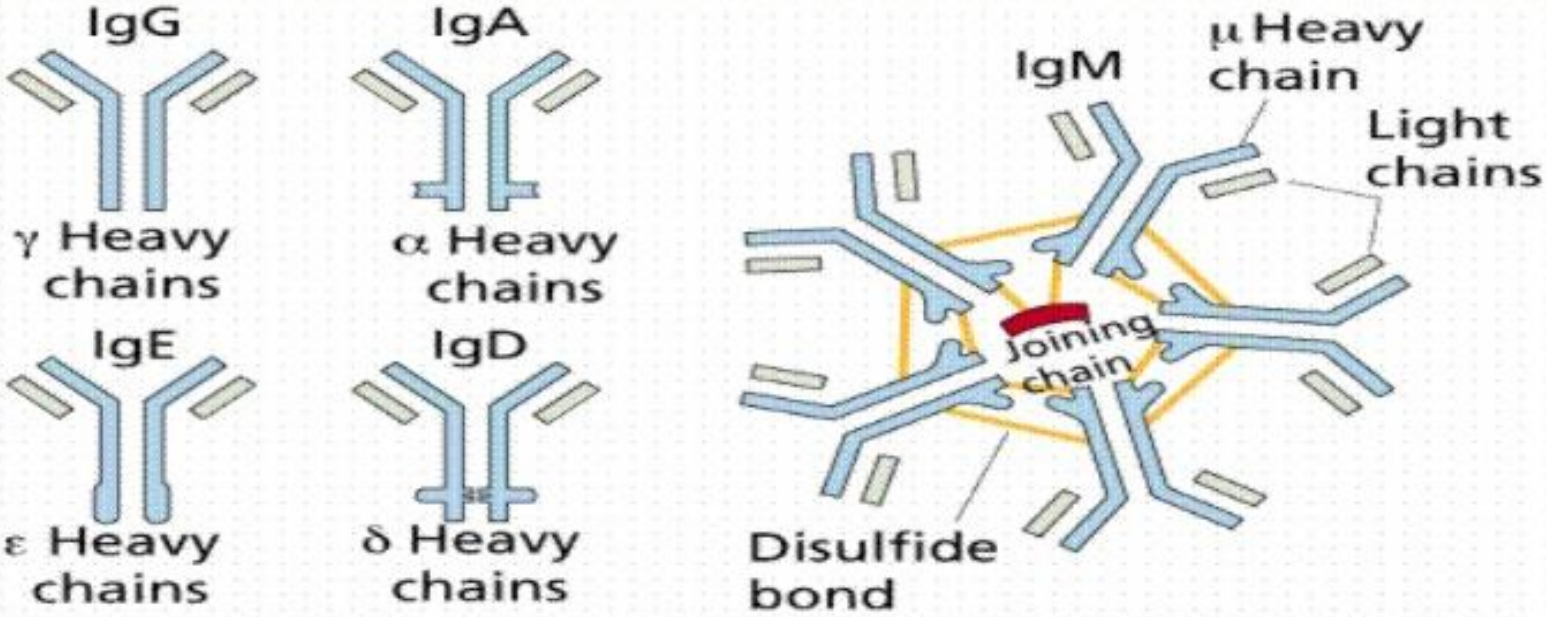
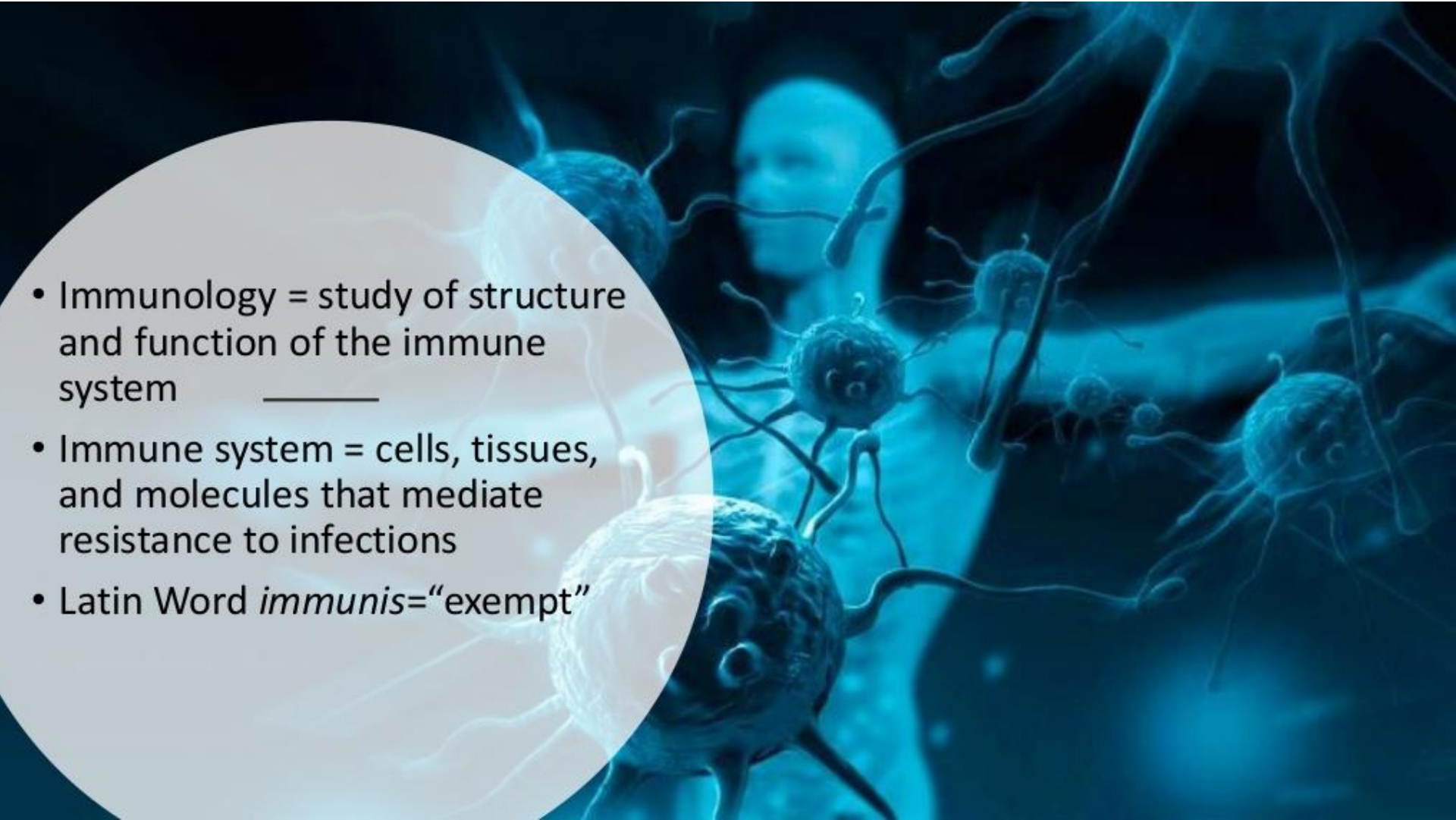
Immunoglobulins



Learning objectives

To understand :

- General Structure of Immunoglobulin
- Types of Immunoglobulins
- Structural variations of different immunoglobulins
- Function of different immunoglobulins
- Clinical significance of Immunoglobulins

