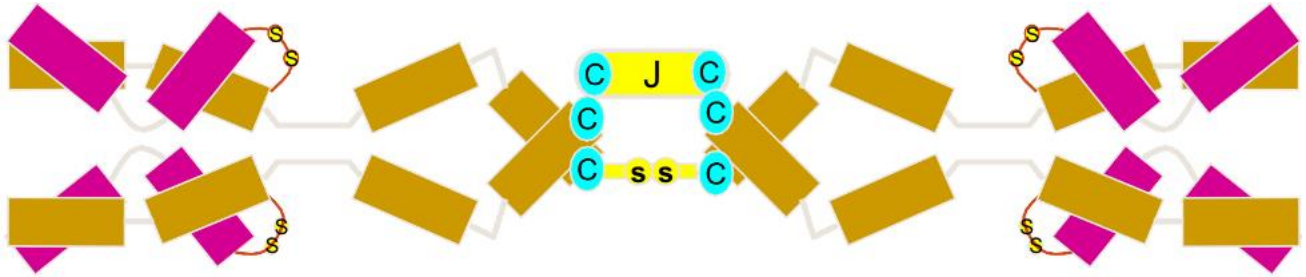


- ✓ Provides immunity to infant's digestive tract & body (translocated)
- ✓ The process of dimerization

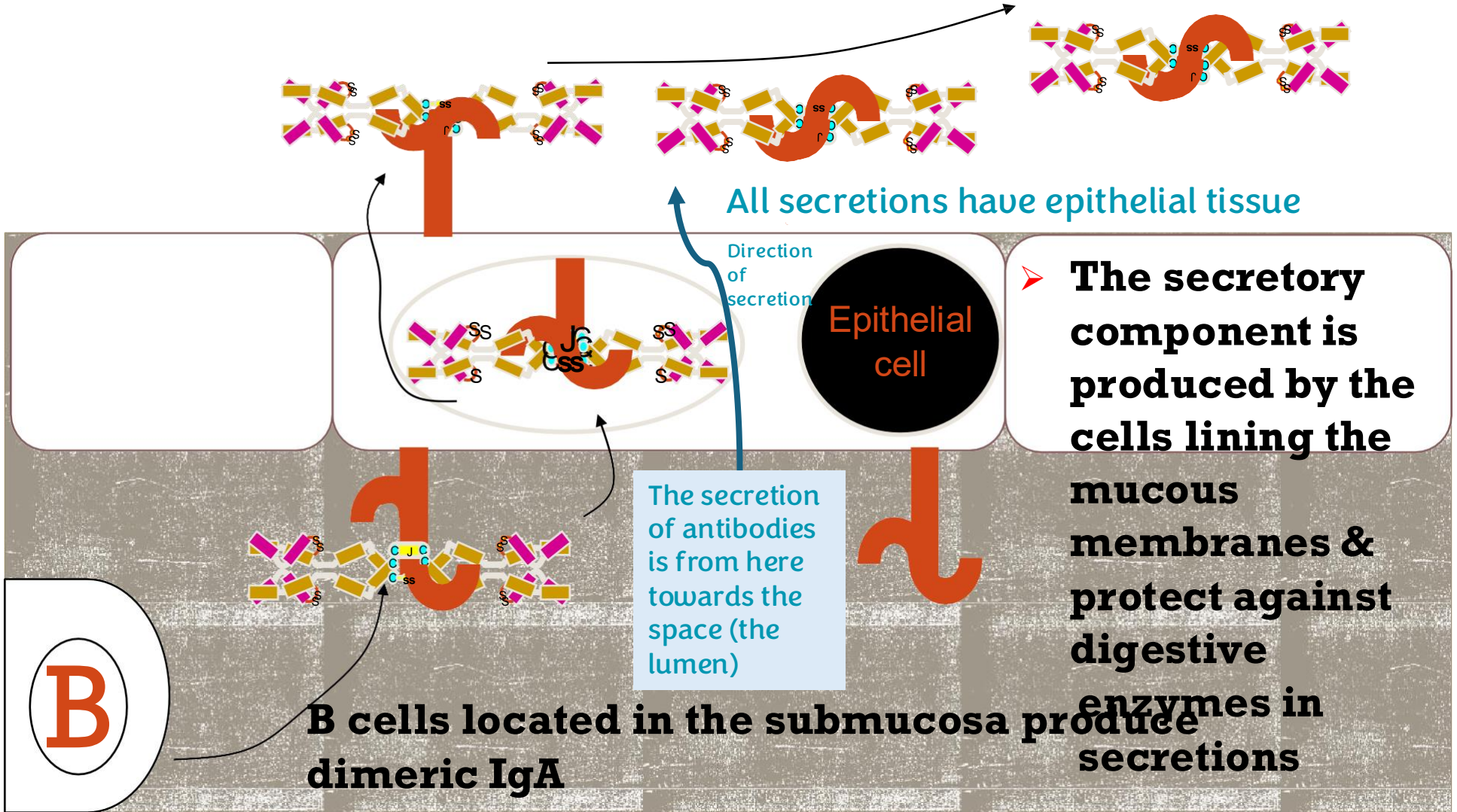
- Newborns receive IgA through their mother's milk, which provides them with immunity.