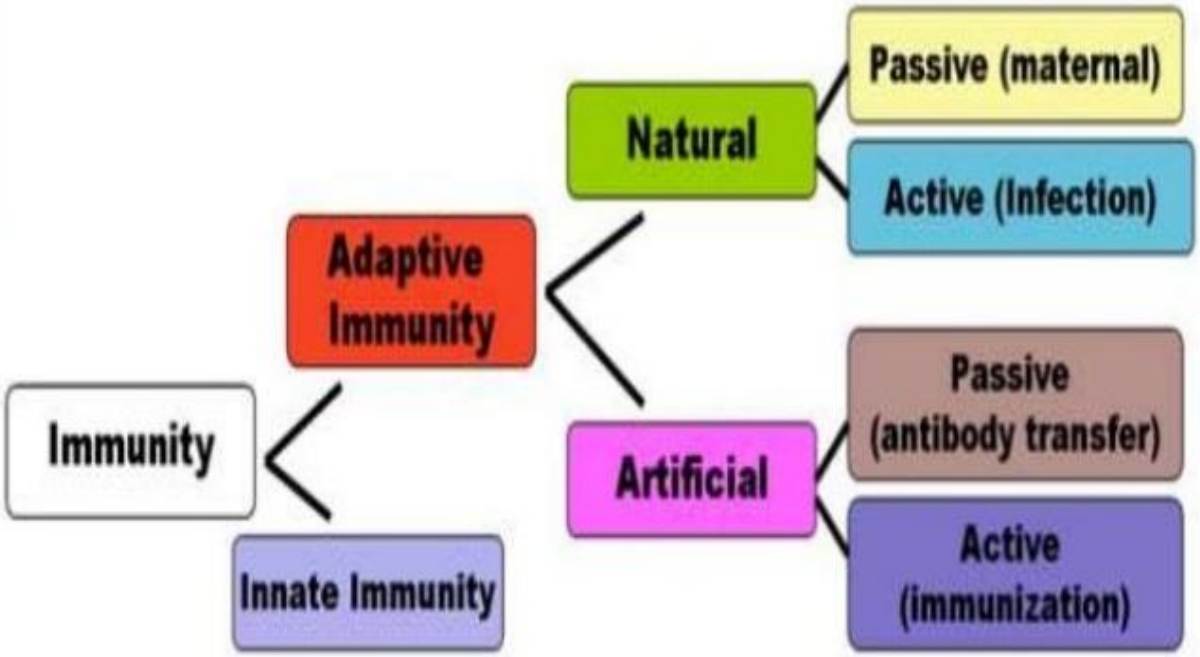


- Immunology = study of structure and function of the immune system _____
- Immune system = cells, tissues, and molecules that mediate resistance to infections
- Latin Word *immunis*="exempt"

Immunity

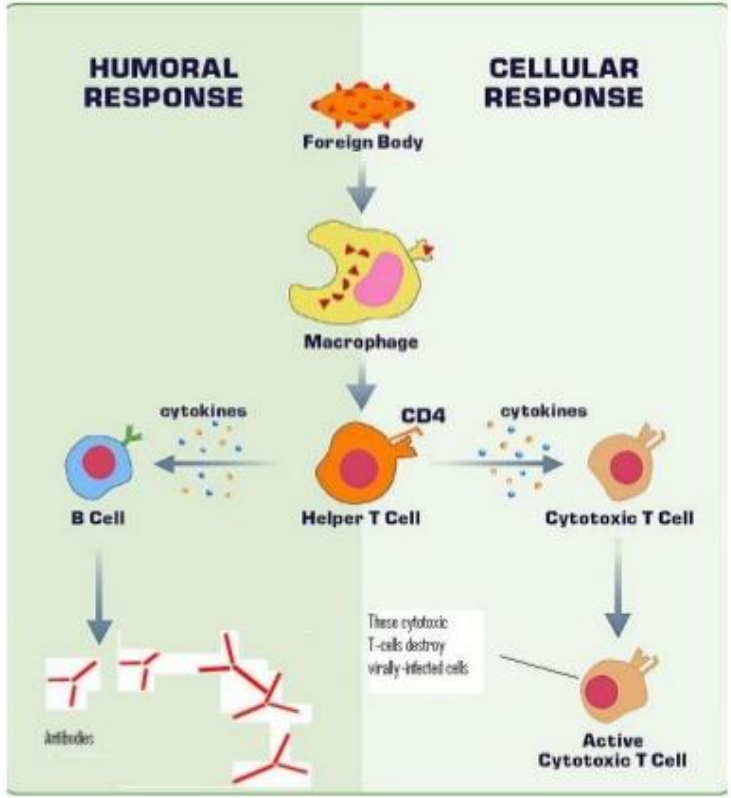
- Immunity = resistance of a host to pathogens and their toxic effects

Types of immunity



Immune response

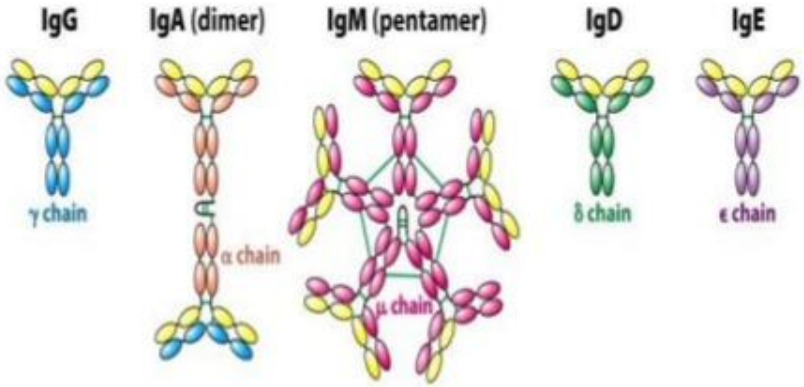
- **Immune response** = collective and coordinated response to the introduction of foreign substances in an individual mediated by the cells and molecules of the immune system



Immunoglobulins

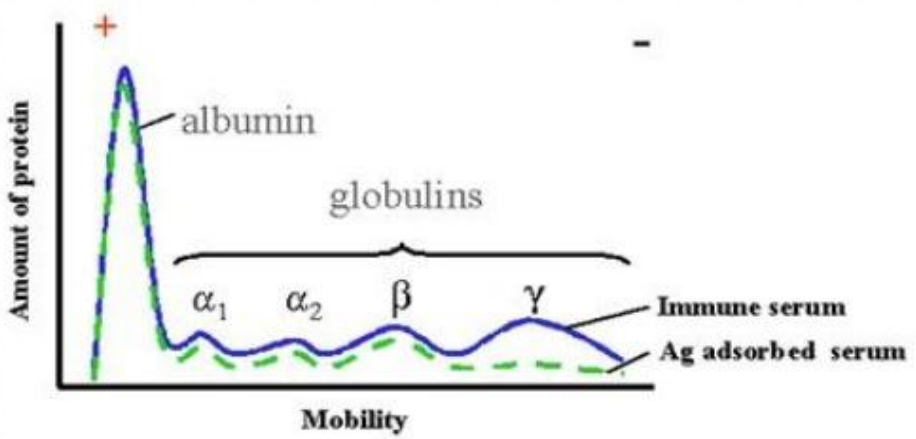
Immunoglobulins are:

- glycoprotein molecules,
- function as antibodies
- produced by plasma cells
- in response to an immunogen.



Immunoglobulins

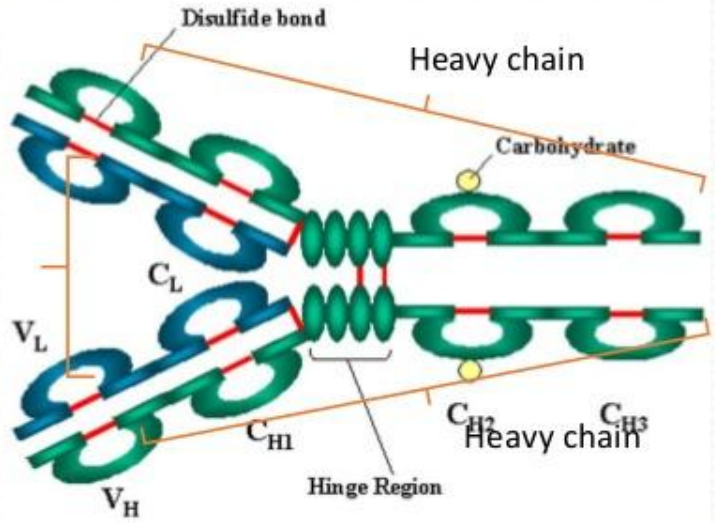
The immunoglobulins derive their name from the finding that they migrate in the region of globulins when antibody-containing serum is placed in an electrical field.