- But where else does the newborn's immunity come from, aside from the IgA in breast milk?

While still in the womb, the newborn received IgG antibodies from the mother through the placenta, since IgG is the only antibody that can cross the placental barrier. These IgG antibodies remain in the newborn's blood for several months until they are gradually degraded, providing passive immunity during this period. This protection continues until the newborn's own B cells mature and begin producing different classes of antibodies – in addition to the IgA supplied through breastfeeding, if present.



IgA & TRANSCYTOSIS



- **The secretory component is produced by the cells lining the mucous membranes & protect against digestive enzymes in secretions**

IgA & TRANSCYTOSIS

Follow steps while focusing on previous figure.

Process of IgA Secretion:

1.Antibodies that have been produced are translocated, and epithelial cells synthesize a **secretory component** (an **S-shaped polypeptide** with a **stalk-like structure**).

2.This secretory component is synthesized on the outer surface of the epithelial cell, facing toward the B lymphocytes, and then it joins with the **IgA dimer**.

3.The entire complex (IgA dimer + secretory component) is internalized into the epithelial cell.

4.The complex is then transported across the cell and expressed on the external surface, despite the presence of proteases and the harsh conditions within the lumen or extracellular spaces.

5.In this environment, **the stalk portion of the secretory component is digested**, but the rest of the secretory component remains attached to the IgA dimer.

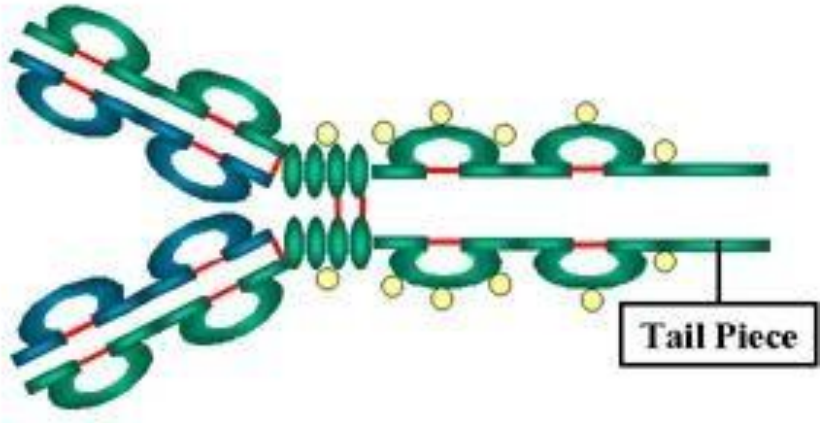
6.This attachment produces a fully functional secretory IgA dimer, stabilized by the secretory component, which allows antigens to bind effectively while maintaining structural protection.

IgD CLASS

- Location: B-cell surface (primarily), blood, and lymph
- Known Functions:
  - ✓In serum: function is unknown
  - ✓On B cell surface: initiate immune response

IgD

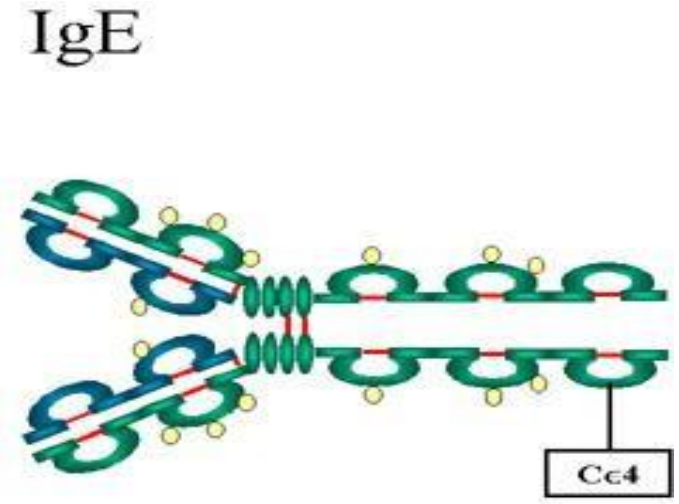
- Structure
  - Monomer
  - Tail piece



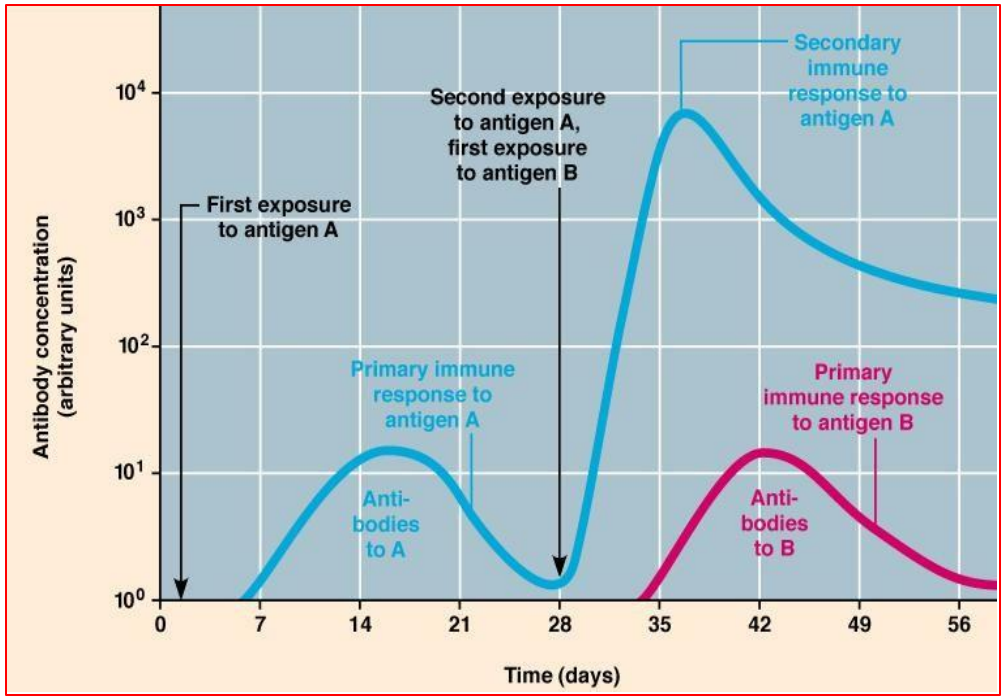
IgE CLASS

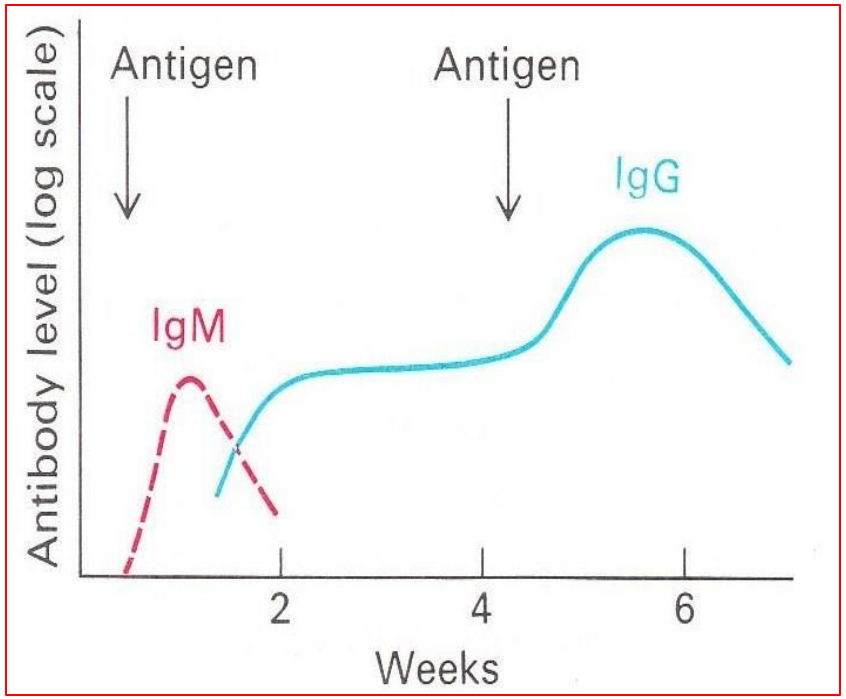
IgE is always related to: allergic reactions an worms

- 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)
  - Possibly lysis of worms



IMMUNOLOGICAL MEMORY





IMMUNOLOGICAL MEMORY

When you are exposed to an antigen for the first time, you experience a strong reaction, but upon the second exposure to the same antigen, the response is much more efficient and controlled. Why is this? This phenomenon is called immunological memory.