Structural characteristics

A. Heavy and Light Chains

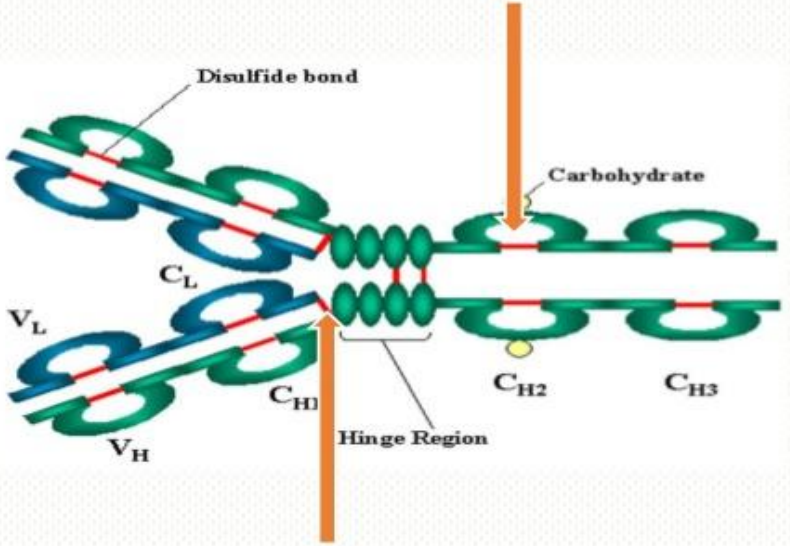
- All immunoglobulins have a four chain structure as their basic unit.
- They are composed of two identical light chains (23kD) and two identical heavy chains (50-70kD)



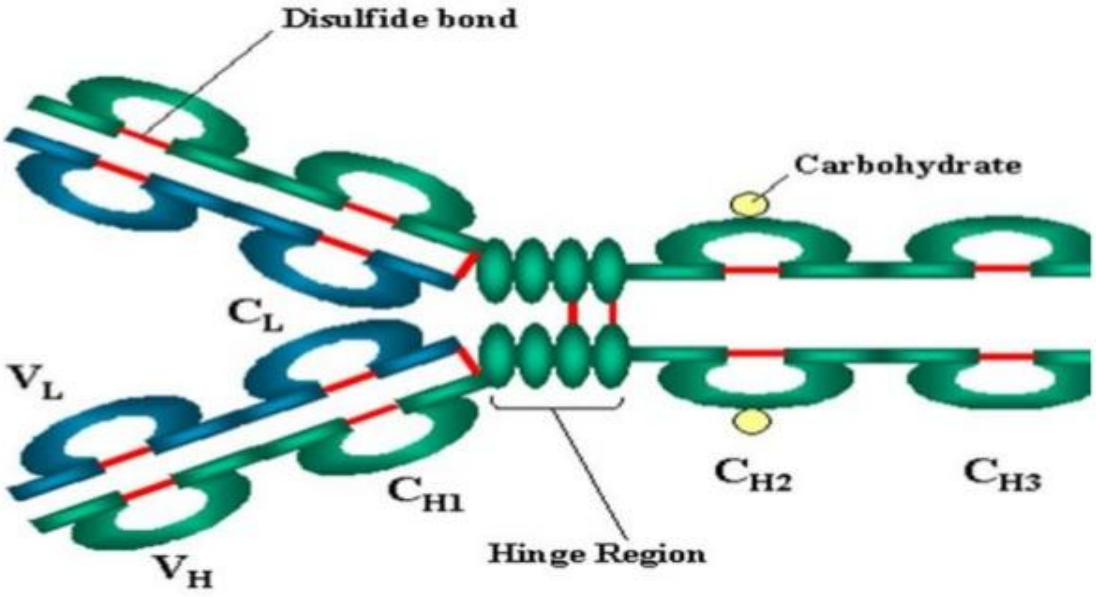
B. Disulfide bonds

- **Inter-chain disulfide bonds -** The heavy and light chains and the two heavy chains are held together by inter-chain disulfide bonds and by non-covalent interactions.
- The number of inter-chain disulfide bonds varies among different immunoglobulin molecules.
- **Intra-chain disulfide bonds** Within each of the polypeptide chains there are also intra-chain disulfide bonds.

Intrachain disulfide bond

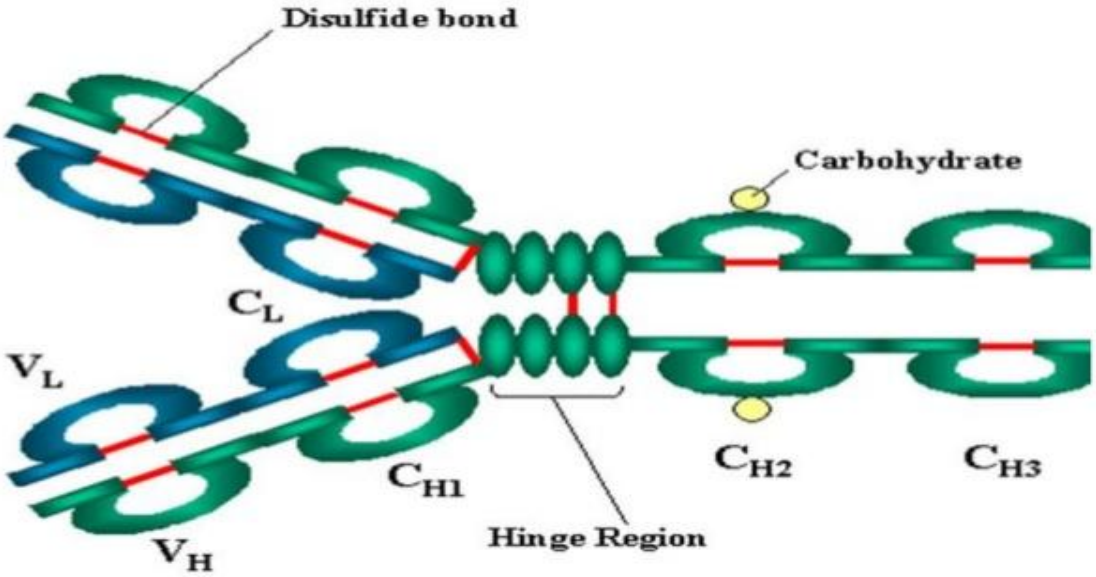


Interchain disulphide bonds



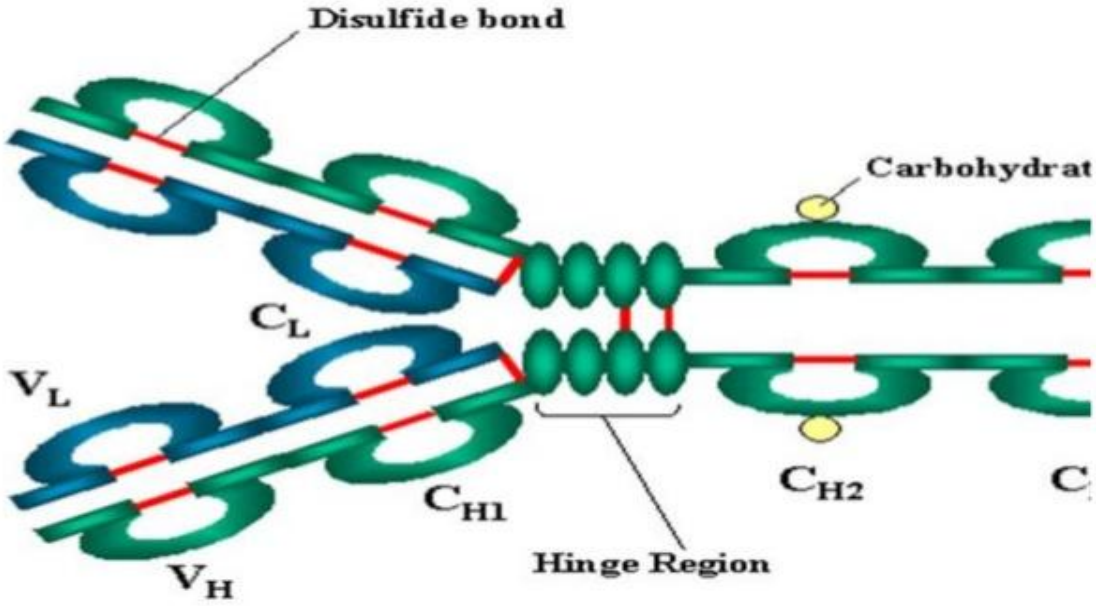
C. Variable (V) and Constant (C) Regions