Here is the explanation:
•During the first encounter with the antigen, the immune response is mediated primarily by IgM.
•During the second encounter with the same antigen, the response is dominated by IgG, which is produced in much higher concentrations.

This raises the question: How can IgG, although it has not directly encountered the antigen before, mount a much stronger and more effective response compared to IgM?

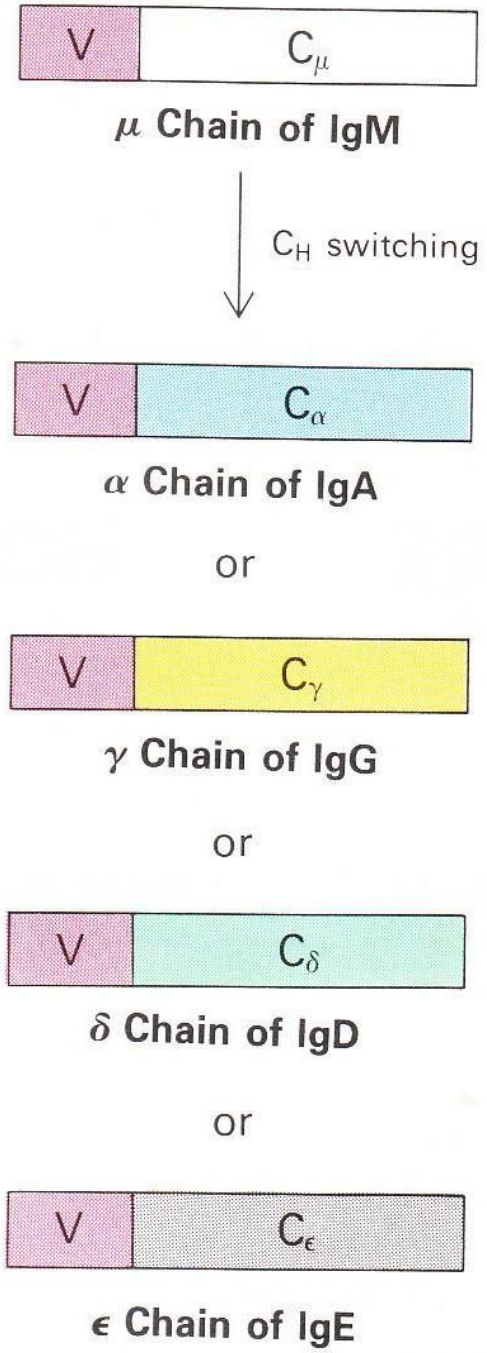
The answer lies in the process called class switching (isotype switching). In this mechanism, IgM-producing B lymphocytes undergo genetic rearrangements that allow them to produce IgG. This switch enables the immune system to respond to the same antigen more powerfully and with greater specificity during subsequent exposures.

CLASS (ISOTYPE) SWITCHING

- Antibodies with identical specificity but of different classes

- Generated in a chronologic order in response to the antigen

- Gene rearrangement: movement of VDJ from a site near one C gene to a site near another C gene

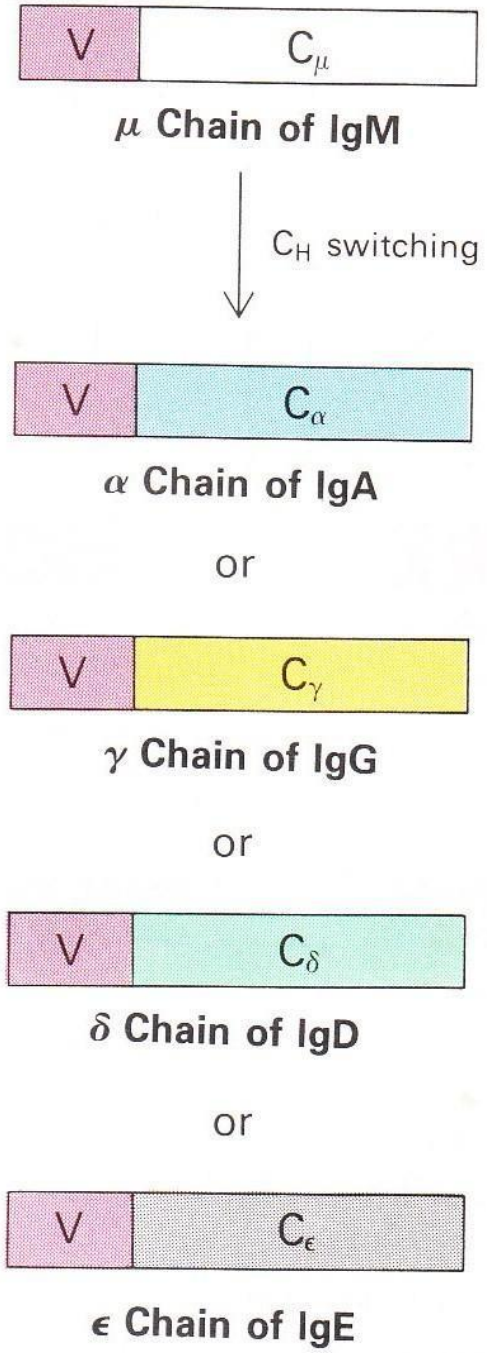


CLASS (ISOTYPE) SWITCHING

- Isotypes are immunoglobulins that share the same variable region but differ in their constant regions. As we have previously seen, the constant region is encoded within the immunoglobulin gene.

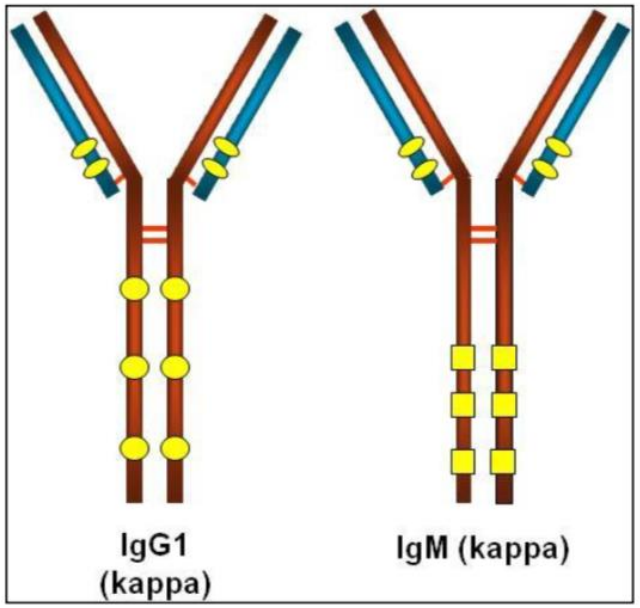
- Class (isotype) switching is the process of gene rearrangement in which the same variable region is coupled with a different constant region within the same gene.

- Through this mechanism, the immune system is able to generate a secondary immune response that recognizes the same antigen but produces a different type of antibody.