- Both the heavy and light chain can be divided into two regions based on variability in the amino acid sequences. These are the
- Light Chain - V_L (110 amino acids) and C_L (110 amino acids)
- Heavy Chain - V_H (110 amino acids) and C_H (330-440 amino acids)



D. Hinge Region

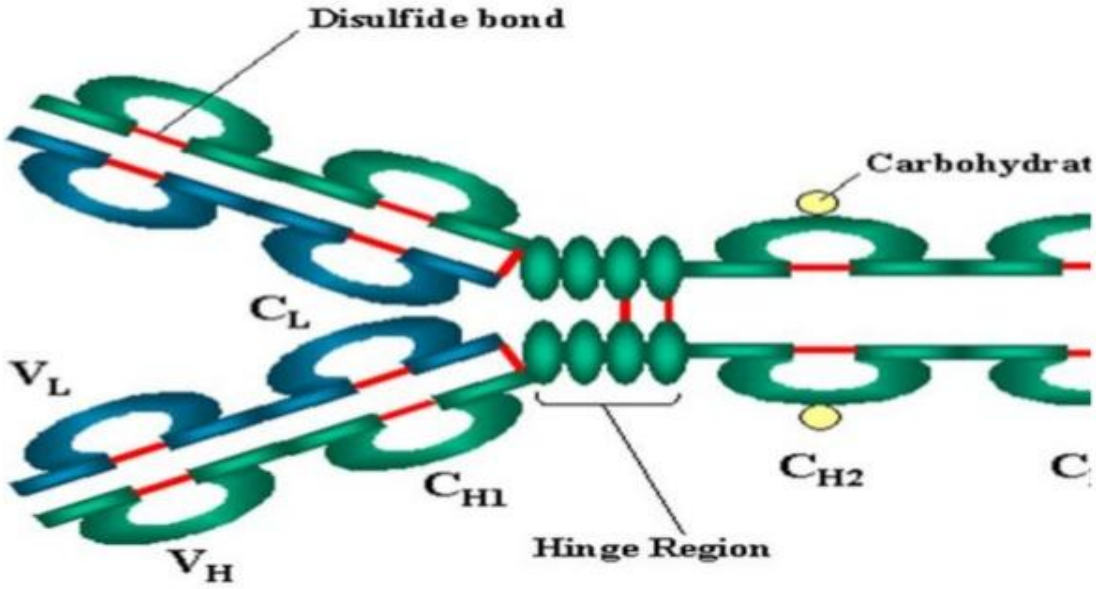
- This is the region at which the arms of the antibody molecule form a Y.
- It is called the hinge region because there is some flexibility in the molecule at this point.



E. Domains

- Three dimensional images of the immunoglobulin molecule show that it is not a straight molecule rather, it is folded into globular regions each of which contains an intra-chain disulfide bond .
- These regions are called **domains**.

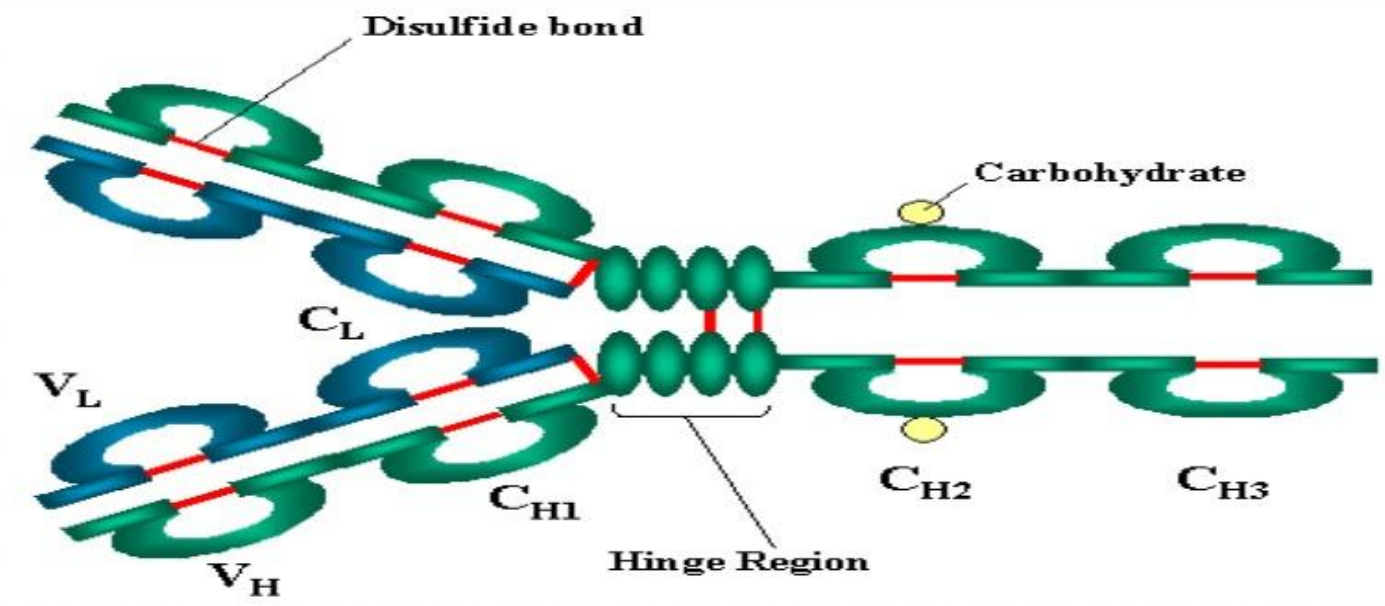
1. Light Chain Domains - V_L and C_L
2. Heavy Chain Domains - V_H, C_{H1},CH_2C_{H3} (or C_{H4})



F. Oligosaccharides

- Carbohydrates are attached to the C_{H2} domain in most immunoglobulins.
- However, in some cases carbohydrates may also be attached at other locations.

Basic structure of immunoglobulins



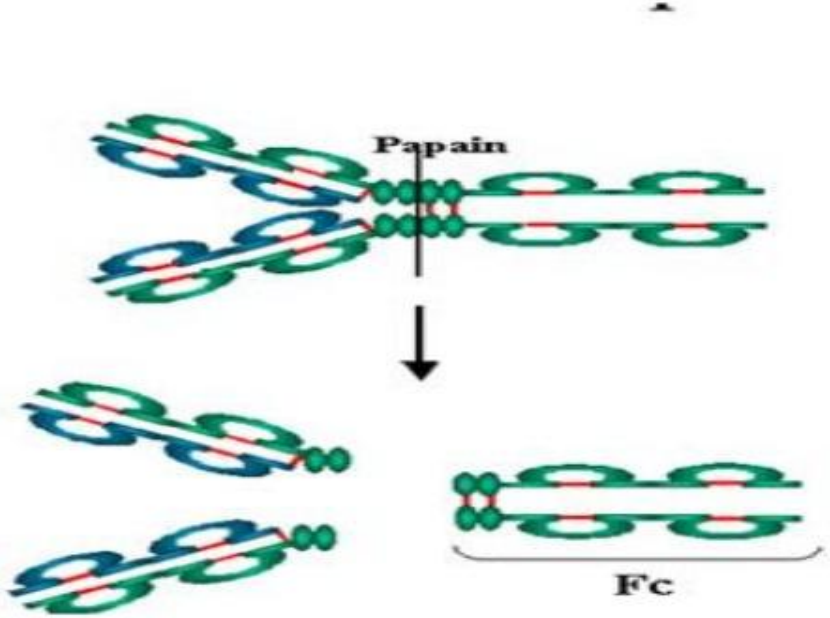
Immunoglobulin fragments: structure/function relationships

Immunoglobulin fragments produced by proteolytic digestion –

A. Fab

Digestion with papain breaks the immunoglobulin molecule in the hinge region before the H-H inter-chain disulfide bond.

This results in the formation of two identical fragments that contain the light chain and the V_H and C_{H1} domains of the heavy chain.

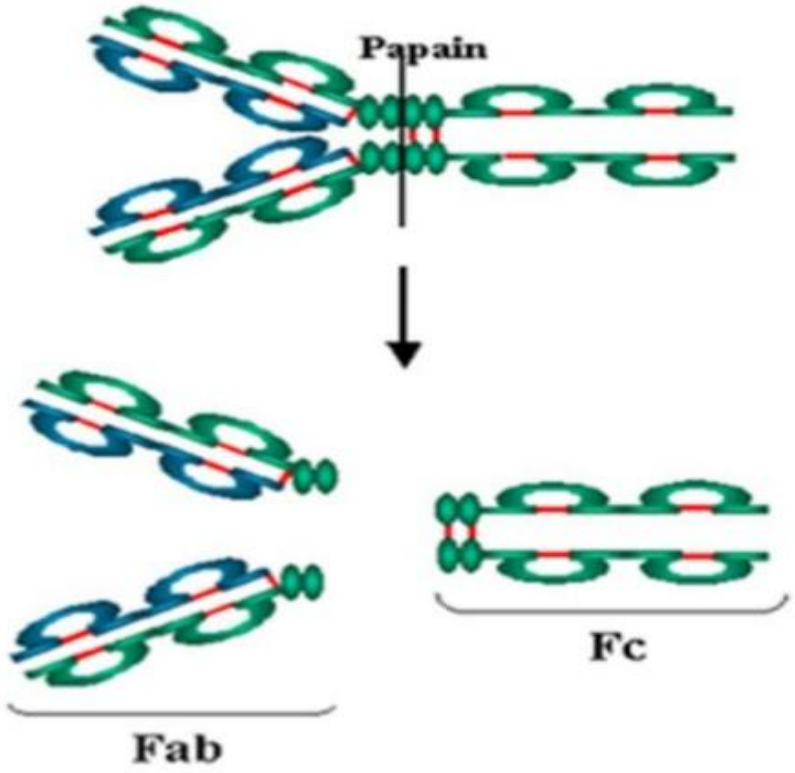


Immunoglobulin fragments by Papain

- **Fab** -These fragments are called the Fab fragments because they contain the **antigen binding** sites of the antibody.
- Each Fab fragment is monovalent whereas the original molecule was divalent.
- The combining site of the antibody is created by both V_H and V_L.

Immunoglobulin fragments by Papain

- **B. Fc**
  Digestion with papain also produces a fragment that contains the remainder of the two heavy chains each containing a C_{H2} and C_{H3} domain.
- This fragment was called Fc because it was easily crystallized.



Structure-function relationship

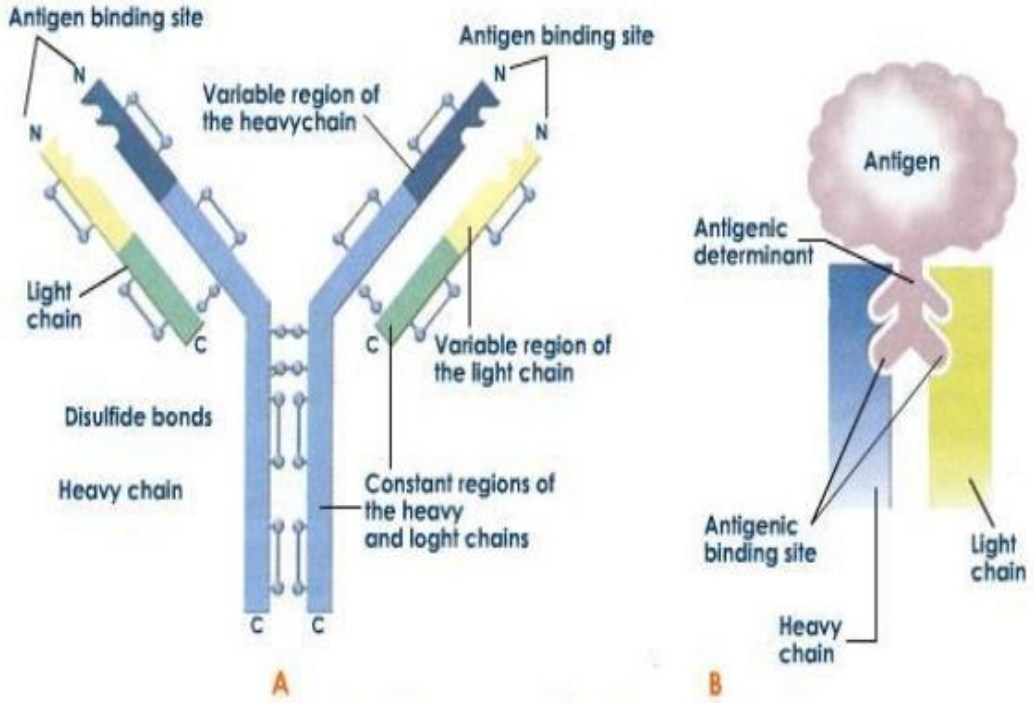
Antigen binding function of Immunoglobulins is carried out by Fab part,

Effector functions -The effector functions are mediated by Fc part of the molecule.

Different functions are mediated by the different domains in this fragment.

General functions of immunoglobulins

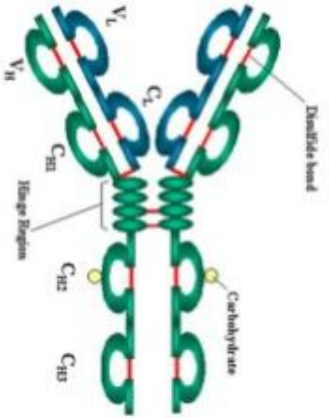
- **A. Antigen binding**
- Antigen binding by antibodies is the primary function of antibodies and can result in protection of the host.
- Each immunoglobulin binds to a specific antigenic determinant.

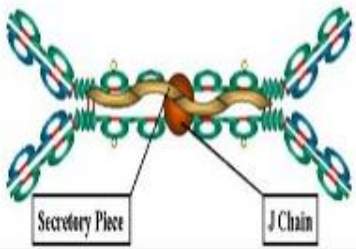


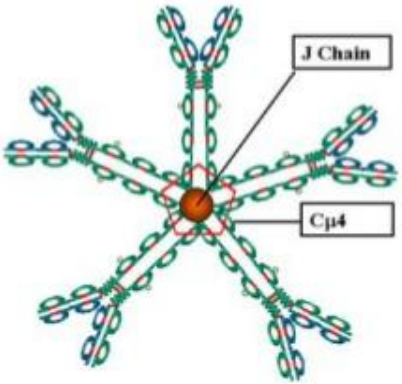
Immunoglobulins : A. Structure, B. Antigen binding site

Valency of antibody

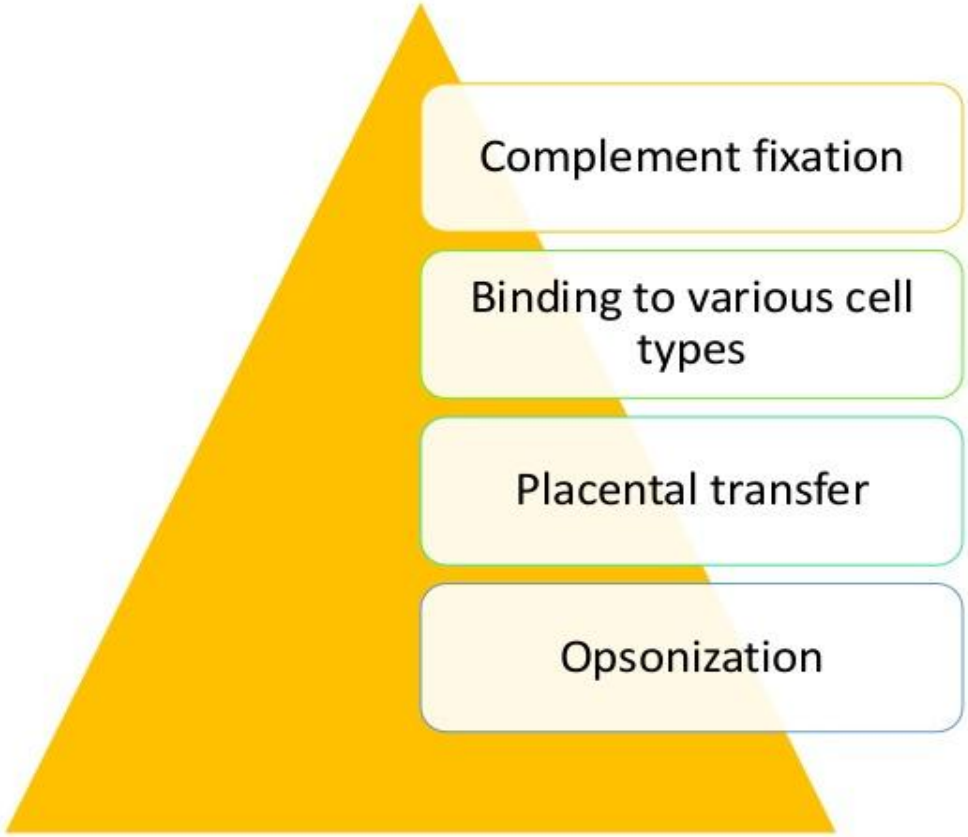
- The valency of antibody refers to the number of antigenic determinants that an individual antibody molecule can bind.
- The valency of all antibodies is at least two and in some instances more.