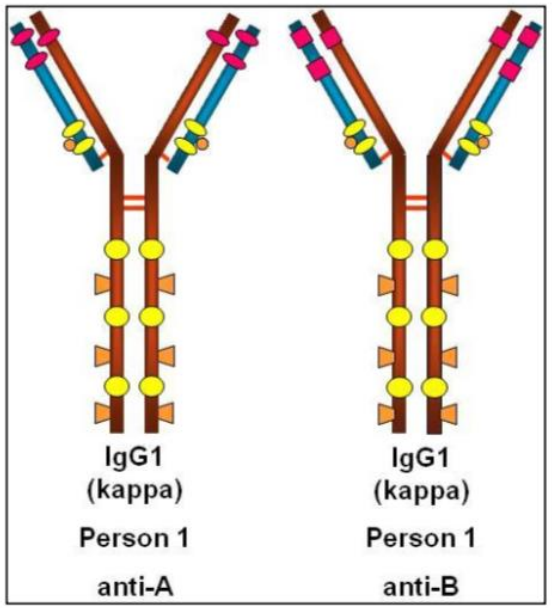
IDIOTYPE VS. ISOTYPES VS. ALLOTYPES

isotypes



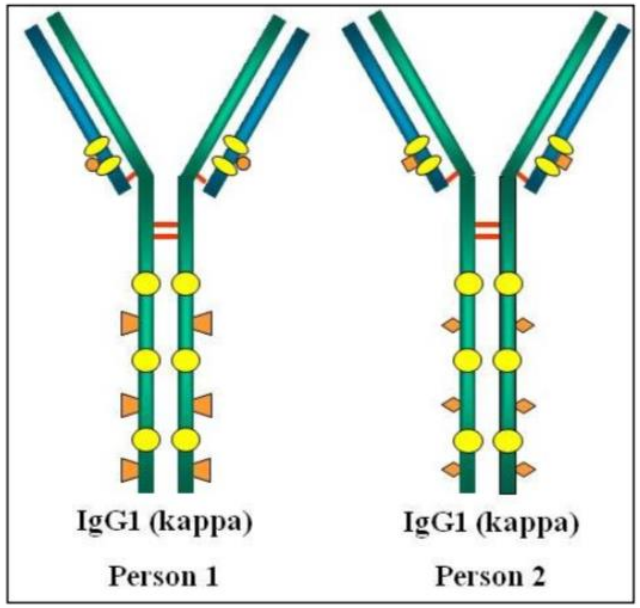
A different class of antibody in the same person that can recognize the same antigen

idiotype



In the same person you have different IgGs to recognize different antigens

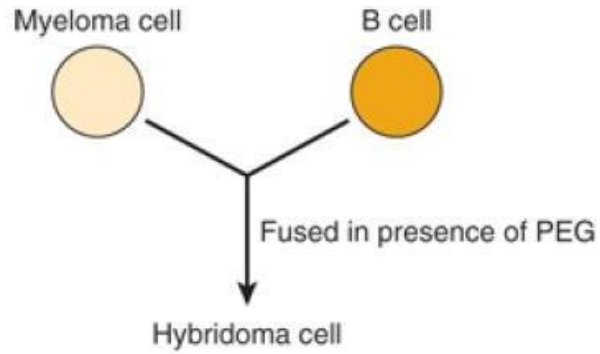
allotypes



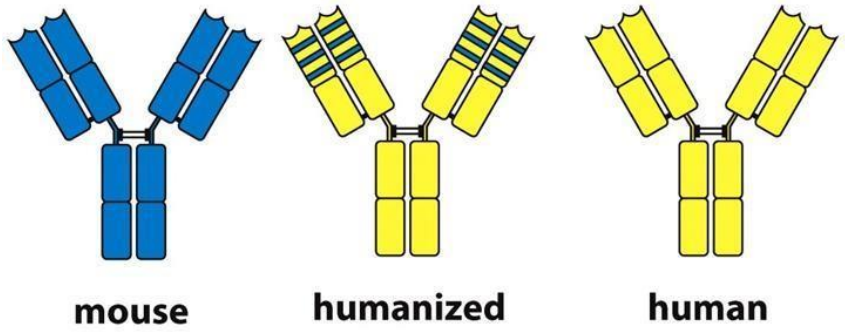
To have the same immunoglobulins in different people (recognizing same antigens).

HYBRIDOMA AND MONOCLONAL ANTIBODIES

- When an antigen is injected into an animal, the resulting antibodies are polyclonal, meaning they are directed against a number of different epitopes on the antigen.
- In order to "create" an immortal B cell that produces a single antibody (monoclonal), a B cell hybridizes with a B cancer cell (myeloma).

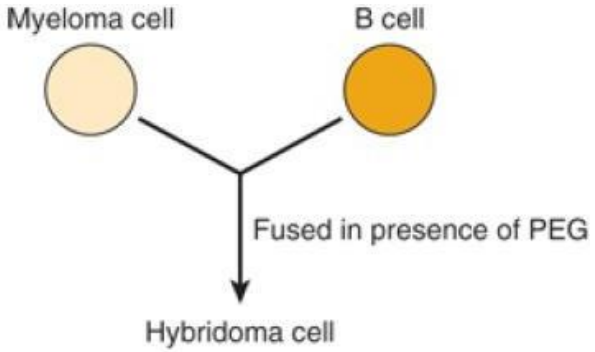


Monoclonal antibodies made in mice can be humanized by attaching the CDRs onto appropriate sites in a human immunoglobulin molecule.



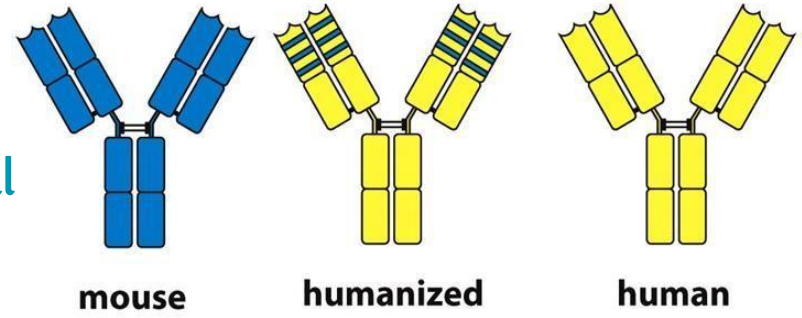
HYBRIDOMA AND MONOCLONAL ANTIBODIES

When a B cell that produces a specific antibody is fused with a myeloma cell (a cancerous cell capable of indefinite growth), the resulting cells are called hybridoma cells. These hybridoma cells inherit the ability to produce a specific type of antibody continuously because of the immortal nature of the myeloma component.