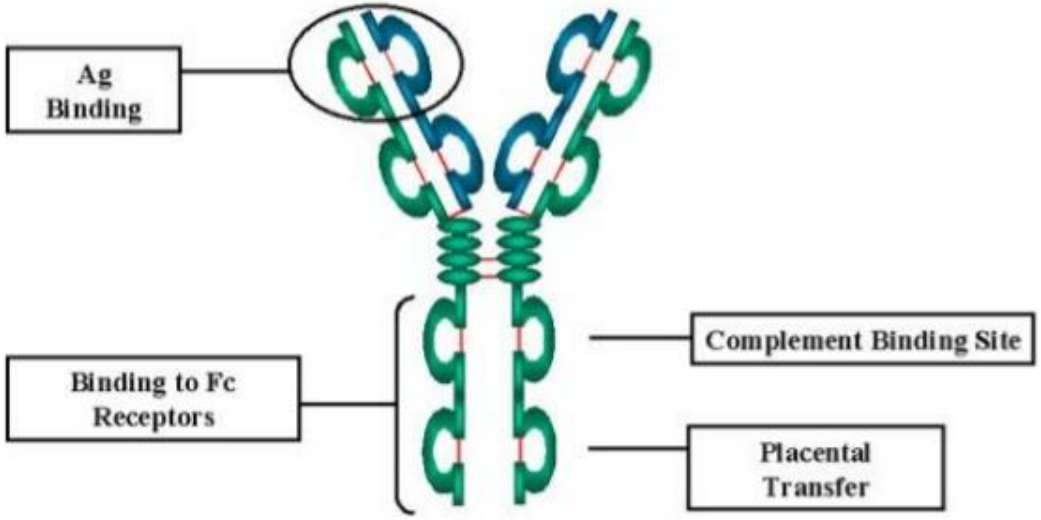


B. Effector Functions



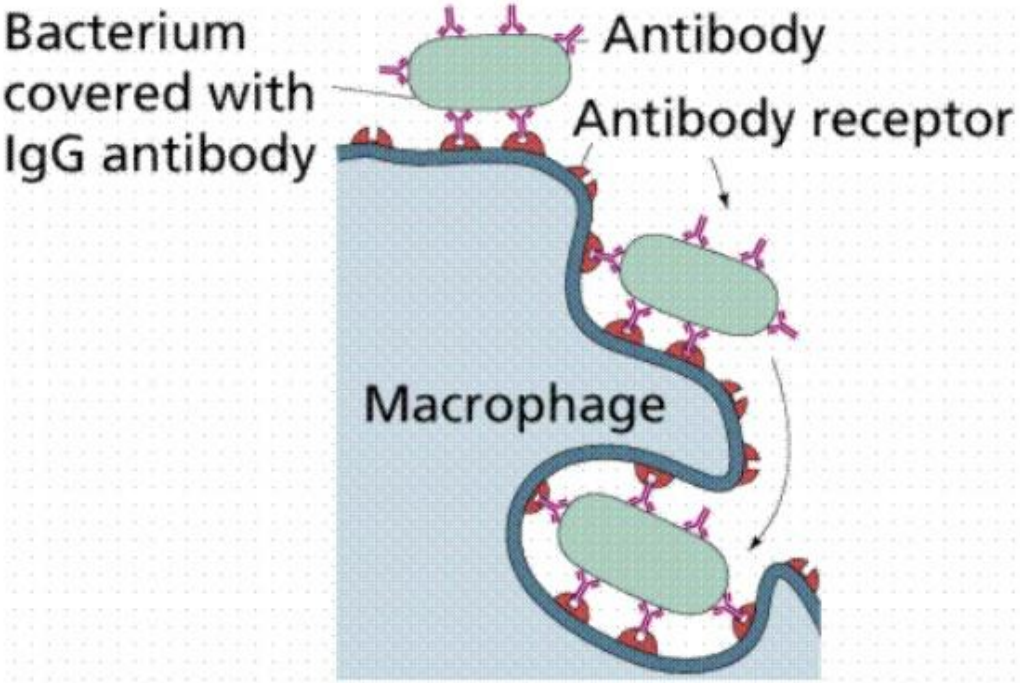
General functions of Immunoglobulins

Immunoglobulin Fragments: Structure/Function Relationships



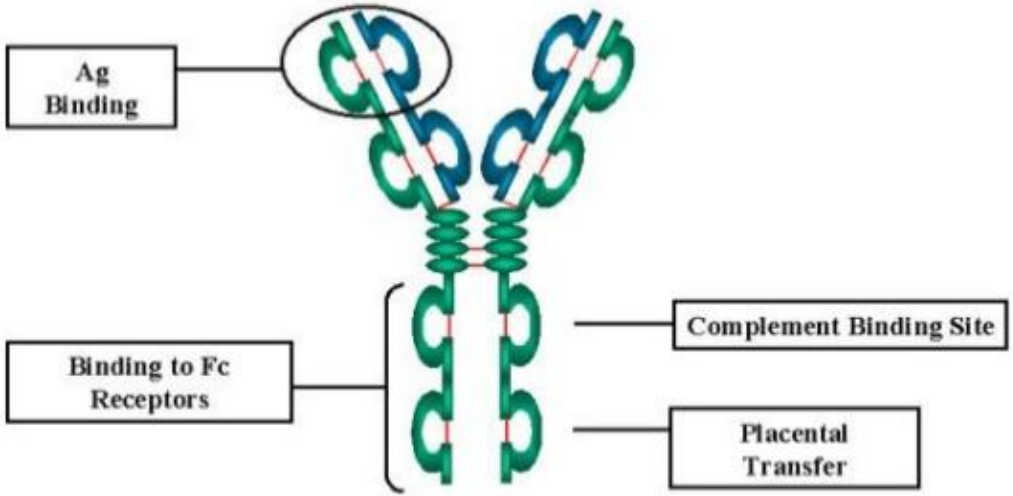
Binding to various cell types

- Phagocytic cells, lymphocytes, platelets, mast cells, and basophils have receptors that bind immunoglobulins.
- This binding can activate the cells to perform some function.



Functions of Immunoglobulins

- Some immunoglobulins also bind to receptors on placental trophoblasts, which results in transfer of the immunoglobulin across the placenta.
- As a result, the transferred maternal antibodies provide immunity to the fetus and newborn.

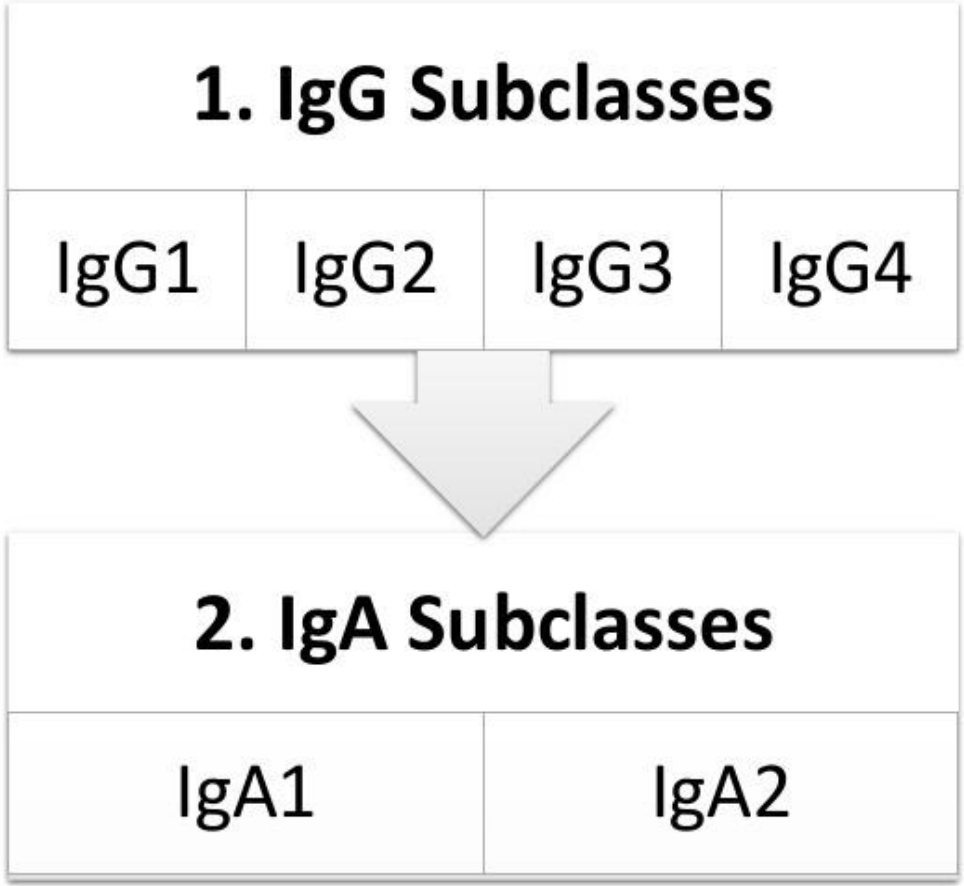


Immunoglobulin classes

- The immunoglobulins can be divided into five different classes, based on differences in the amino acid sequences in the constant region of the heavy chains.

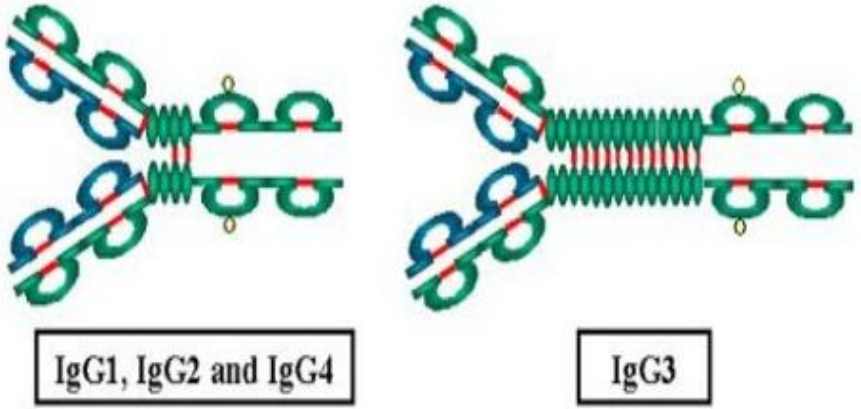
1. IgG - Gamma heavy chains
2. IgM - Mu heavy chains
3. IgA - Alpha heavy chains
4. IgD - Delta heavy chains
5. IgE - Epsilon heavy chains

Immunoglobulin Subclasses



Immunoglobulin G (IgG)- Structure

- All IgG's are monomers (7S immunoglobulin).
- The subclasses differ in the number of disulfide bonds and length of the hinge region.

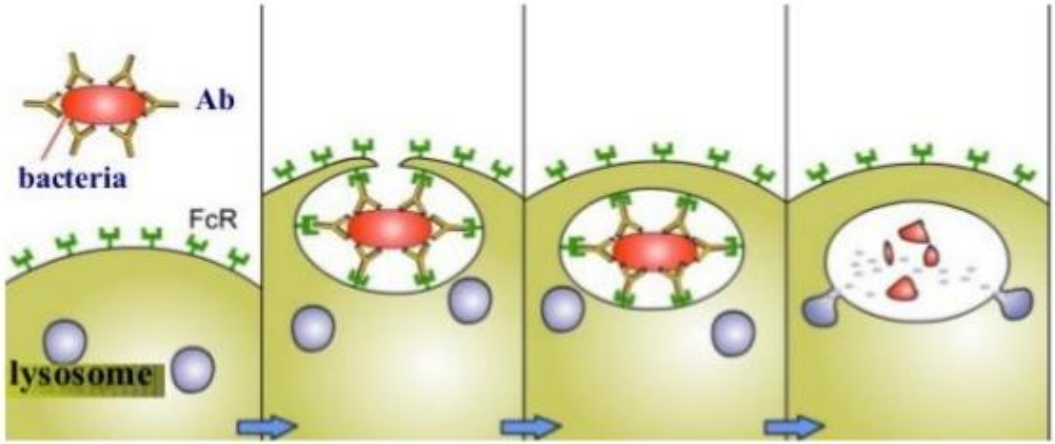


Immunoglobulin G (IgG)-Properties

- Major Ig in serum
- Major Ig in extravascular spaces
- Only Ig that crosses placenta
- Complement fixation
- Opsonization

Opsonization

- The term **opsonin** is used to describe substances that enhance phagocytosis.
- IgG is a good opsonin.
- The antibody prepares the antigen for killing by the phagocytic cells.
- Macrophages, monocytes and neutrophils and some lymphocytes have Fc receptors for the Fc region of IgG.
- A consequence of binding to the Fc receptors on such cells is that the cells can now internalize the antigen better.



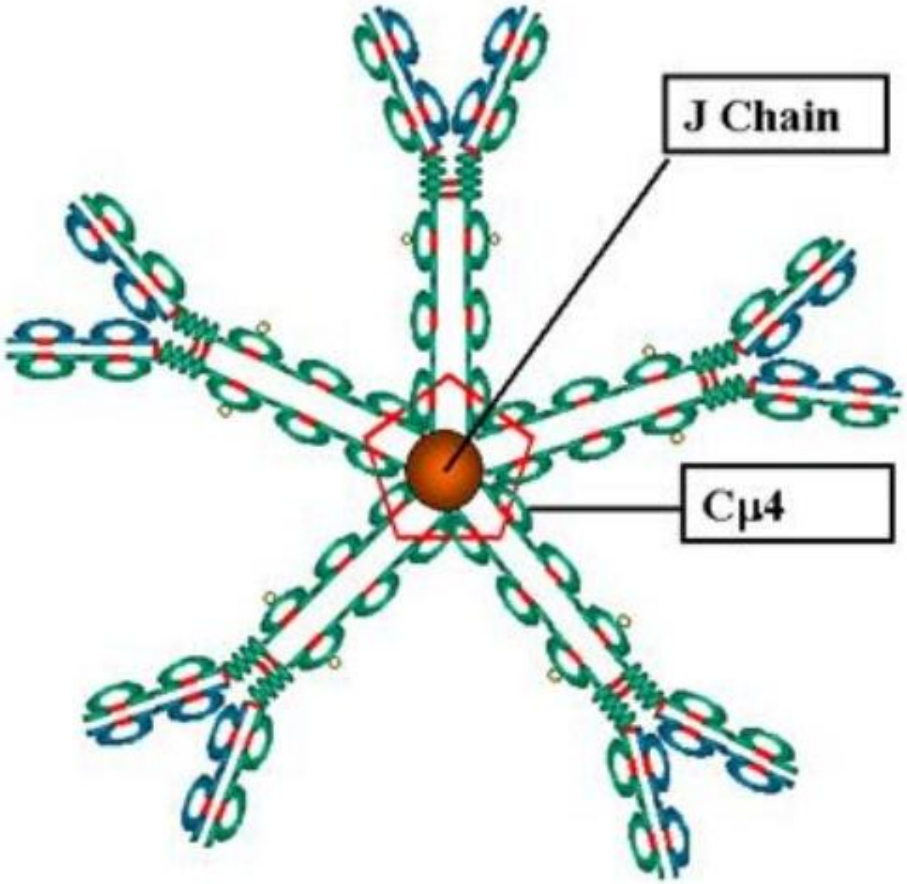
IgG- Function

- Secreted in high quantities in secondary exposures
- Cross the placenta
- Major functions / applications
  - neutralize microbes and toxins
  - opsonize antigens for phagocytosis
  - activate the complement
  - protect the newborn

- 4-fold rise or fall indicates active infection
- A single positive sample indicates past exposure

IgM- Structure

- IgM normally exists as a pentamer (19S immunoglobulin) but it can also exist as a monomer.
- In the pentameric form all heavy chains are identical and all light chains are identical.
- The valence is theoretically 10.



IgM- Properties

Third most common serum Ig.

First Ig to be made by the fetus

First Ig to be made by a virgin B cells when stimulated by antigen

IgM- Properties (contd.)

A good complement fixing Ig.

Very efficient in leading to the lysis of microorganisms.

A good agglutinating Ig.

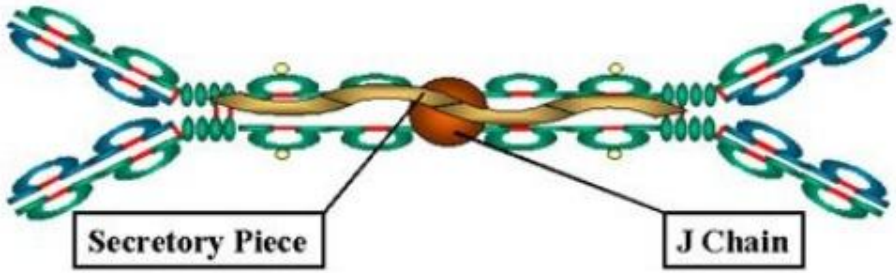
IgM

- Secreted initially during primary infection
- Cannot cross the placenta
- Major functions / applications
  - secreted first during primary exposure
  - activates the complement
  - used as a marker of recent infection

- Presence in newborn means infection
- Single positive sample in serum or CSF indicates recent or active infection
- Used to detect early phase of infection

Ig A- Structure

- Serum IgA is a monomer,
- IgA found in secretions(sIgA)is a dimer.
- J chain is associated with dimeric form.
- A **secretory piece or T piece is also associated with secretory Ig A.**
- sIgA is sometimes referred to as 11S immunoglobulin



IgD-Structure and Properties

1. Structure

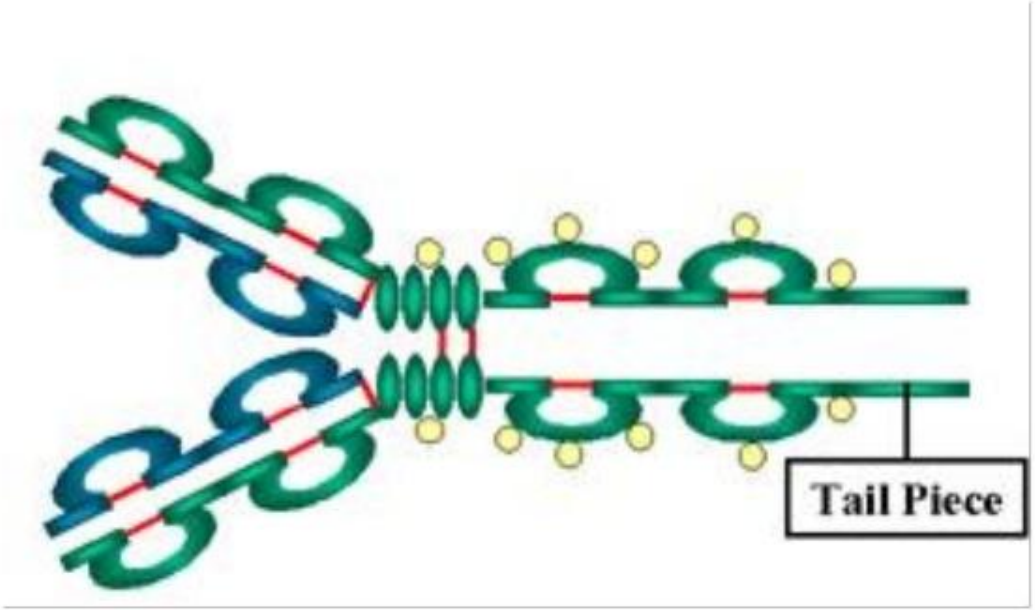
IgD exists only as a monomer.

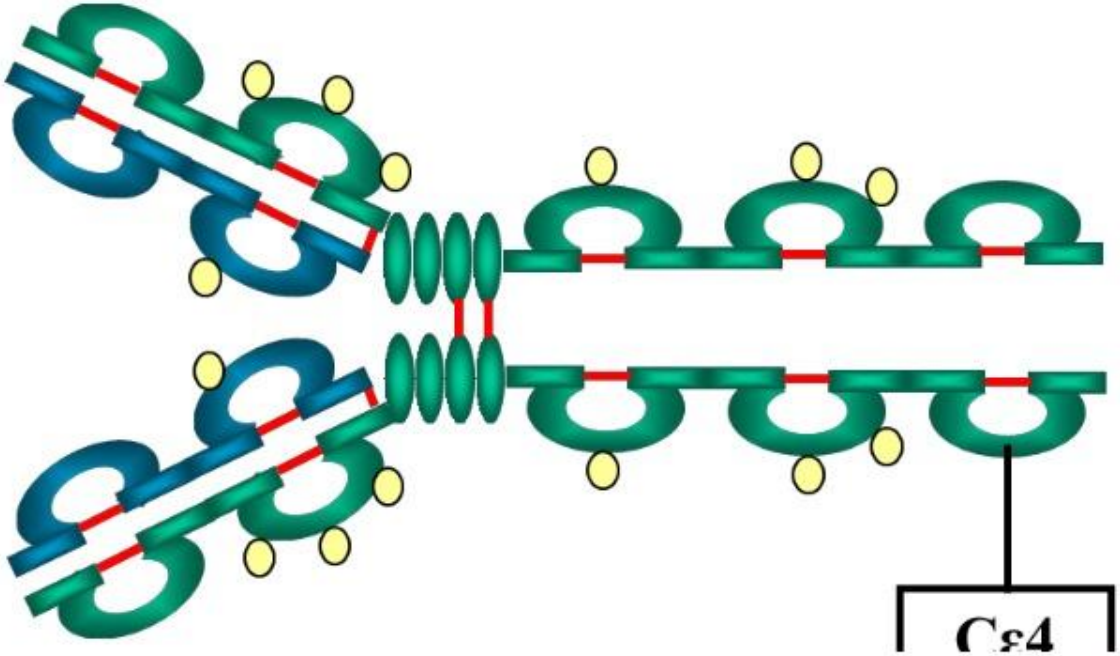
2. Properties

a) IgD is found in low levels in serum; its role in serum is uncertain.

b) IgD is primarily found on B cell surfaces where it functions as a receptor for antigen.

c) IgD does not bind complement





IgE-Structure

- IgE exists as a monomer and has an extra domain in the constant region.

IgE

- Mediates type I hypersensitivity
- Monomeric
- Major functions / applications
  - associated with anaphylaxis
  - plays a role in immunity to helminthic parasites

Serodiagnosis of infectious and non infectious allergies (e.g., allergic bronchopulmonary aspergillosis, parasitic diseases)

Summary

- Immunoglobulins are glycoproteins
- There are five immunoglobulins based on variations in the heavy chain.
- IgG is the only antibody for placental transfer of immunity.
- Ig M is the most potent agglutinating antibody.
- Ig A acts as a mucosal barrier.
- IgE is the antibody for allergies.
- IgD and IgM are present on the surface of B lymphocytes.

Functions of Immunoglobulins- an overview