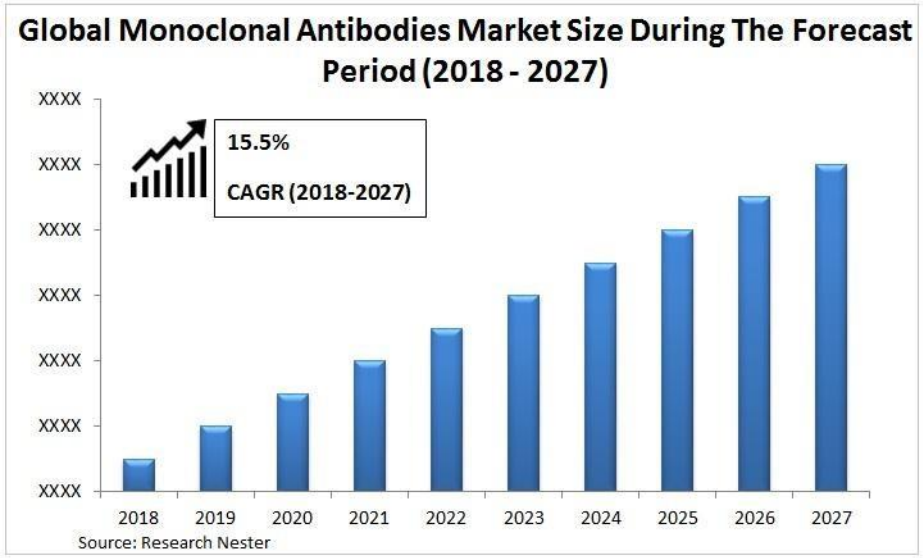
How is this achieved? A hybridoma cell can be introduced into an animal, which is then injected with the target antigen. This stimulates the animal's immune system to generate large quantities of the desired antibodies. Blood is subsequently collected from the animal, and the antibodies present are purified and refined.

This process enables the production of large amounts of antibodies that specifically recognize the antigen of interest, because the animal was exposed to that particular antigen.



BENEFITS OF MONOCLONAL ANTIBODIES

- Measure the amounts of many individual proteins and molecules (e.g. plasma proteins, steroid hormones).
- Determine the nature of infectious agents (e.g. types of bacteria).
- Used to direct therapeutic agents to tumor cells.
- Used to accelerate the removal of drugs from circulation when they reach toxic levels.



BENEFITS OF MONOCLONAL ANTIBODIES

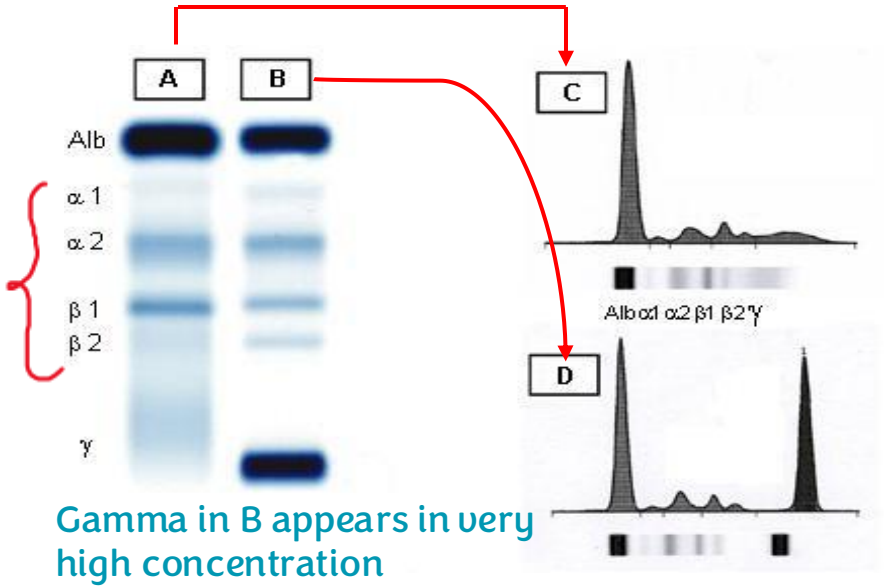
By measuring the number of interactions between an antibody and its corresponding antigen, it is possible to determine the concentration of the antigen. For example, if a specific antibody against a particular bacterium is added to a solution and precipitation occurs, this indicates the presence of that bacterium, and the reverse is also true.

When these antibodies are directed toward tumor cells, they can be used to deliver therapeutic drugs specifically to the tumor, because the antibodies can recognize unique markers present on tumor cells but absent on normal cells. This approach is known as targeted drug therapy using immunoglobulins.

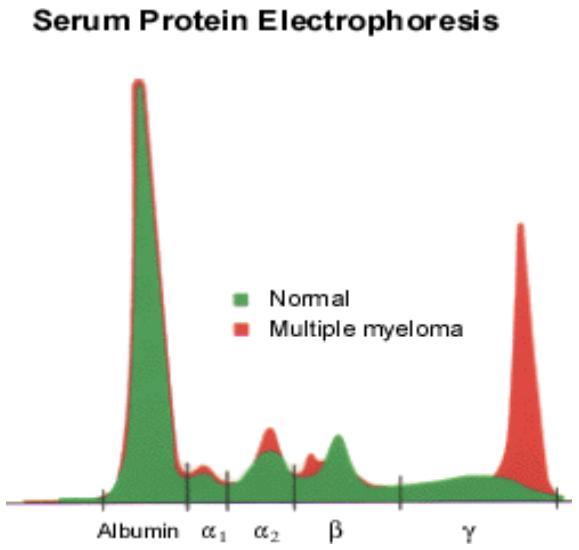
DISEASES

- 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)

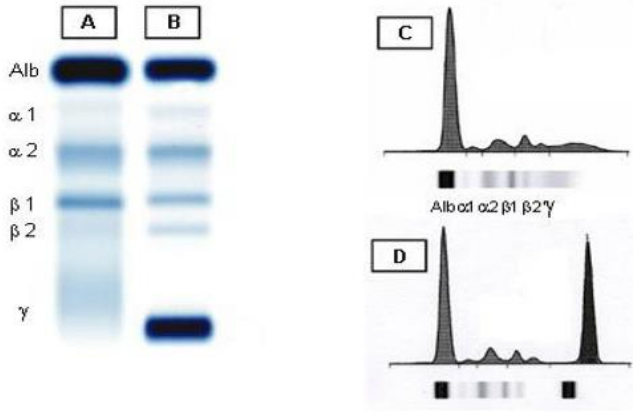
They separate if you give them certain amount of time



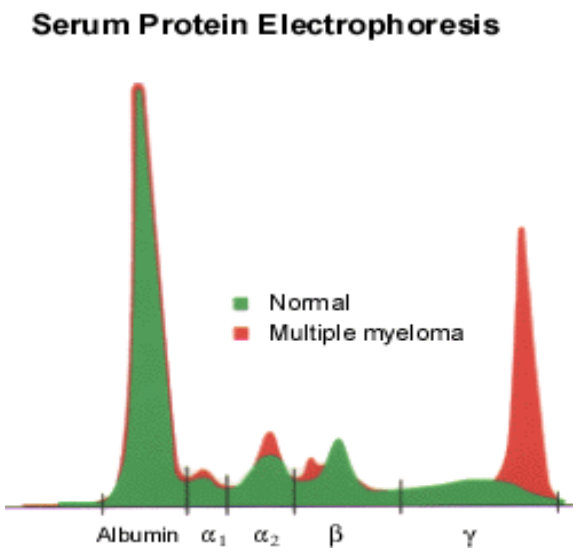
Gamma in B appears in very high concentration



DISEASES



In D the immunoglobulin is very huge, this case is what we call multiple myeloma which is cancer cells that affect B lymphocytes



There are five distinct populations of B lymphocytes (plasma cells), and each population produces one type of immunoglobulin: IgA, IgD, IgE, IgM, or IgG. When the concentration of a specific antibody class is markedly increased, this results in the appearance of a sharp band on the electrophoresis profile. In contrast, when all antibody classes are elevated, the profile shows a broad band with increased intensity.

There are diseases that can be evaluated using gel electrophoresis or its densitometric representation, such as agammaglobulinemia. In this term, emia refers to the blood, gammaglobulin refers to antibodies, and a indicates depletion or absence.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 37; left corner	Domains in the heavy chains, variable-> C_H1 constant-> C_H3	Domains in the heavy chains, variable-> V_H constant-> C_H1, C_H2, C_H3
V1 → V2			

رسالة من الفريق العلمي: