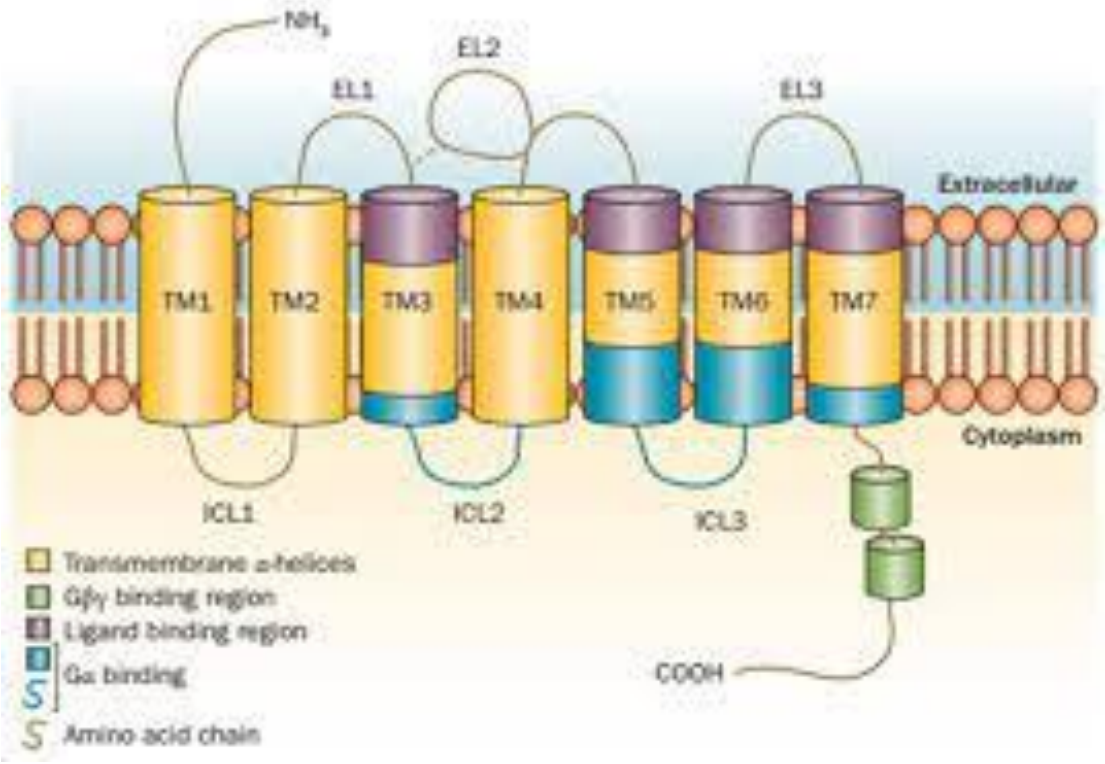
Biology of Immune System (22Z00C32)

GPCRs in innate immunity

GPCR

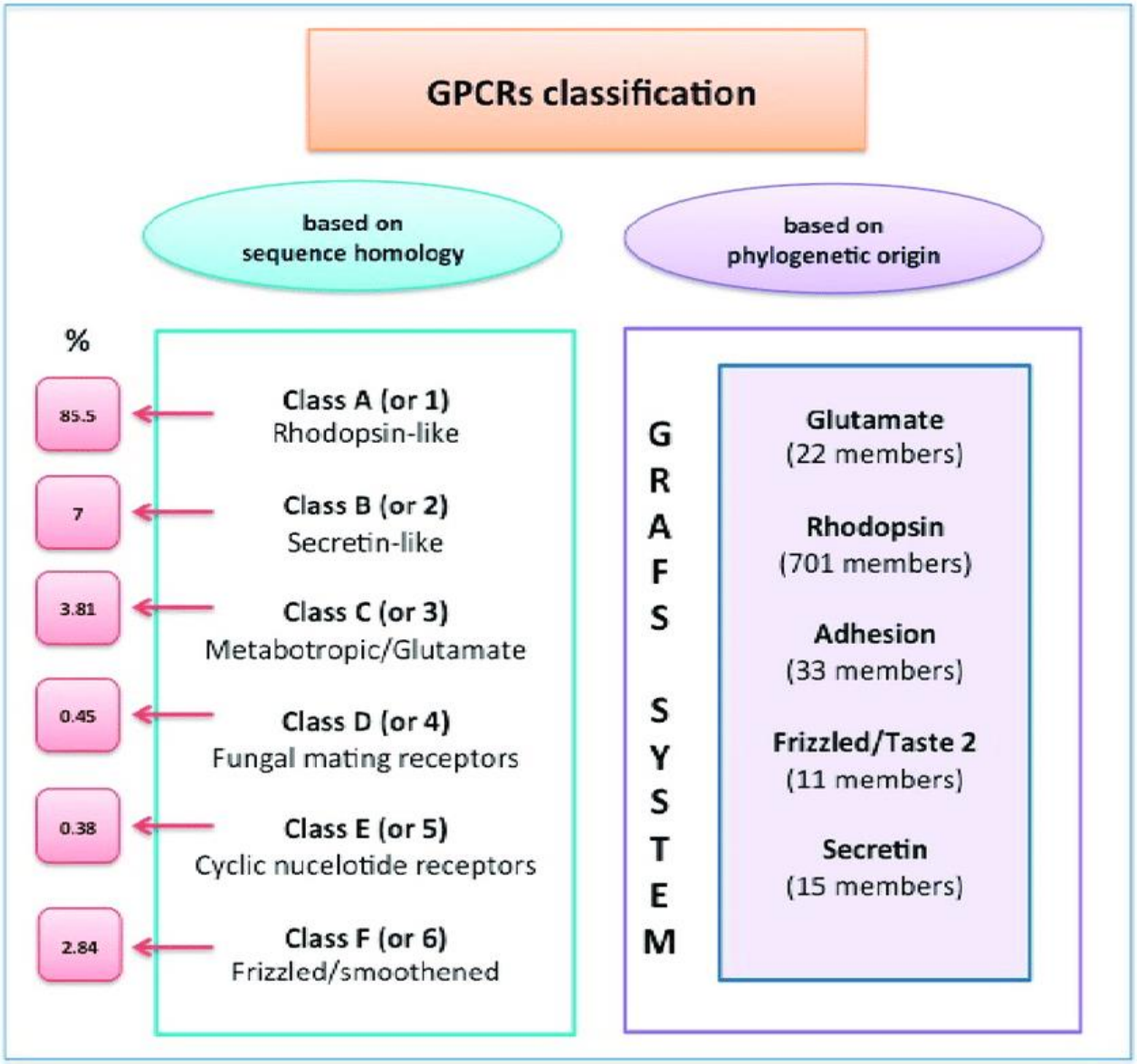
- Cell surface receptors in eukaryotes
- Ligand-coupled proteins - found in the transmembrane region of the cell surface and function primarily as transducers of extracellular stimuli into intracellular signals that elicit cellular responses.
- In humans, over 800 GPCRs have been identified in the genome (>3% of human genome) and are associated with various ligands such as hormones, neurotransmitters, growth factors, chemokines, ions, odorant molecules, and even light photons.
- These ligands are known to bind to only around 200–300 GPCRs, while the remaining GPCRs are considered orphan receptors as no ligand or function has been identified so far. Many of the remaining GPCRs are thought to be sensory in function

- GPCRs have a common structure of seven transmembrane α-helical segments (H1–H7) joined with three intracellular (I1, I2, and I3) and three extracellular (E1, E2, and E3) loops, an extracellular N-, and an intracellular C-terminus.

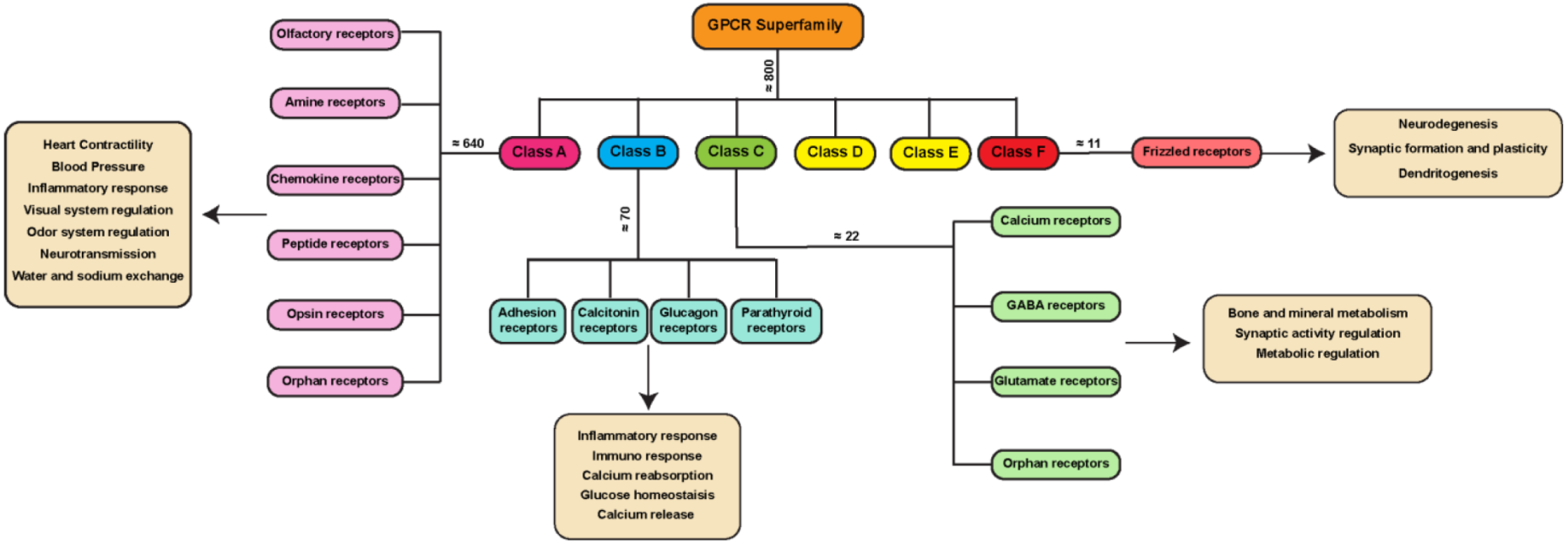


G-protein coupled receptors (GPCRs) classification.

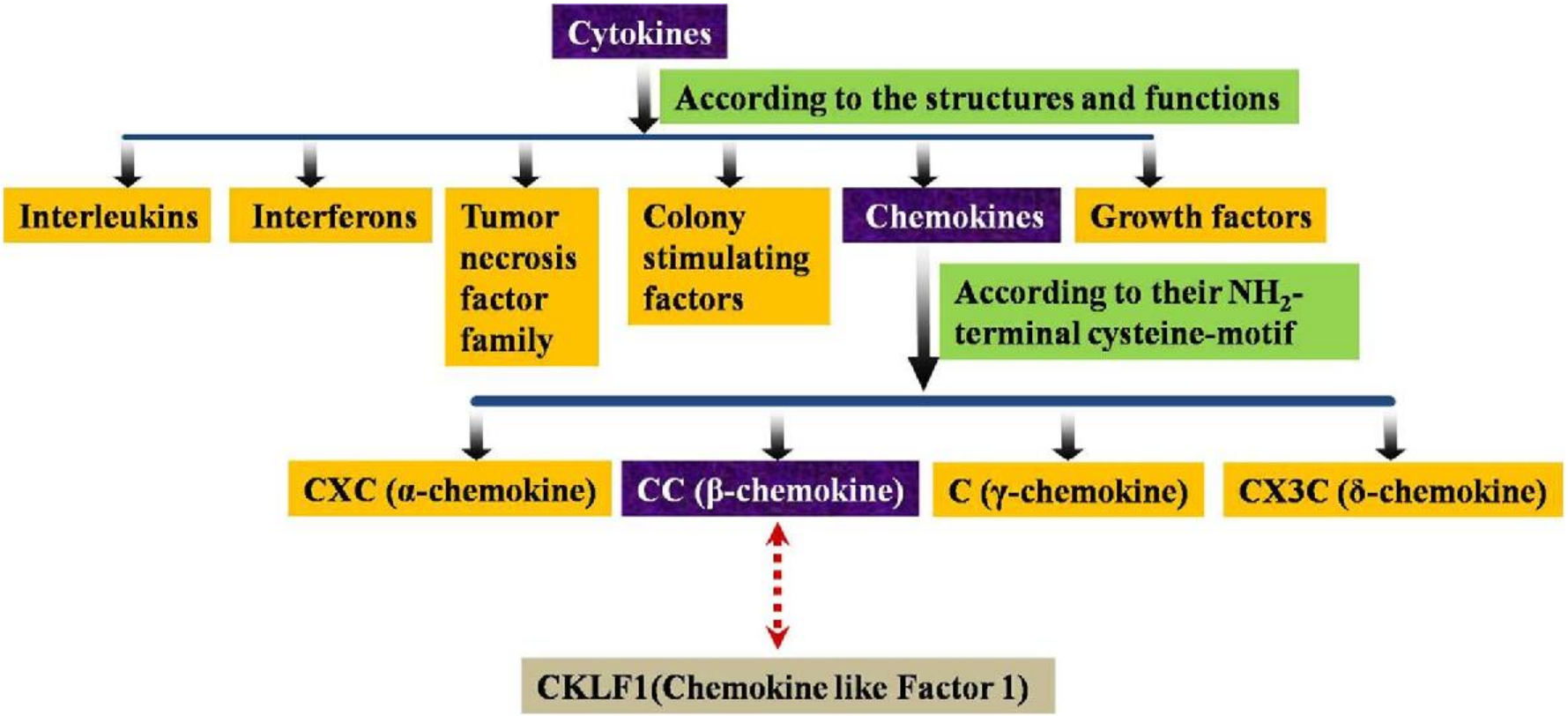
The International Union of Pharmacology (IUPHAR) classification (left column) applies to both vertebrates and invertebrates **Class D and E are unique to invertebrates**



The GRAPH system applies specifically to vertebrates

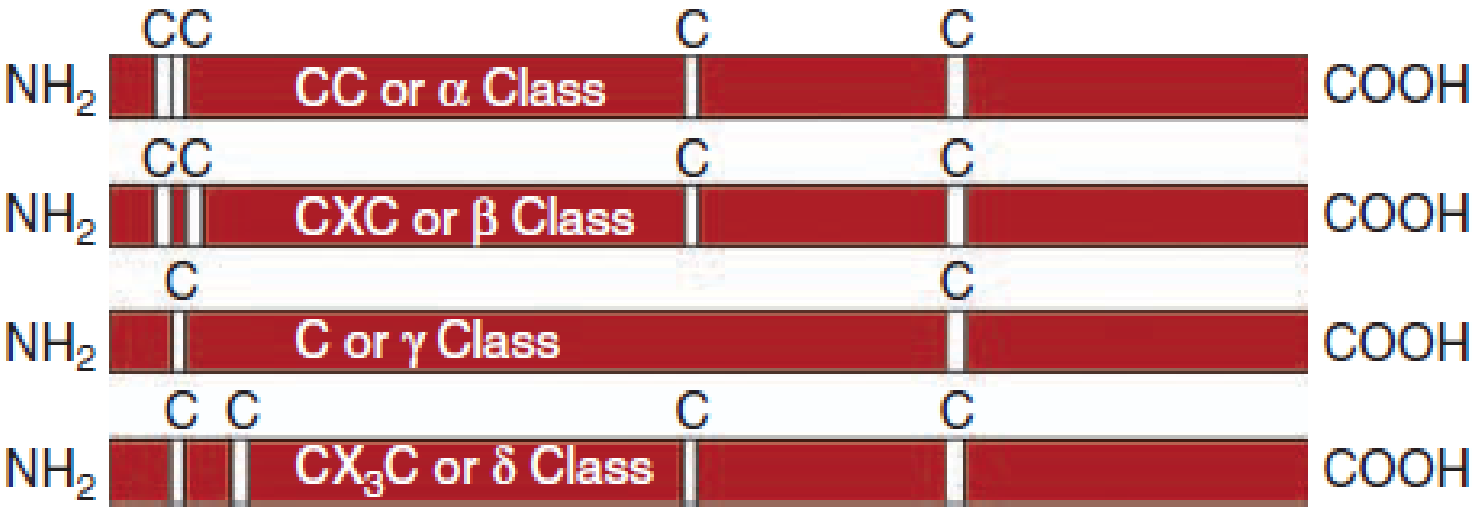

GPCR Superfamily
≈ 800
Class A
Class B
Class C
Class D
Class E
Class F
≈ 640
≈ 11
Olfactory receptors
Amine receptors
Chemokine receptors
Peptide receptors
Opsin receptors
Orphan receptors
Heart Contractility
Blood Pressure
Inflammatory response
Visual system regulation
Odor system regulation
Neurotransmission
Water and sodium exchange
Frizzled receptors
Neurodegenesis
Synaptic formation and plasticity
Dendritogenesis
≈ 70
Adhesion receptors
Calcitonin receptors
Glucagon receptors
Parathyroid receptors
Inflammatory response
Immuno response
Calcium reabsorption
Glucose homeostaisis
Calcium release
≈ 22
Calcium receptors
GABA receptors
Glutamate receptors
Orphan receptors
Bone and mineral metabolism
Synaptic activity regulation
Metabolic regulation

Cytokines and chemokines



g. 1. Chemokines are a group of cytokines with chemotaxis. CKLF1 may represent a new family of chemokines, so Han et al. named it chemokine like factor

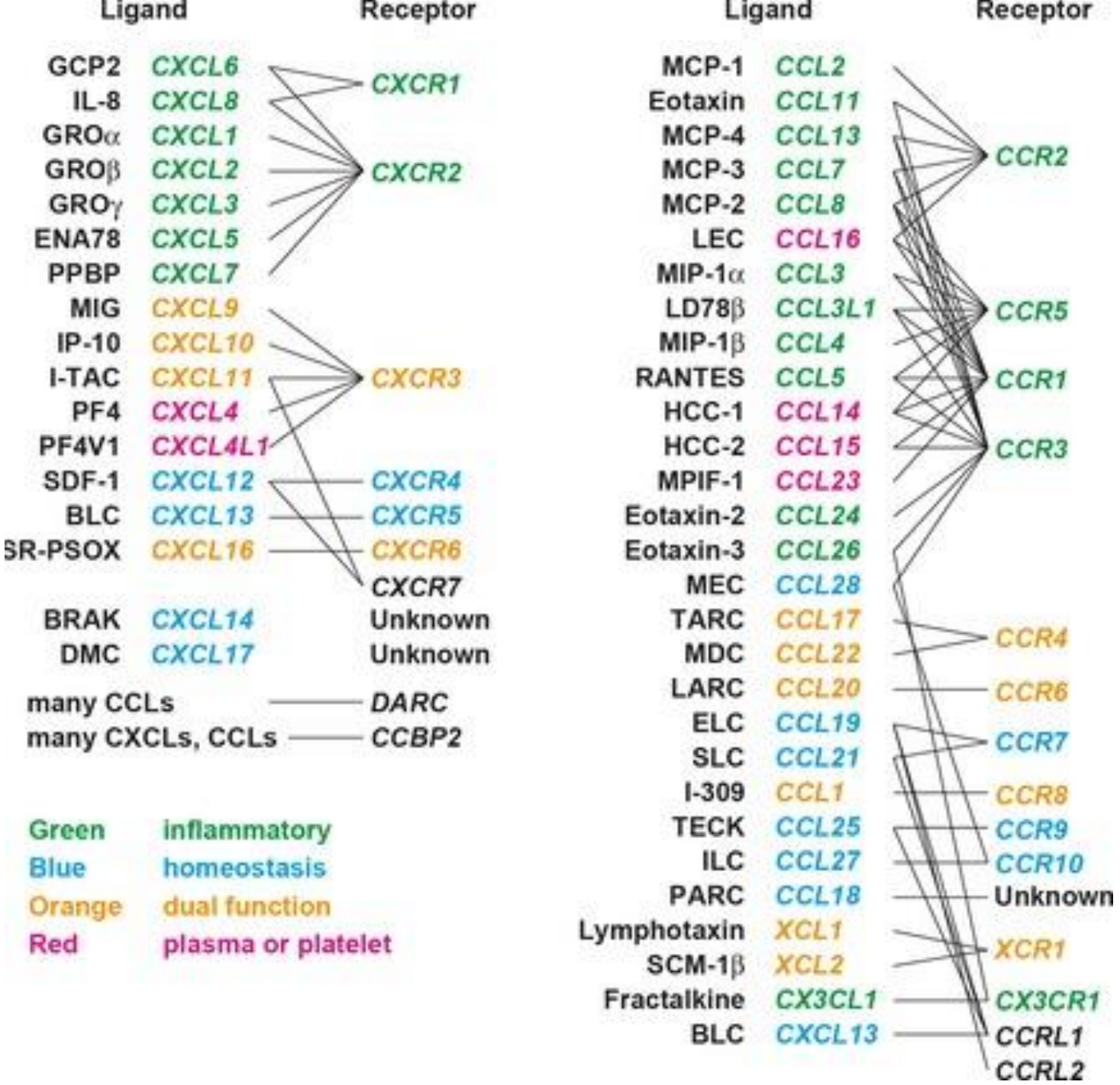
- According to the relative position of cysteine residues, members of this large family have been classified into four subfamilies (CXC, CC, C and CX3C).
- by the **position of four conserved cysteine residues**



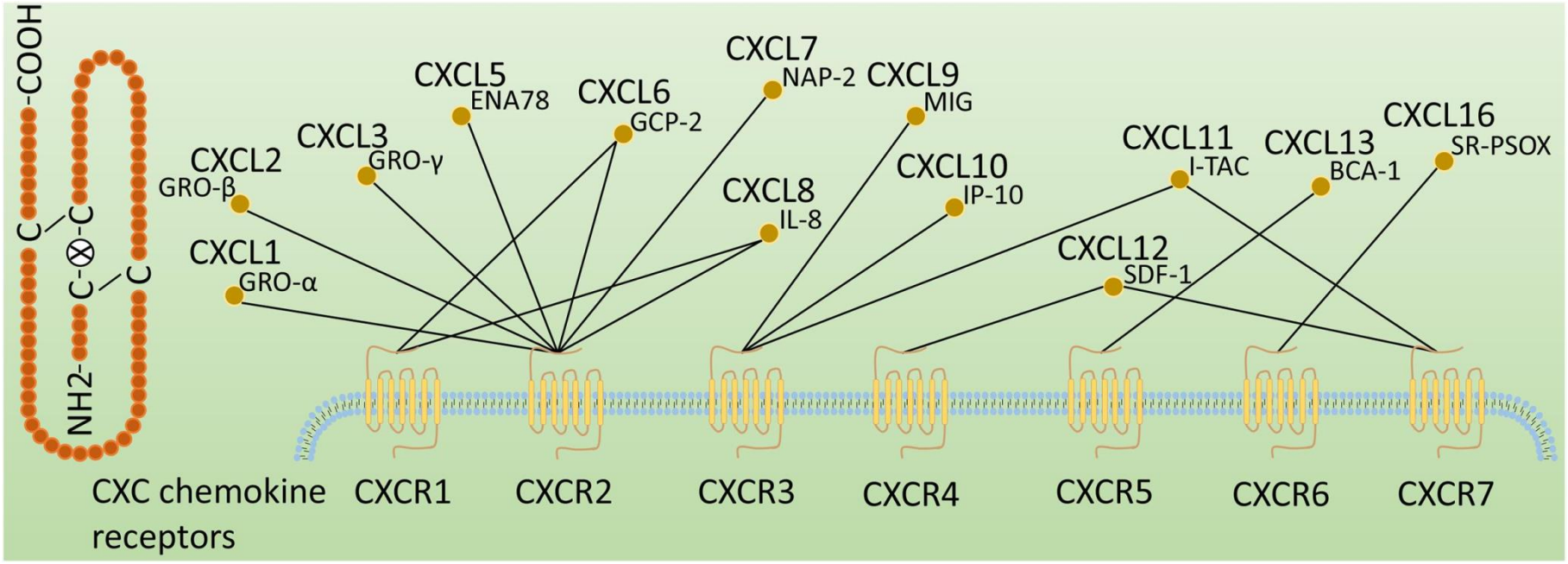
CXC	CC	C	CX3C
CXCR1	CCR1	CX CR1	CX3 CR1
CXCR2	CCR2		
CXCR3	CCR3		
CXCR4	CCR4		
CXCR5	CCR5		
CXCR6	CCR6		
	CCR7		
	CCR8		
	CCR9		
	CCR10		

Inflammatory Disease	Infiltrate	Chemokine
Acute respiratory distress syndrome	Neutrophil	Interleukin-8; GRO-α, -β, -γ; ENA-78
 Asthma	Eosinophil, T cell, monocyte, basophil	MCP-1, -4; MIP-1α; eotaxin; RANTES
Bacterial pneumonia	Neutrophil	Interleukin-8, ENA-78
Sarcoidosis	T cell, monocyte	IP-10
 Glomerulonephritis	Monocyte, T cell, neutrophil	MCP-1, RANTES, IP-10
Rheumatoid arthritis  Osteoarthritis	Monocyte, neutrophil	MIP-1α, MCP-1, interleukin-8, ENA-78
		MIP-1β
 Atherosclerosis	T cell, monocyte	MCP-1, -4; IP-10
 Inflammatory bowel disease	Monocyte, neutrophil, T cell, eosinophil	MCP-1, MIP-1α, eotaxin, IP-10, interleukin-8
 Psoriasis	T cell, neutrophil	MCP-1, IP-10, MIG, GRO-β, interleukin-8
 Bacterial meningitis	Neutrophil, monocyte	Interleukin-8; GRO-α; MCP-1; MIP-1α, -1β
Viral meningitis	T cell,	MCP-1,

- There are some nonconforming chemokines:
  - **lymphotactin** has only **one pair of cysteines** and a single disulfi de bond
  - fractalkine has a CXXXC motif at the N-terminus
- **Fractalkine** is also unusual in that it is produced attached to a cell-bound mucin stalk, a property shared by the CXC chemokine CXCL16
- This allows them to also function as adhesion molecules, tethering cells expressing the cognate receptor.
- **The Duffy antigen receptor for chemokines** (DARC) which can bind chemokines of both classes and has a role in clearance of chemokines.
- This receptor is present on erythrocytes and endothelial cells, whereas a second receptor, D6 is located primarily on the lymphatic endothelium and is involved in the selective uptake of inflammatory chemokines


Ligand
Receptor
GCP2 CXCL6
IL-8 CXCL8
GROα CXCL1
GROβ CXCL2
GROγ CXCL3
ENA78 CXCL5
PPBP CXCL7
MIG CXCL9
IP-10 CXCL10
I-TAC CXCL11
PF4 CXCL4
PF4V1 CXCL4L1
SDF-1 CXCL12
BLC CXCL13
SR-PSOX CXCL16
BRAK CXCL14
DMC CXCL17
many CCLs
many CXCLs, CCLs
CXCR1
CXCR2
CXCR3
CXCR4
CXCR5
CXCR6
CXCR7
Unknown
Unknown
DARC
CCBP2
Green inflammatory
Blue homeostasis
Orange dual function
Red plasma or platelet
Ligand
Receptor
MCP-1 CCL2
Eotaxin CCL11
MCP-4 CCL13
MCP-3 CCL7
MCP-2 CCL8
LEC CCL16
MIP-1α CCL3
LD78β CCL3L1
MIP-1β CCL4
RANTES CCL5
HCC-1 CCL14
HCC-2 CCL15
MPIF-1 CCL23
Eotaxin-2 CCL24
Eotaxin-3 CCL26
MEC CCL28
TARC CCL17
MDC CCL22
LARC CCL20
ELC CCL19
SLC CCL21
I-309 CCL1
TECK CCL25
ILC CCL27
PARC CCL18
Lymphotaxin XCL1
SCM-1β XCL2
Fractalkine CX3CL1
BLC CXCL13
CCR2
CCR5
CCR1
CCR3
CCR4
CCR6
CCR7
CCR8
CCR9
CCR10
Unknown
XCR1
CX3CR1
CCRL1
CCRL2

Classification of CXCR

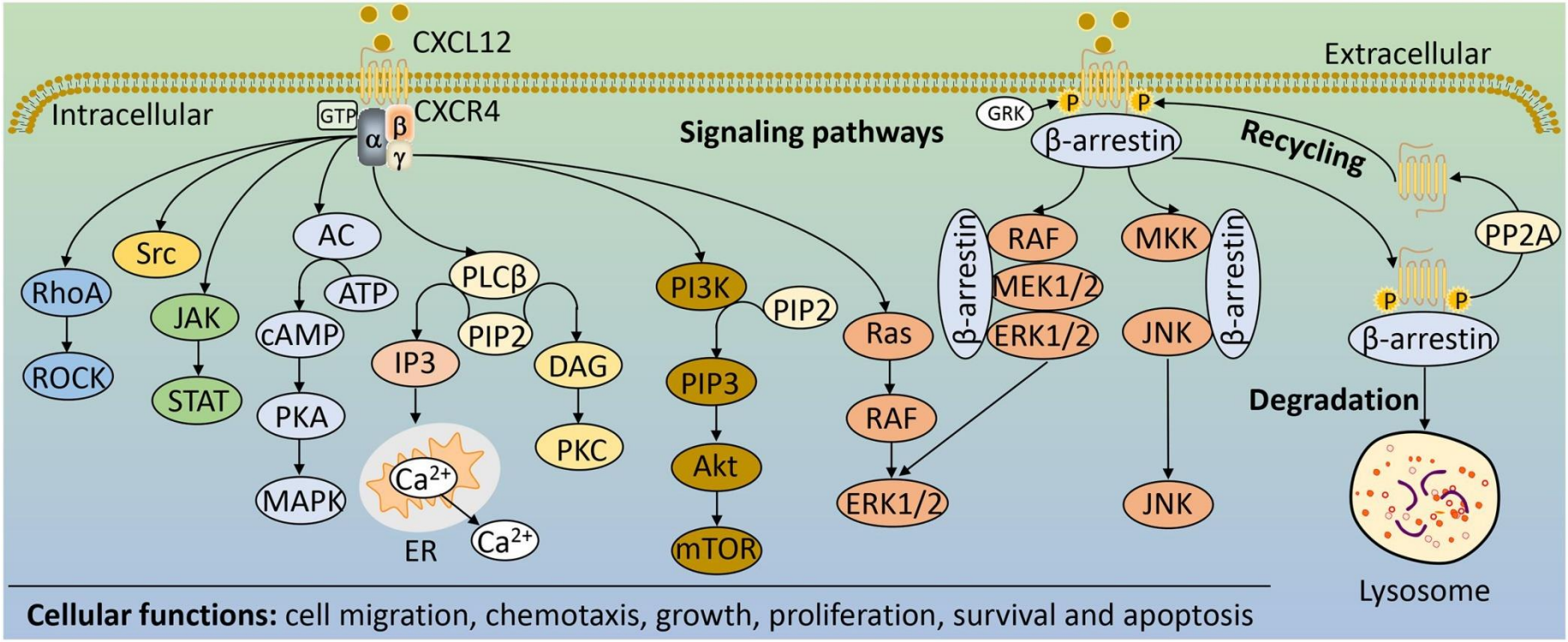


Classification of CXC chemokine receptors

- CXC chemokine receptors are classified **according to the ligands they bind**, followed by an R (representing receptor) and a number corresponding to the order of discovery.

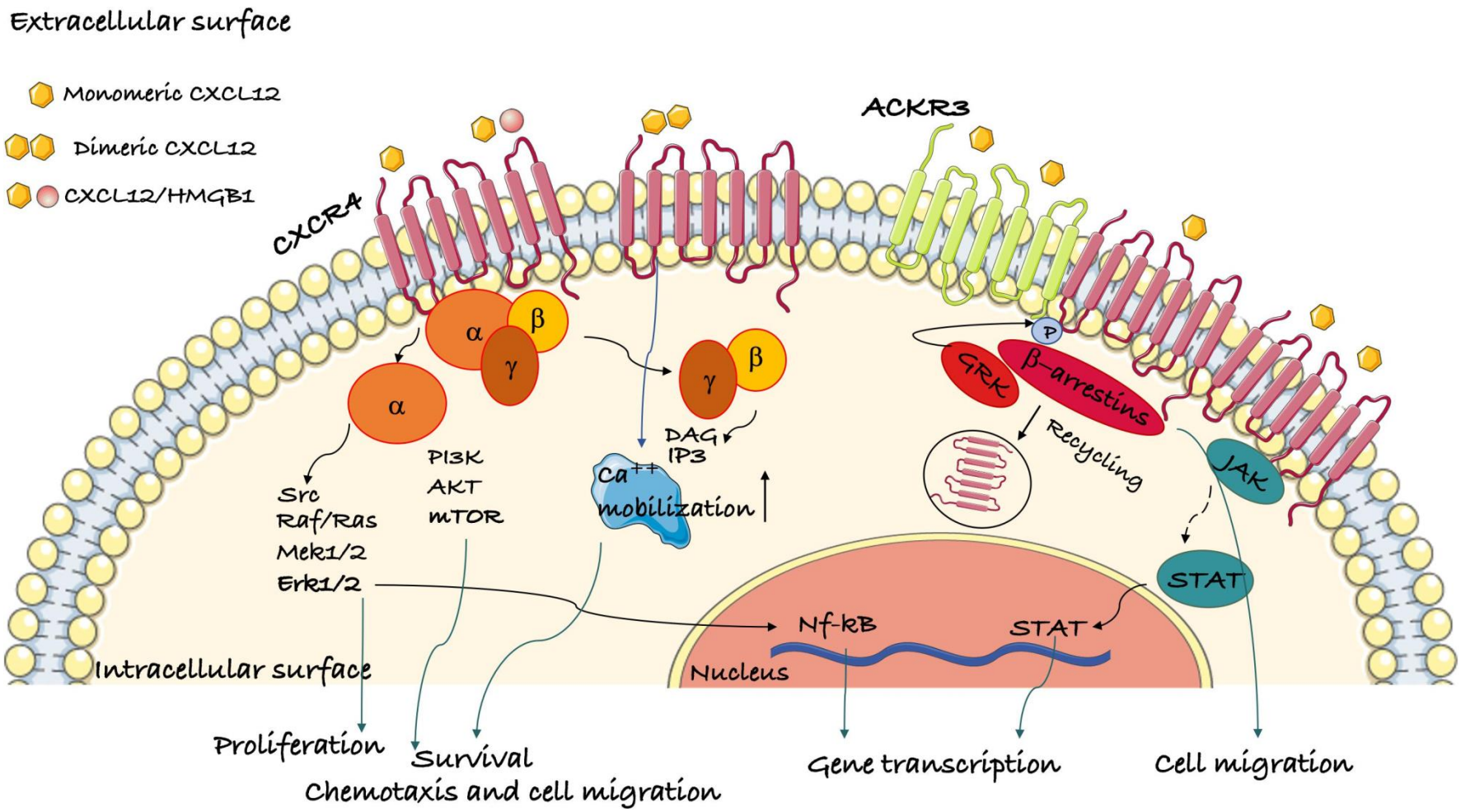
CCRs	Roles
CCR1 & 2	pathogenesis of inflammation and fibrosis
CCR3	angiogenesis and tumors
CCR4	development of hematopoietic and nervous systems, and modulates different cellular functions, including cell migration, chemotaxis, differentiation, growth, activation, proliferation, survival and apoptosis
CCR5	immunomodulation
CCR6 & CCR7	regulation of inflammation and cellular functions

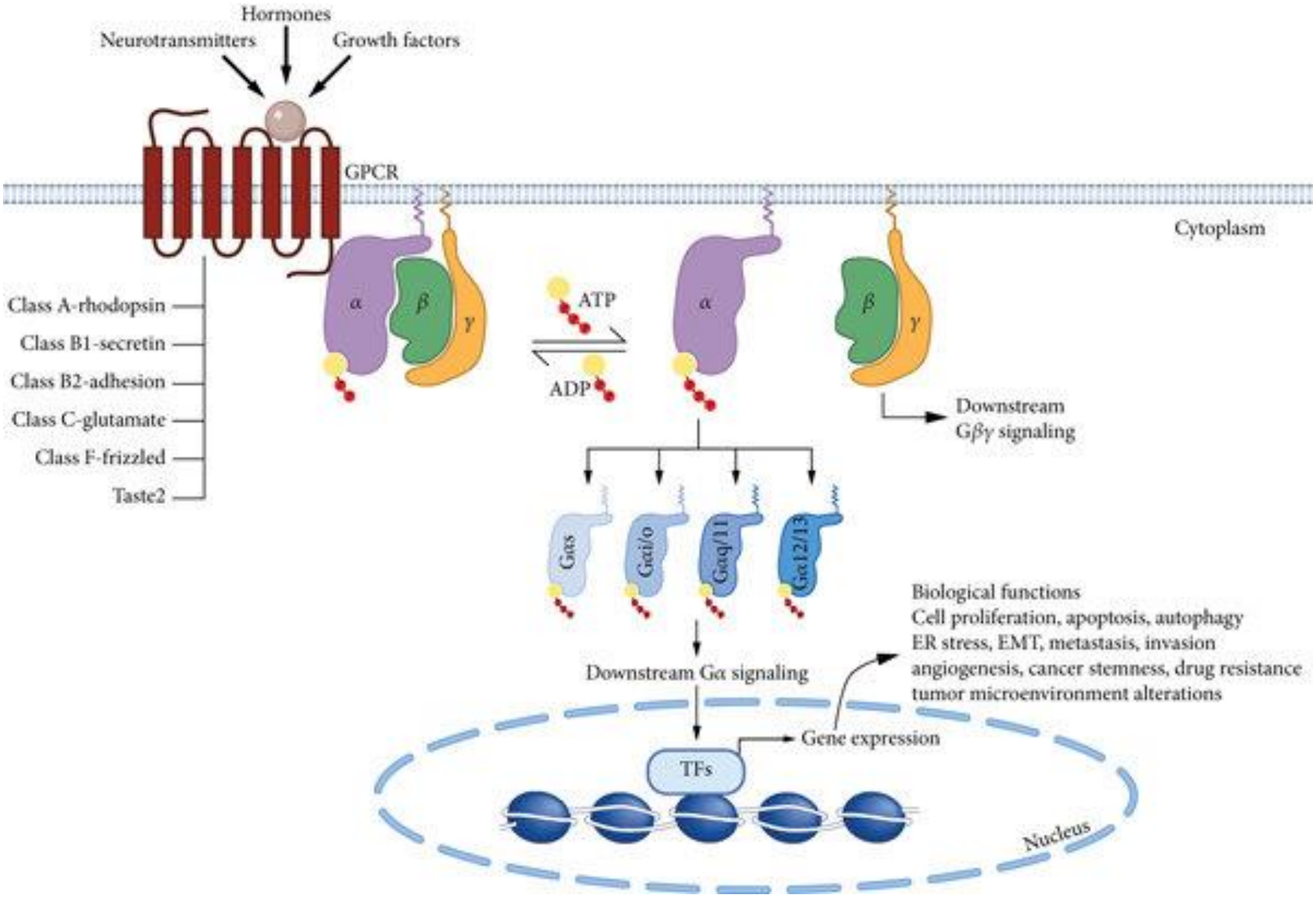
- CXCR4 signaling is mainly mediated by proteins that interact with receptors, including heterotrimeric G proteins, G protein receptor kinases (GRKs) and β-arrestin adapter proteins
- CXCL12 binding to CXCR7 usually leads to β-arrestin mediated signaling



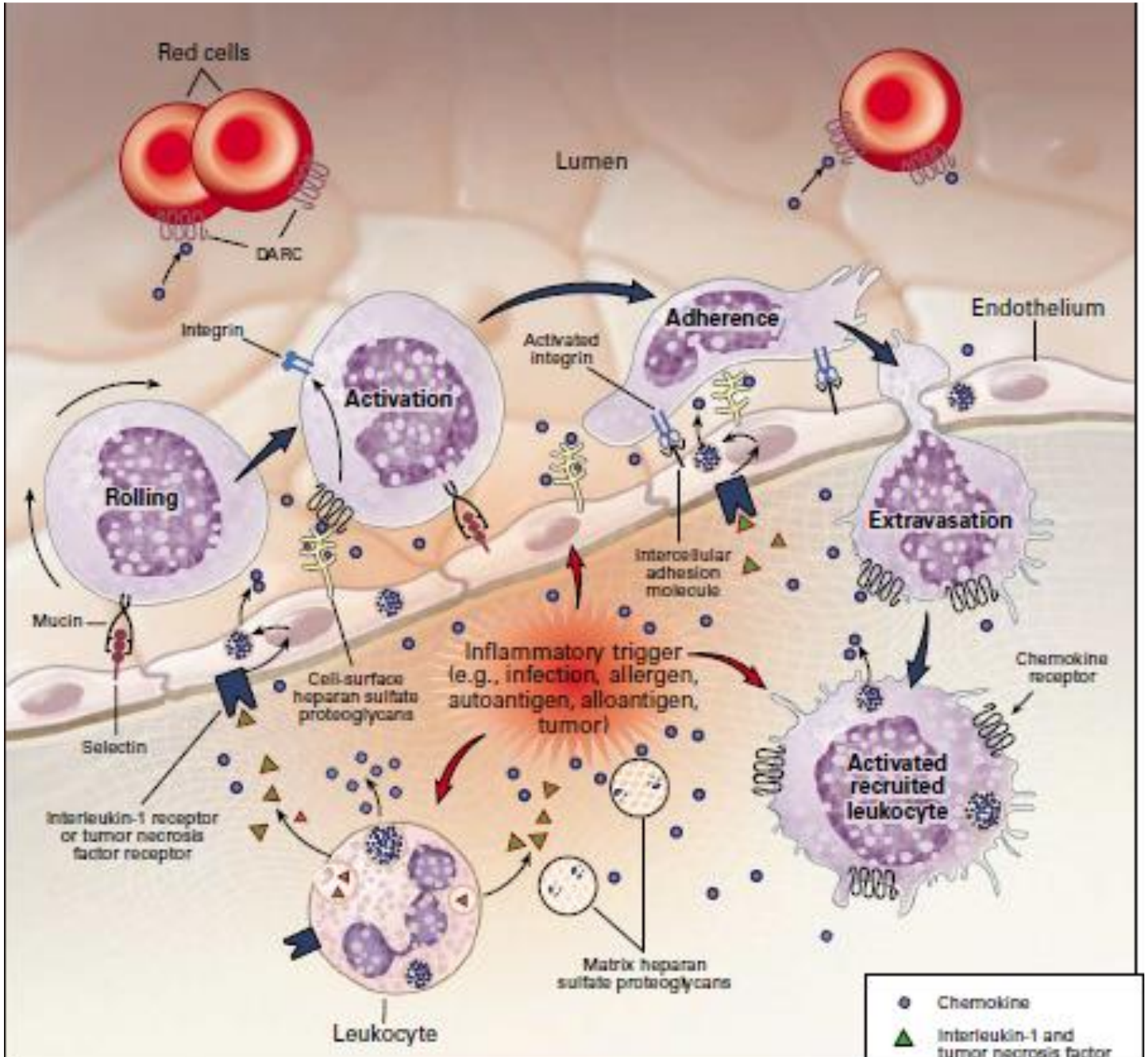
GPCR Activation-Signal Amplification and Inactivation-Desensitization Add Further Regulatory Complexities

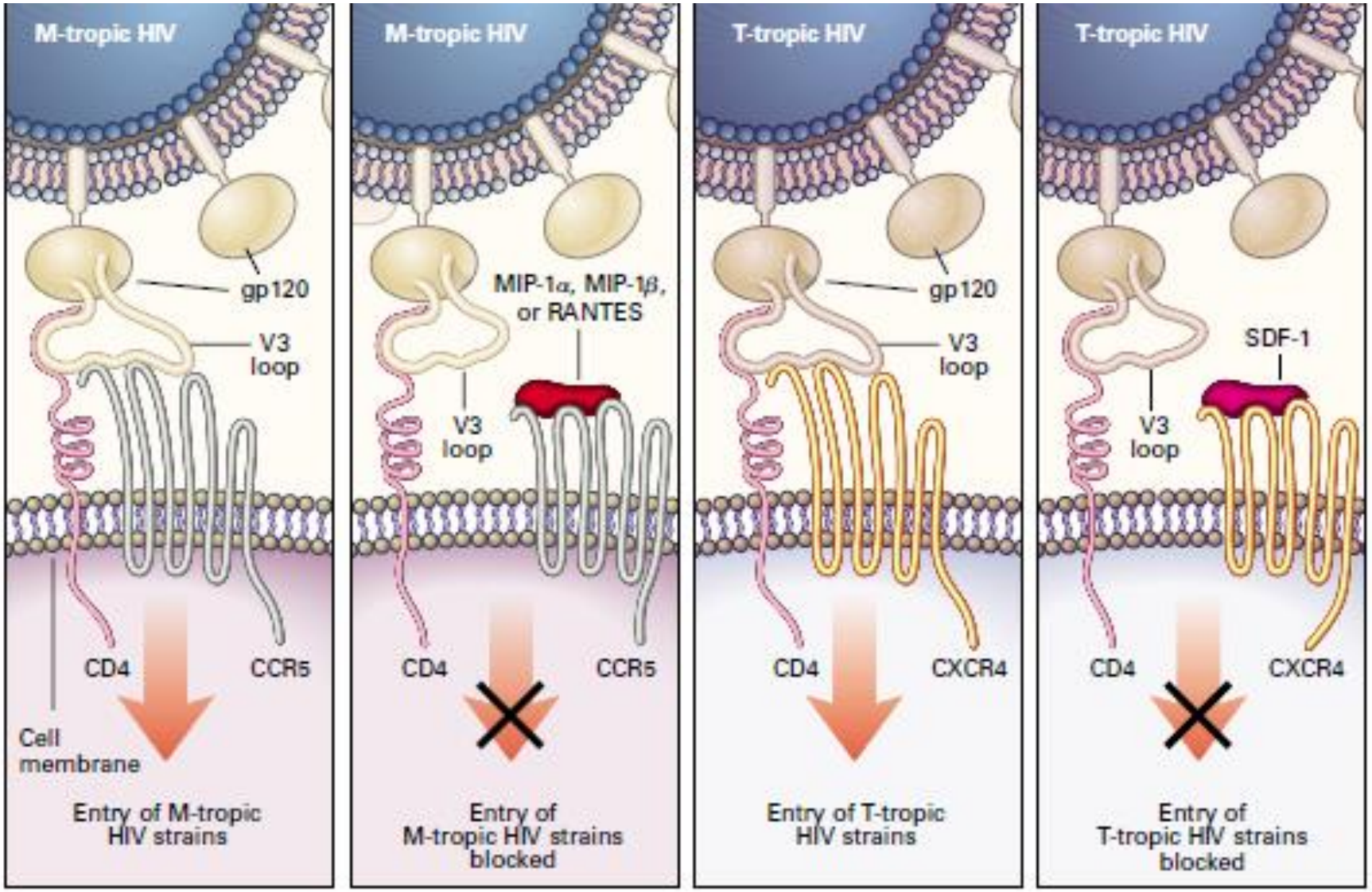
- GPCR receptor activation is triggered by a ligand binding to different domains, according to the GPCR class and to the biochemical proprieties of the ligand; this occurs to stimulate G protein signaling through the conformational change in the seven-transmembrane region of the receptor that enables the insertion of the α5 helix of the Gα subunit.
- WNTs bind to the cysteine-rich domain of the receptor, inducing a molecular switch mechanism that involves the interaction between critical residues in TM6 and TM7 helices
- Most GPCRs can activate different signal cascades in response to extracellular stimuli, thus providing the opportunity to have a diversification of the type of intracellular signaling, for example, through different second messengers. Moreover, the magnitude of the signaling cascade initiated by GPCR is amplified by many orders in each step, for example, through the multiple activation of many adenylyl cyclases by a single G-protein molecule
-

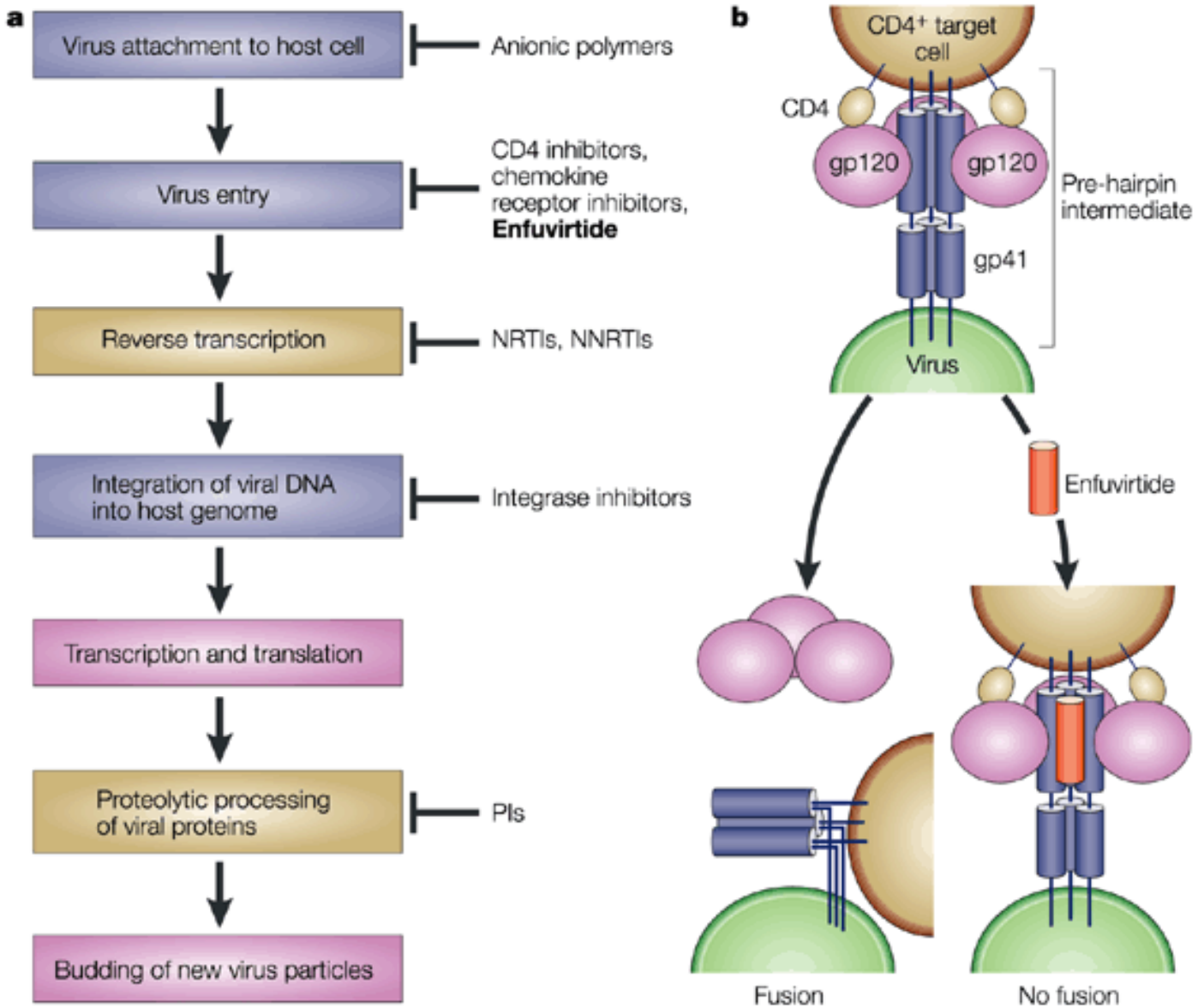

Extracellular surface
Monomeric CXCL12
Dimeric CXCL12
CXCL12/HMGB1
CXCR4
ACKR3
α
β
γ
α
γ
β
P
GRK
β-arrestins
Recycling
JAK
STAT
DAG
IP3
Ca++
mobilization
PI3K
AKT
mTOR
Src
Raf/Ras
Mek1/2
Erk1/2
Nf-kB
STAT
Nucleus
Intracellular surface
Proliferation
Survival
Chemotaxis and cell migration
Gene transcription
Cell migration


Hormones
Neurotransmitters
Growth factors
GPCR
Cytoplasm
Class A-rhodopsin
Class B1-secretin
Class B2-adhesion
Class C-glutamate
Class F-frizzled
Taste2
α
β
γ
ATP
ADP
Downstream
Gβγ signaling
Gαs
Gαi/o
Gαq/11
Gα12/13
Downstream Gα signaling
Biological functions
Cell proliferation, apoptosis, autophagy
ER stress, EMT, metastasis, invasion
angiogenesis, cancer stemness, drug resistance
tumor microenvironment alterations
Gene expression
TFs
Nucleus

ROLE IN LEUKOCYTE MOVEMENT




M-tropic HIV
gp120
V3 loop
CD4
CCR5
Cell membrane
Entry of M-tropic HIV strains
M-tropic HIV
MIP-1α, MIP-1β, or RANTES
V3 loop
CD4
CCR5
Entry of M-tropic HIV strains blocked
T-tropic HIV
gp120
V3 loop
CD4
CXCR4
Entry of T-tropic HIV strains
T-tropic HIV
SDF-1
V3 loop
CD4
CXCR4
Entry of T-tropic HIV strains blocked

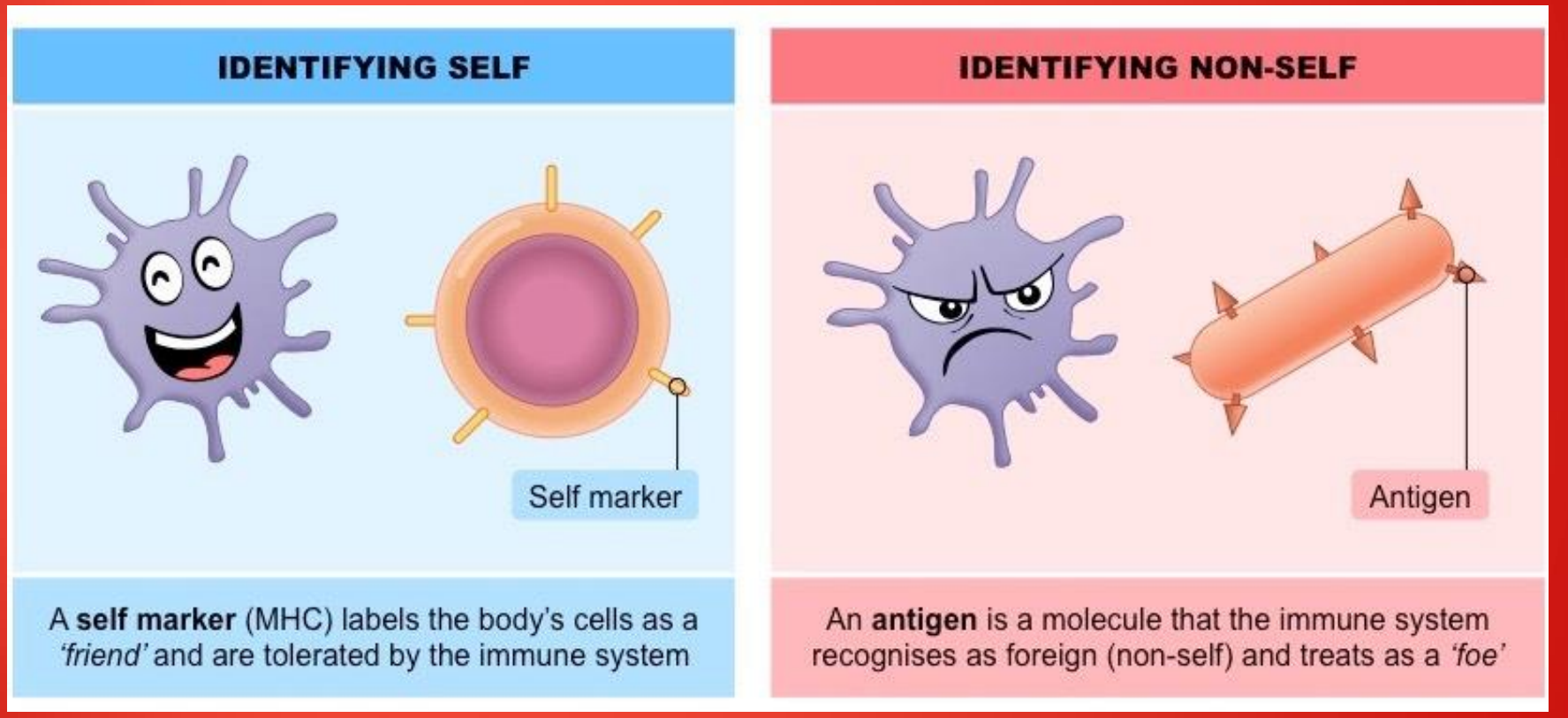

a
Virus attachment to host cell
Anionic polymers
Virus entry
CD4 inhibitors, chemokine receptor inhibitors, Enfuvirtide
Reverse transcription
NRTIs, NNRTIs
Integration of viral DNA into host genome
Integrase inhibitors
Transcription and translation
Proteolytic processing of viral proteins
PIs
Budding of new virus particles
b
CD4+ target cell
CD4
gp120
gp120
gp41
Pre-hairpin intermediate
Virus
Enfuvirtide
Fusion
No fusion

Biology of Immune System
[22ZOOC32]

Structure and Types of Antigens

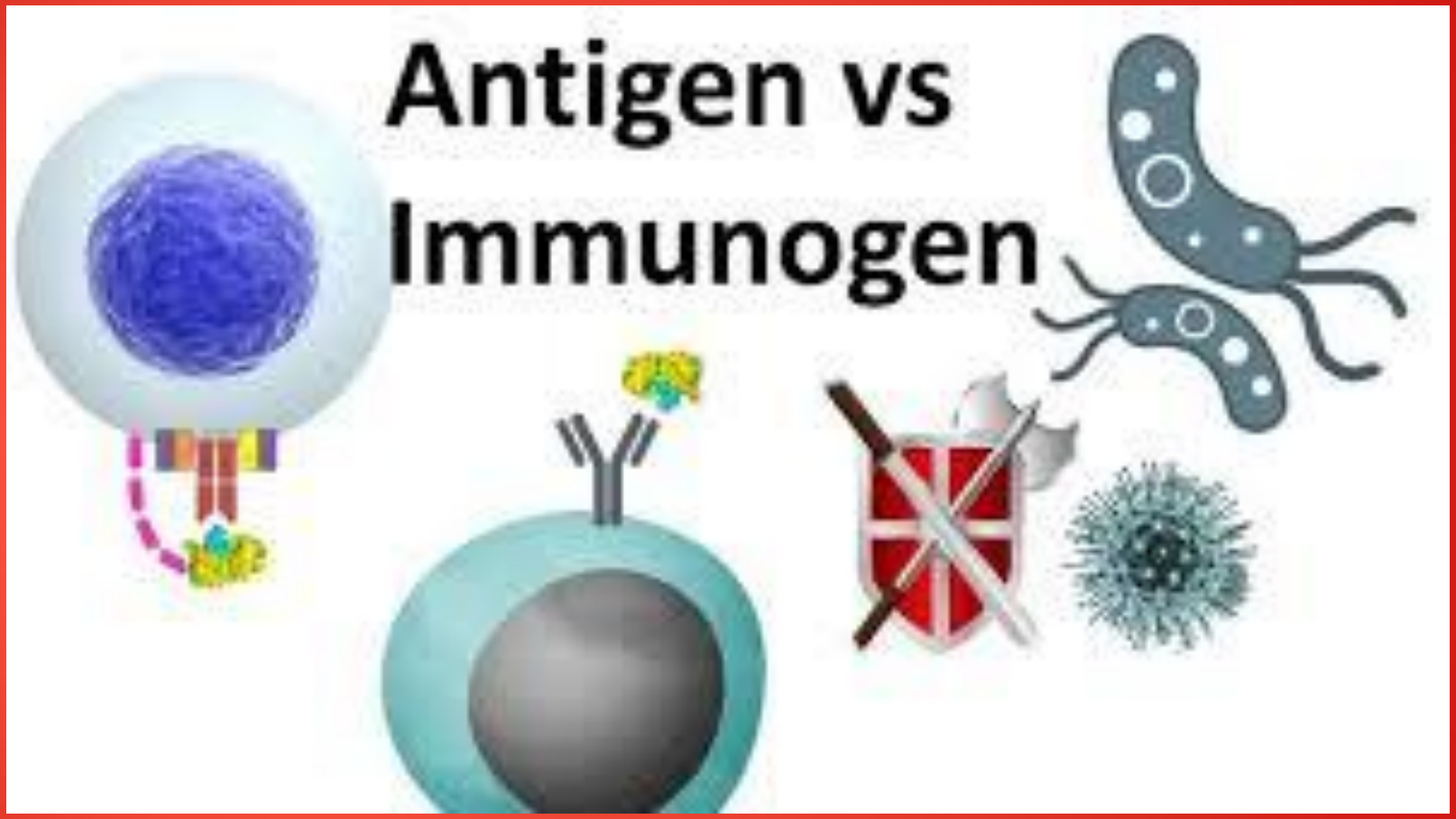
I am coming…

Friend or Foe



Self vs non-self

Antigen vs Immunogen



Substances which stimulate an immune response – immunogens

a molecule or group of molecules which bind specific receptors but may not alone induce an immune response

CHARACTERISTICS OF ANTIGENS AND IMMUNOGENS

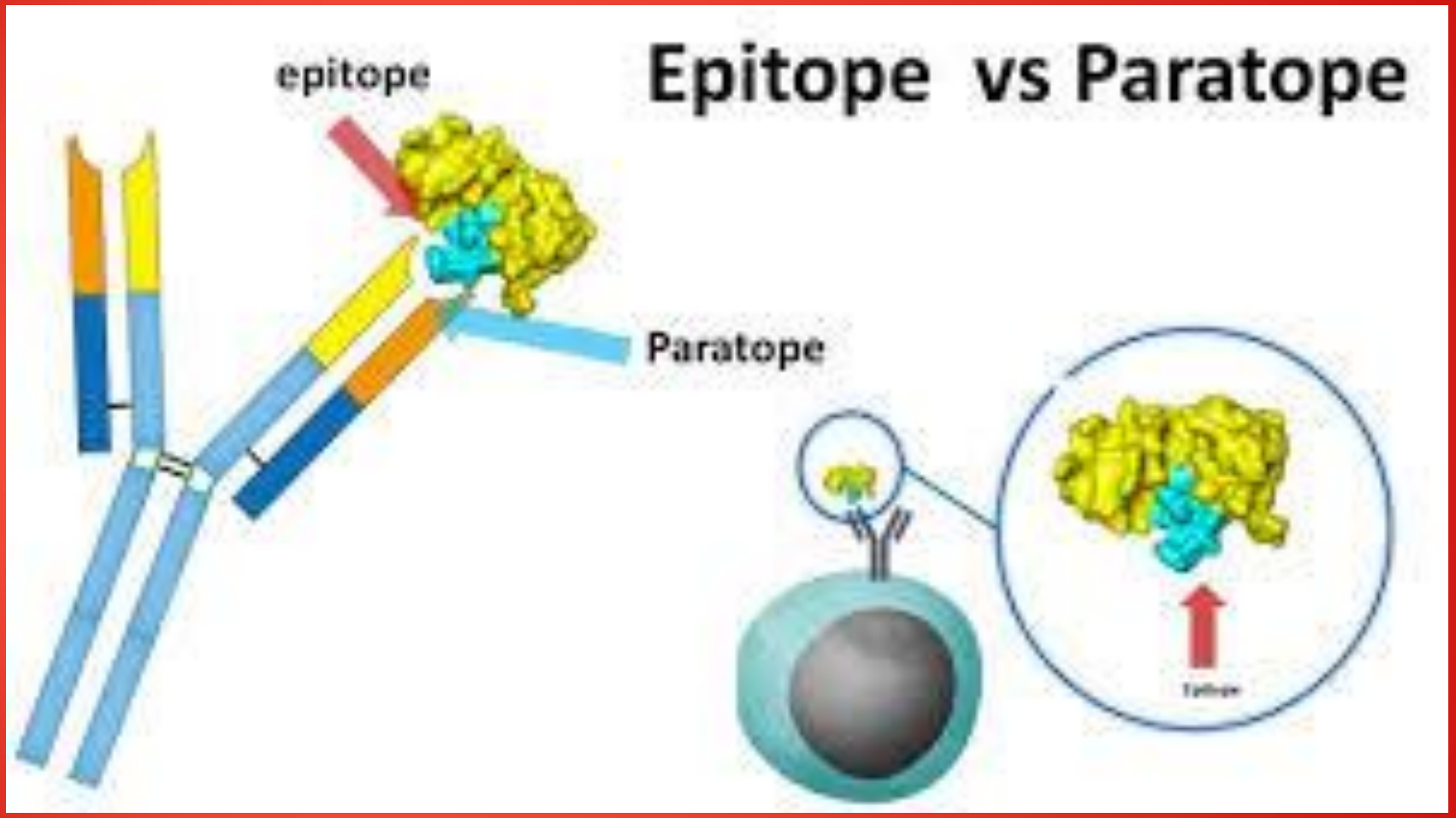
ANTIGENS

1. Any substance that can react with antigenspecific receptors found on the surface of certain white blood cells
2. Interact in a specific way with the immune system, it cannot by itself stimulate an immune response; other stimuli are required

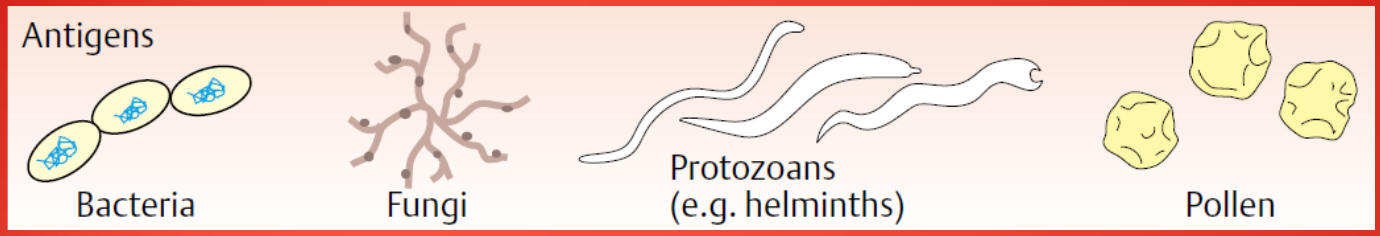
IMMUNOGENS

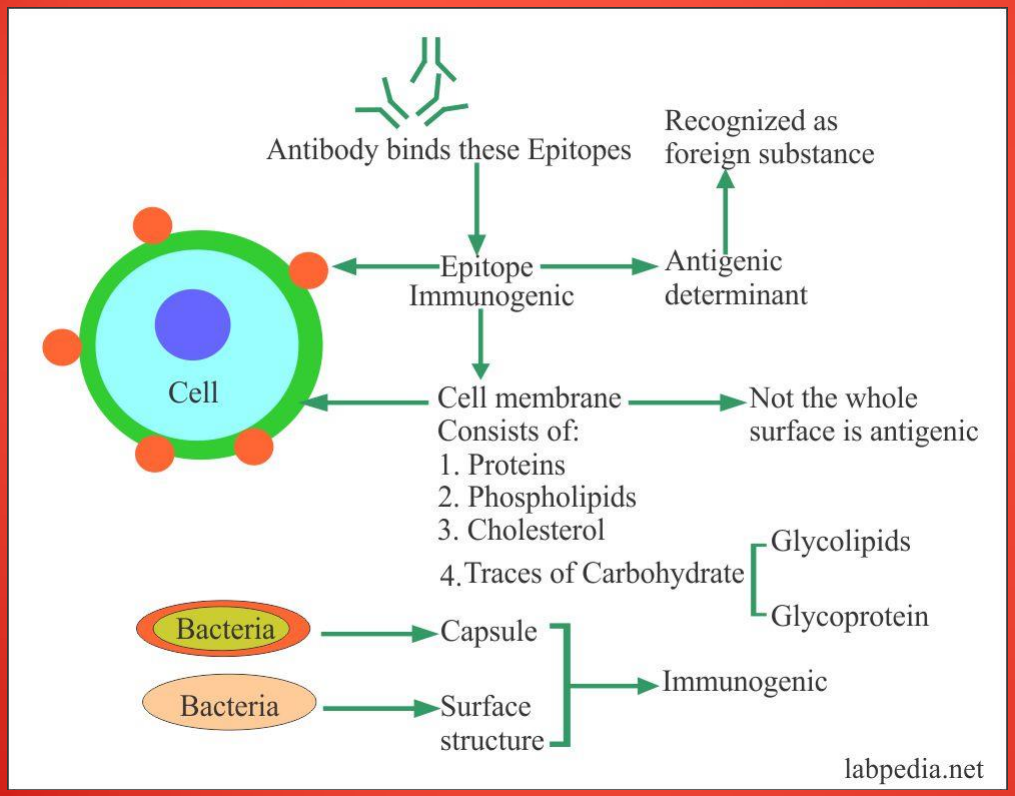
1. Any molecule (or group of molecules) that can induce an immune response
2. **All immunogens are antigens but not all antigens are immunogens**

Epitope vs Paratope



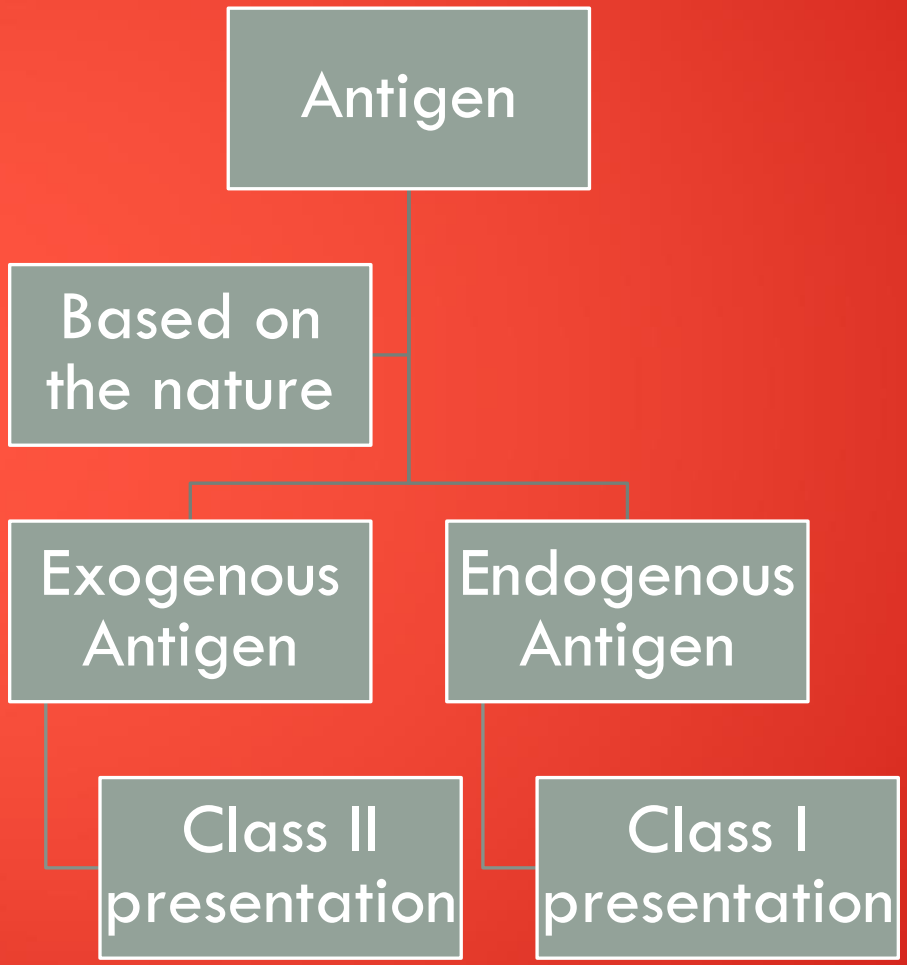
Antigens



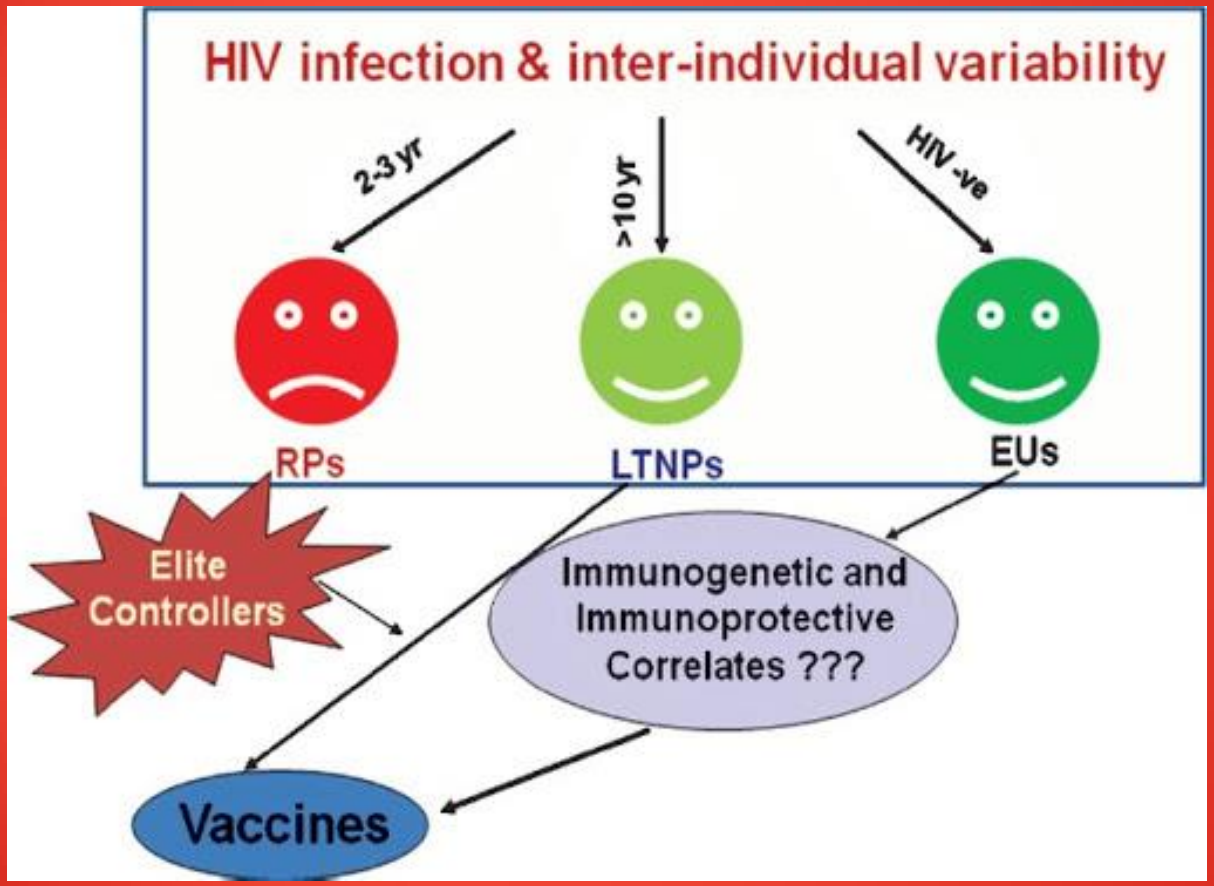


- An antigen may be protein, lipid, carbohydrate or any combination of these
- may be soluble or particulate
- simple or complex with many different antigenic determinants
  - a bacterium may have antigenic determinants on the cell wall, the flagellum or on pili
- many different antigenic determinants each of which comprises a small number of amino acids or sugar residues

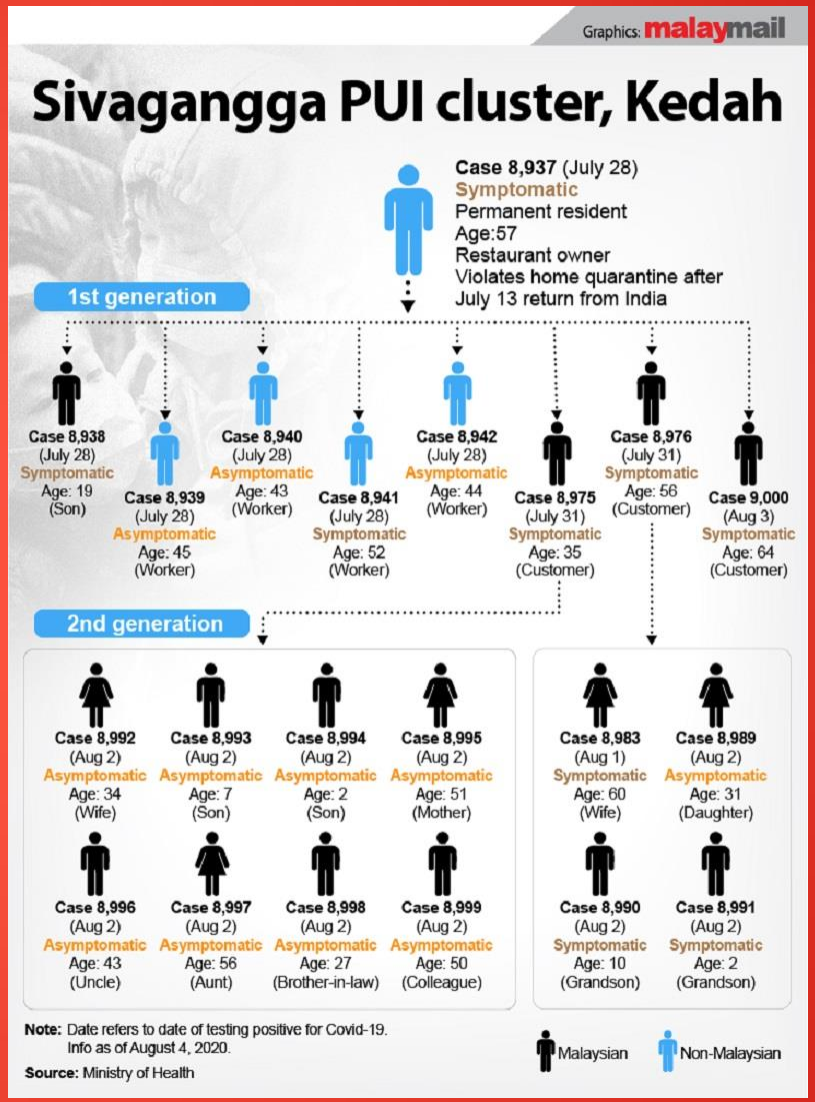
Classification of Antigens



If the same antigen is introduced in different population…

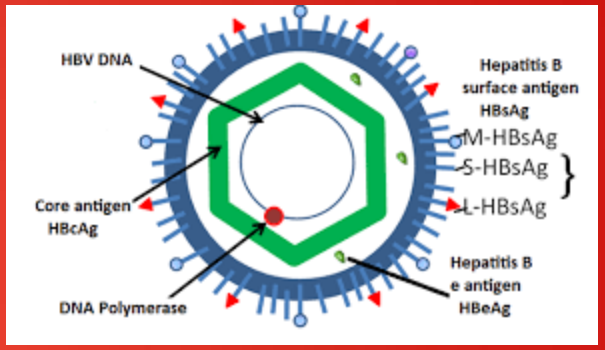


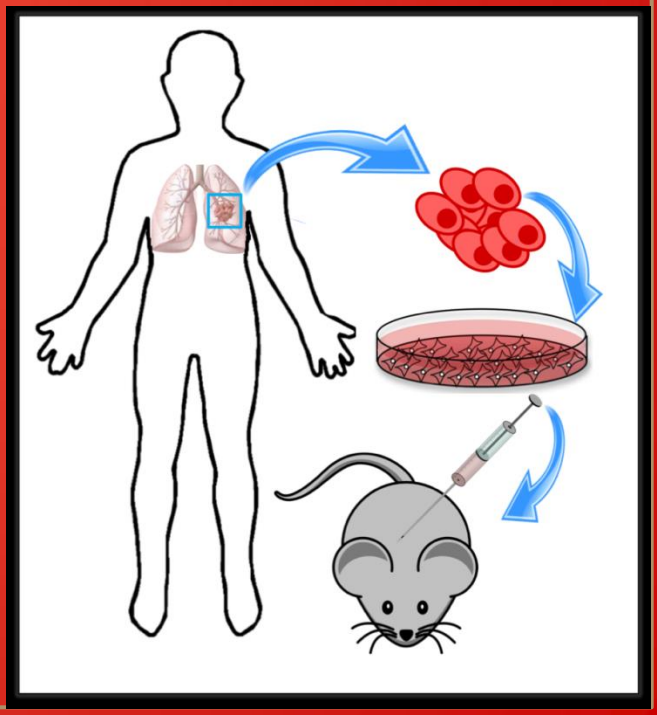
- The epitope recognition is quite different
- Range of recognition under genetic control

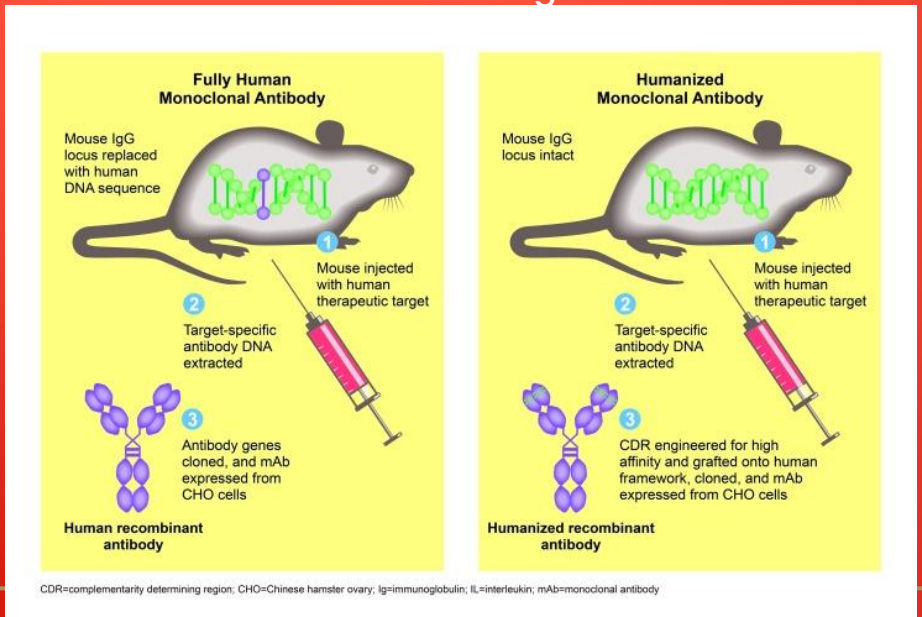

Graphics: malaymail
Sivagangga PUI cluster, Kedah
Case 8,937 (July 28)
Symptomatic
Permanent resident
Age:57
Restaurant owner
Violates home quarantine after
July 13 return from India
1st generation
Case 8,938 (July 28) Symptomatic Age: 19 (Son)
Case 8,939 (July 28) Asymptomatic Age: 45 (Worker)
Case 8,940 (July 28) Asymptomatic Age: 43 (Worker)
Case 8,941 (July 28) Symptomatic Age: 52 (Worker)
Case 8,942 (July 28) Asymptomatic Age: 44 (Worker)
Case 8,975 (July 31) Symptomatic Age: 35 (Customer)
Case 8,976 (July 31) Symptomatic Age: 56 (Customer)
Case 9,000 (Aug 3) Symptomatic Age: 64 (Customer)
2nd generation
Case 8,992 (Aug 2) Asymptomatic Age: 34 (Wife)
Case 8,993 (Aug 2) Asymptomatic Age: 7 (Son)
Case 8,994 (Aug 2) Asymptomatic Age: 2 (Son)
Case 8,995 (Aug 2) Asymptomatic Age: 51 (Mother)
Case 8,996 (Aug 2) Asymptomatic Age: 43 (Uncle)
Case 8,997 (Aug 2) Asymptomatic Age: 56 (Aunt)
Case 8,998 (Aug 2) Asymptomatic Age: 27 (Brother-in-law)
Case 8,999 (Aug 2) Asymptomatic Age: 50 (Colleague)
Case 8,983 (Aug 1) Symptomatic Age: 60 (Wife)
Case 8,989 (Aug 2) Asymptomatic Age: 31 (Daughter)
Case 8,990 (Aug 2) Symptomatic Age: 10 (Grandson)
Case 8,991 (Aug 2) Symptomatic Age: 2 (Grandson)
Note: Date refers to date of testing positive for Covid-19.
Info as of August 4, 2020.
Source: Ministry of Health
Malaysian
Non-Malaysian

Surface antigen

- Injecting human cells into mice (where they are recognised as foreign) meant that mice produced antibodies to the different molecules on the surfaces of the cells.
- principle that was exploited in the production of monoclonal antibodies.
- a molecule on the surface of a cell (i.e. inserted through the membrane of the cell) may also be referred to as a surface antigen







FACTORS AFFECTING IMMUNOGENICITY

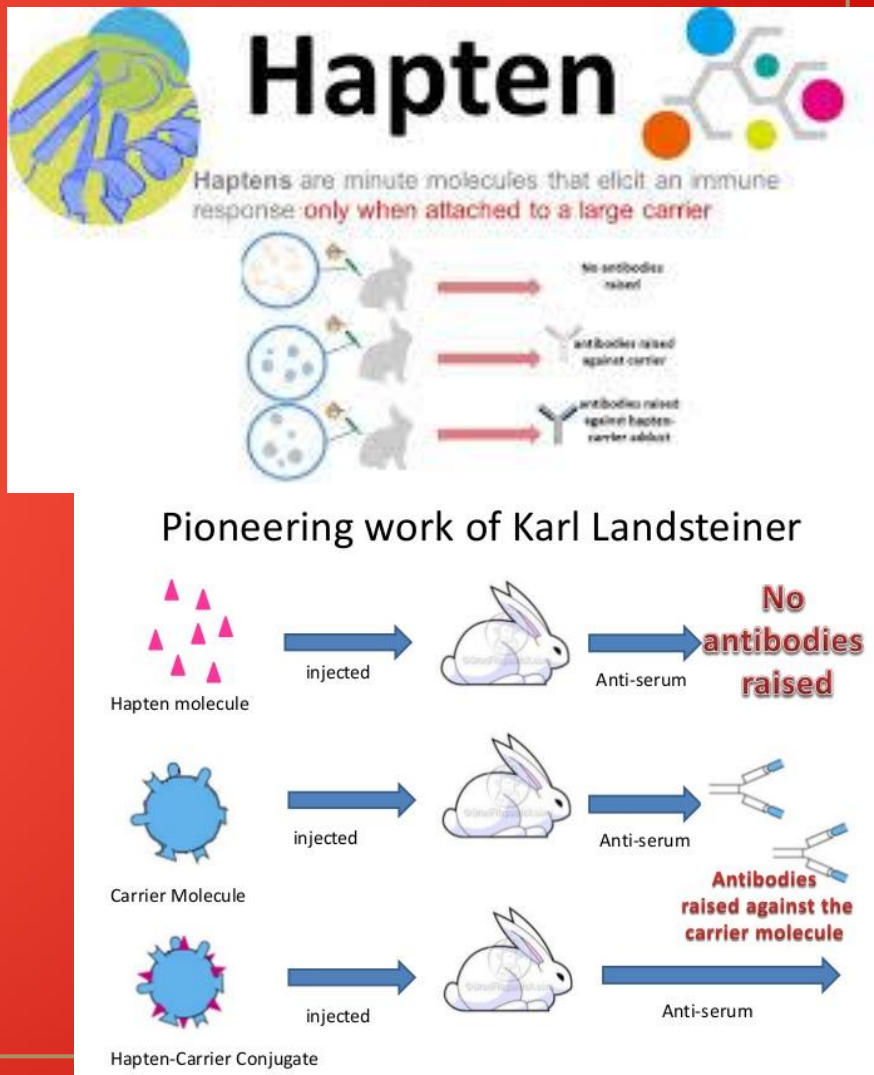
- FOREIGNNESS
- SIZE
- CHEMICAL COMPLEXITY
- ROUTE OF ADMINISTRATION
- DOSE
- HOST GENETIC MAKE-UP

FOREIGNNESS

- Design of the immune system – To eliminate anything – not belong to the normal healthy body
- Capable of distinguishing between ‘self’ and ‘non-self’
- Recognised as foreign (not in related)
- a molecule may not be immunogenic in the normal host, if it is introduced into a different host, it may become so…
- Eg. Rabbit serum albumin injected into a rabbit will not be immunogenic. But the same molecule injected into a dog will stimulate an immune response

SIZE

- The size of a molecule appears to affect its immunogenicity.
- substances with molecular weights >100 kDa are potent immunogens,
- <10 kDa may not stimulate an immune response at all.
- Some small molecules may contain antigenic determinants and can bind antigen-specific receptors on cells, they are not large enough to stimulate an effective immune response.
- These molecules may be made immunogenic by attaching them to a larger molecule known as a **carrier.**
- Under these circumstances, the small antigenic molecule is known as a **hapten**

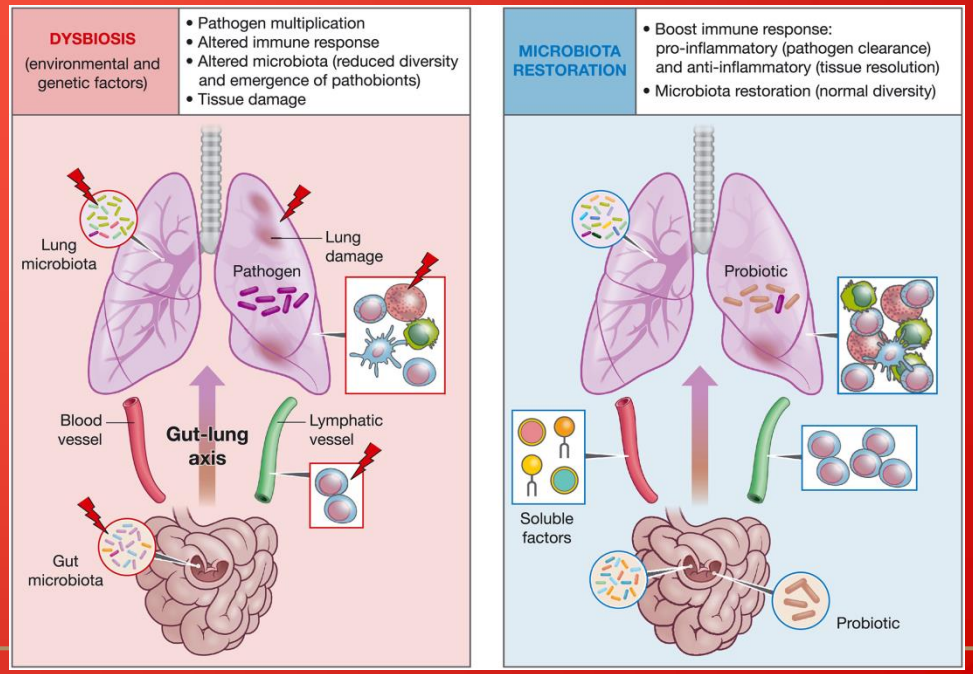


CHEMICAL COMPLEXITY

- The chemical complexity of a molecule may affect its ability to stimulate an immune response.
- Large polymers of amino acids might be expected to be good
- immunogens (because of their size) but only prove to be so when they consist of a mixture of amino acids.
- The type of amino acids present in a peptide also affects its immunogenicity.
- **Aromatic amino acids** make a molecule more immunogenic than non-aromatic molecules because non-covalent, hydrophobic, forces govern the interaction between an antigen and its specific receptor on a cell.

ROUTE OF ADMINISTRATION

- The type of immune response elicited by an immunogen may be very different at one particular site in the body compared to another.
- Thus, the route by which an antigen gains access to the immune system may affect its immunogenicity.
- For example an organism that normally causes infection when introduced in the lungs (a respiratory pathogen) may be destroyed by the acid in the gut if swallowed.



DOSE

- The dose of an antigen may also affect its ability to be immunogenic.
- Given at too high or too low a dose, the immune system may fail to respond to an antigen, which at the correct dose is immunogenic.
- This failure to respond - immunological tolerance

HOST GENETIC MAKE-UP

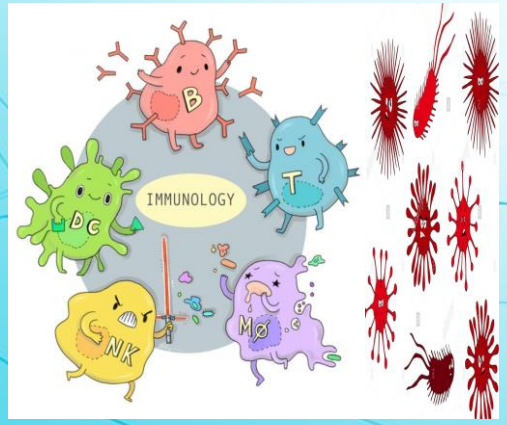
- An individual's ability to mount an immune response is genetically controlled, then the genetic make-up of the host - play a role in determining the relative immunogenicity of a molecule.
- some antigens, which stimulate an immune response in man are non-immunogenic in other animals.

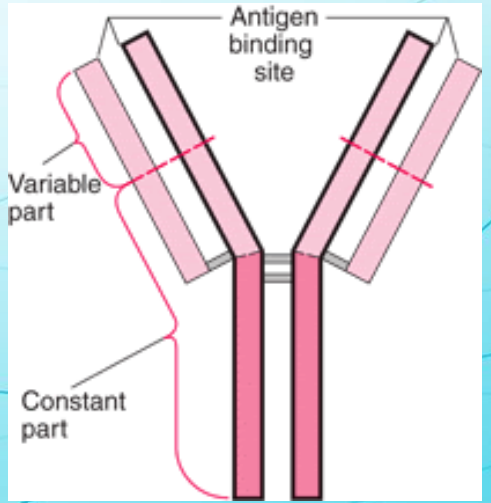
Biology of Immune System [22ZOOC32]

Immunoglobulins – Structure and its types

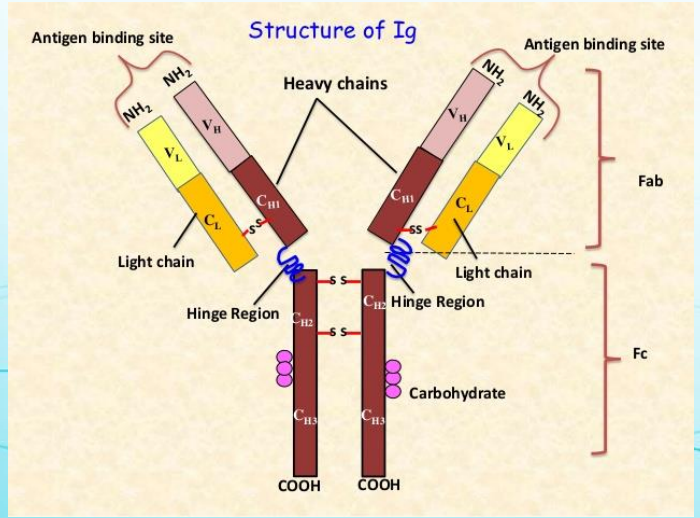
Basic structure of Antibody

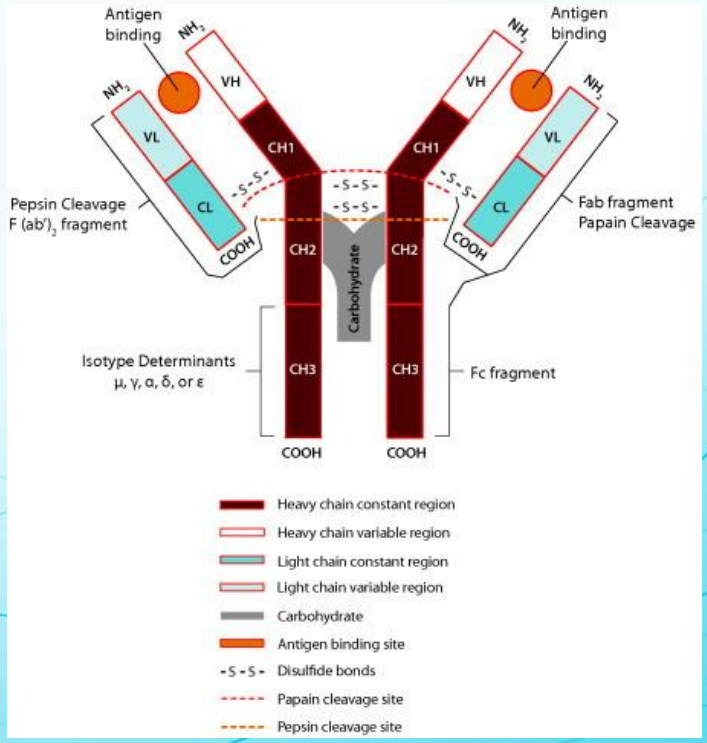
* Dedicating his work for the determining the structure of the immunoglobulin molecule.
* 1972 - delman and Porter shared the Nobel Prize in Physiology or Medicine
* **2** functional domains
  * confers antigen specificity - antigen-binding fragment (Fab),
  * drives antibody function - crystallizable fragment (Fc)
* Each antibody has **2 Fab domains** and **one Fc domain**, generating a 'Y'-shaped or 'T'-shaped molecule that can either exist as a monomer or form multimers (the latter in the case of IgM and IgA).



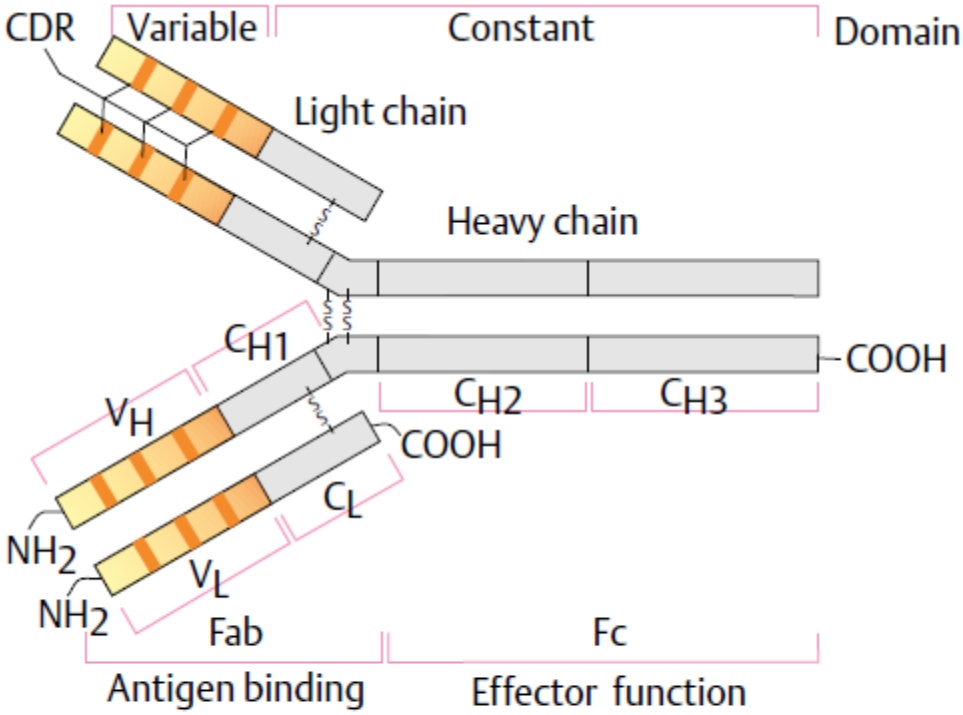


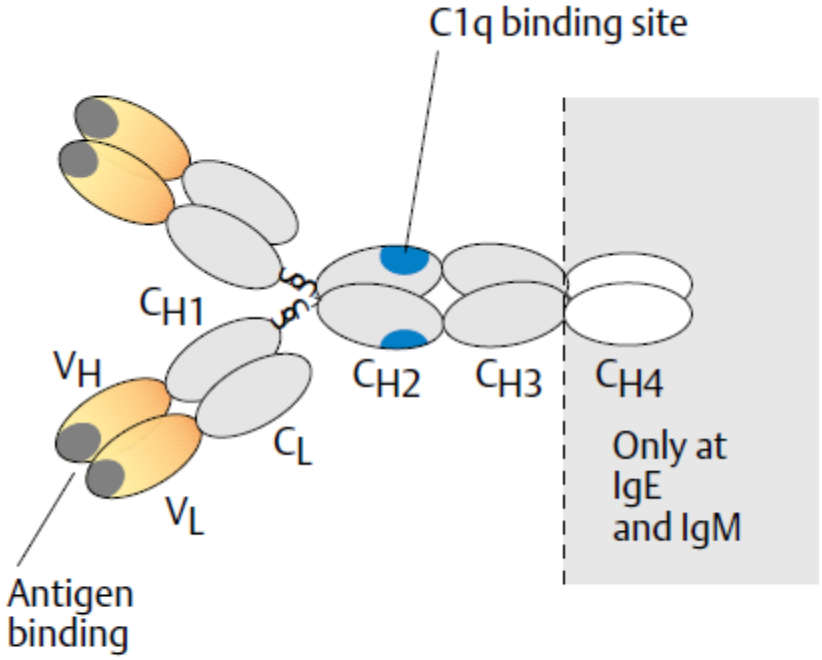
* B cell antigen receptors are immunoglobulins expressed on the surface of mature B cells
* Glycoproteins composed of two identical heavy (H) chains (mw 50000-70000Da) and two identical light (L) chains (mw 25000 Da).
* Two types of light chains, denoted kappa (κ) and lambda (γ)
* Cysteine residues form bridges between the individual chains of an immunoglobulin molecule





Structure of Immunoglobulin

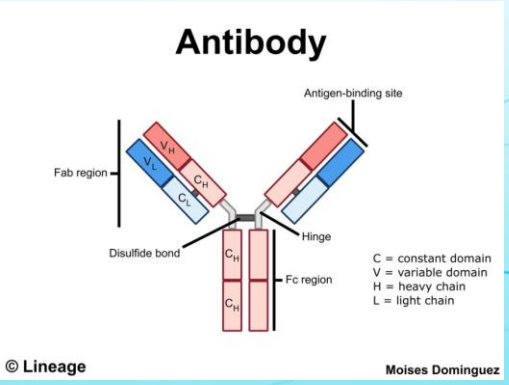




CDR = complementarity-determining region
Fab = antigen-binding fragment
Fc = crystallizable fragment

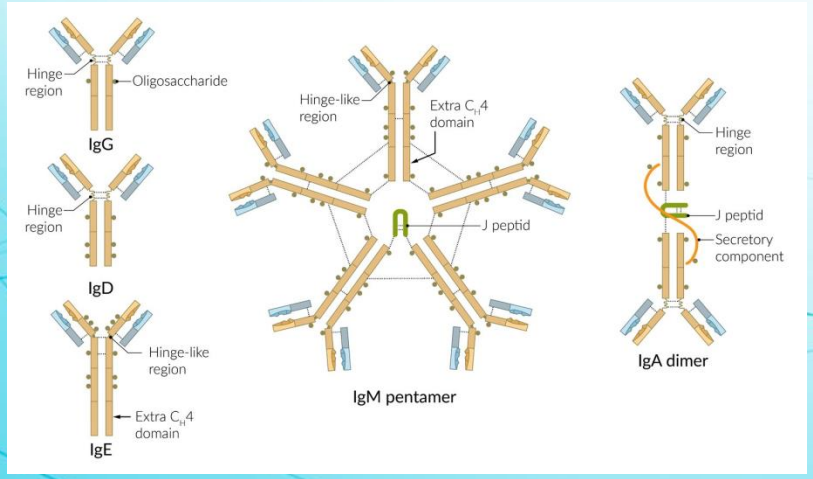
V_H = variable domain of heavy chains
V_L = variable domain of light chains
$C_{H/L}$ = constant domain of heavy / light chains

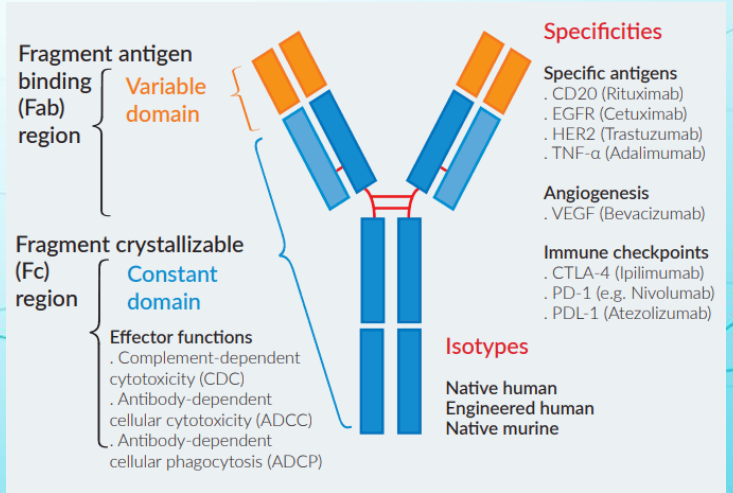
* **Antibody - antigen-binding fragment (Fab)**
* Fab domains are essential to the adaptive nature of the humoral response and evolve during an immune response to improve affinity to a foreign antigen.
* **Antigen binding region**
* The combined variable regions of the light and heavy chains define the **antigen binding site**.
* There are two identical binding sites on each monomeric antibody molecule.
* The interaction between the antigen and the antibody binding site involves both hydrophobic and ionic components.
* The strength of the interaction between one antigen binding site and its monovalent antigen determines the **affinity of the interaction.**
* **Antibody *avidity, the overall binding energy*** of all of the antigen binding sites with antigen.



Antibody - Crystallizable fragment (Fc)

* The Fc domain, - referred to as the **constant domain**, also changes rapidly during an immune response to elicit distinct innate immune effector functions
* The Fc domain variants include five isotypes (IgM, IgD, IgG, IgA and IgE), each with unique structural features that impact antibody function



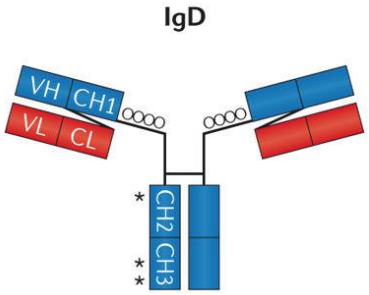


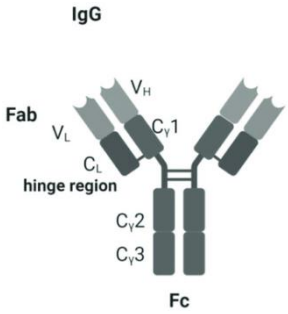
Light chains

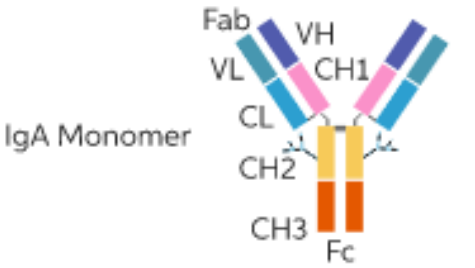
* Light chains are composed of variable and constant regions.
* The constant region, **kappa or lambda, distinguishes the two classes of light chains.**
* A single antibody molecule will have **either two kappa or two lambda light chains**, but never a mixture of the two.
* In humans, the predominant light chain is **kappa**.
* lambda chains are invariant in the population, kappa chains demonstrate allotype (presence of allelic forms of the same protein in the population).
* Kappa chain **allotypes are referred to as K_m.**
* Consist of two large regions of approximately equal size
* C_L varies little from one Ig to another
* V_L exhibits enormous ***degree of variability***
* Both C_L and V_L domains consists of about **110 aminoacids**

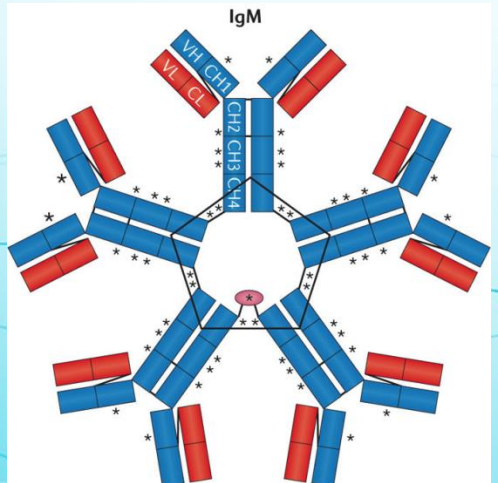
Heavy Chain

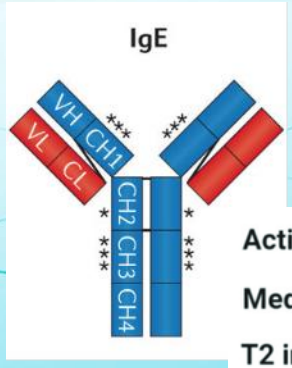
* One Variable V_H domain with around 110 aminoacids & 3 constant (C_H) domains [except I_gM and I_gE – 4 constant domains; extra heavy-chain constant domain]
* Different domains of a given I_gs – But have a similar globular structrue (presence of multiple β-pleated sheets and disulfide bonds)
* Heavy chains are composed of a variable and a constant region. Five major classes of heavy chains can be distinguished with different constant regions, designated by the Greek letters alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ).
* These constant regions give rise to the antibody isotypes I_gA, I_gD, I_gE, I_gG and I_gM respectively.
* Allotypic forms of the I_gA and I_gG heavy chains gives rise to allotypes designated **A_m** and **G_m**, respectively.











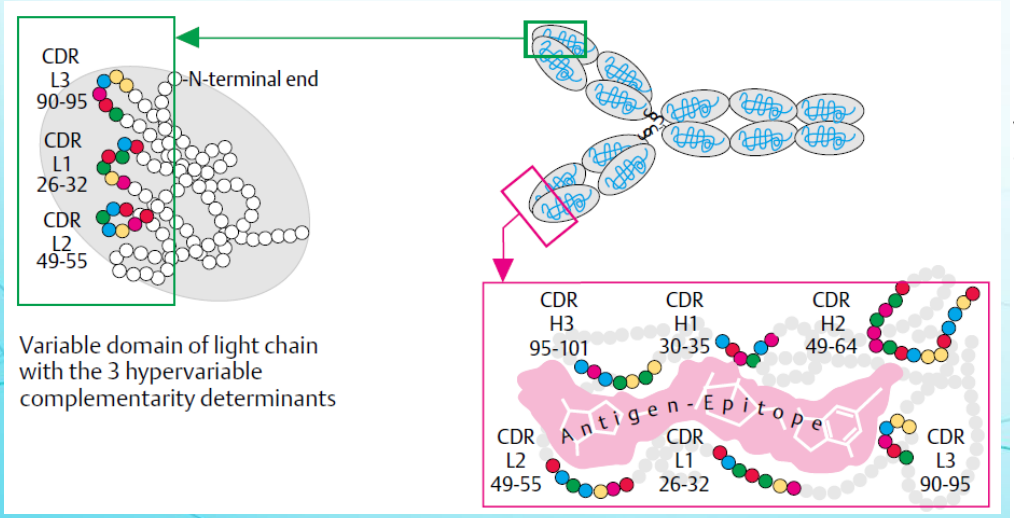
Activation of mast cells and basophils

Mediator and cytokine release

T2 inflammatory cascade activation

Hyper variable Regions

- Variable domains of Light and Heavy chains contains regions – extreme variable aminoacid sequences (so it named as Hyper variable regions)
- 6-8 aminoacids around position 30,50, and 93 of light chains
- 6-8 aminoacids around position 32,55, and 98 of Heavy chains
- Determine the specificity of antigen binding (CDR-Complementarity determining Regions)
- Hypervariable regions can also serve as **antigenic determinants (idiotopes).**
- The collection of **idiotopes in a given antibody defines the idiotype. Consequently,** antibodies generated to the collection of idiotopes on a single antibody molecule are termed **anti-idiotypic antibodies.**



Immunoglobulin Structure-Function Relationship

- Cell surface antigen receptor on B cells

  Allows B cells to sense their antigenic environment

  Connects extracellular space with intracellular signalling machinery

- Secreted antibody

  Neutralisation

  Arming/recruiting effector cells

  Complement fixation

Immunoglobulin (I_g)

Composed of **2 identical heavy chains and two identical light chains** linked by **disulfide bonds**

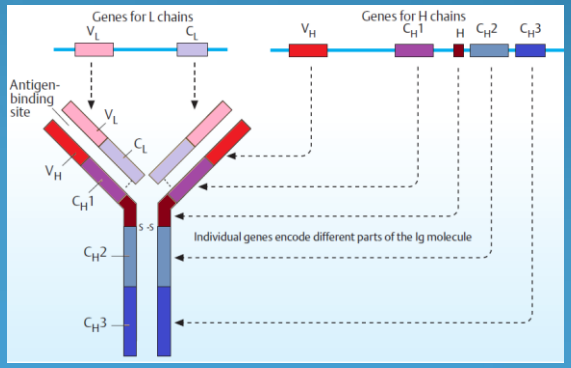
Each chain is made up of a **variable region** and a **constant region**.

The **light chain variable region** is composed of segments designated **“V” and “J”, while the heavy chain variable region is composed** of **“V”, “D”, and “J” segments,**

“V”- Variable

“D”- Diversity, and

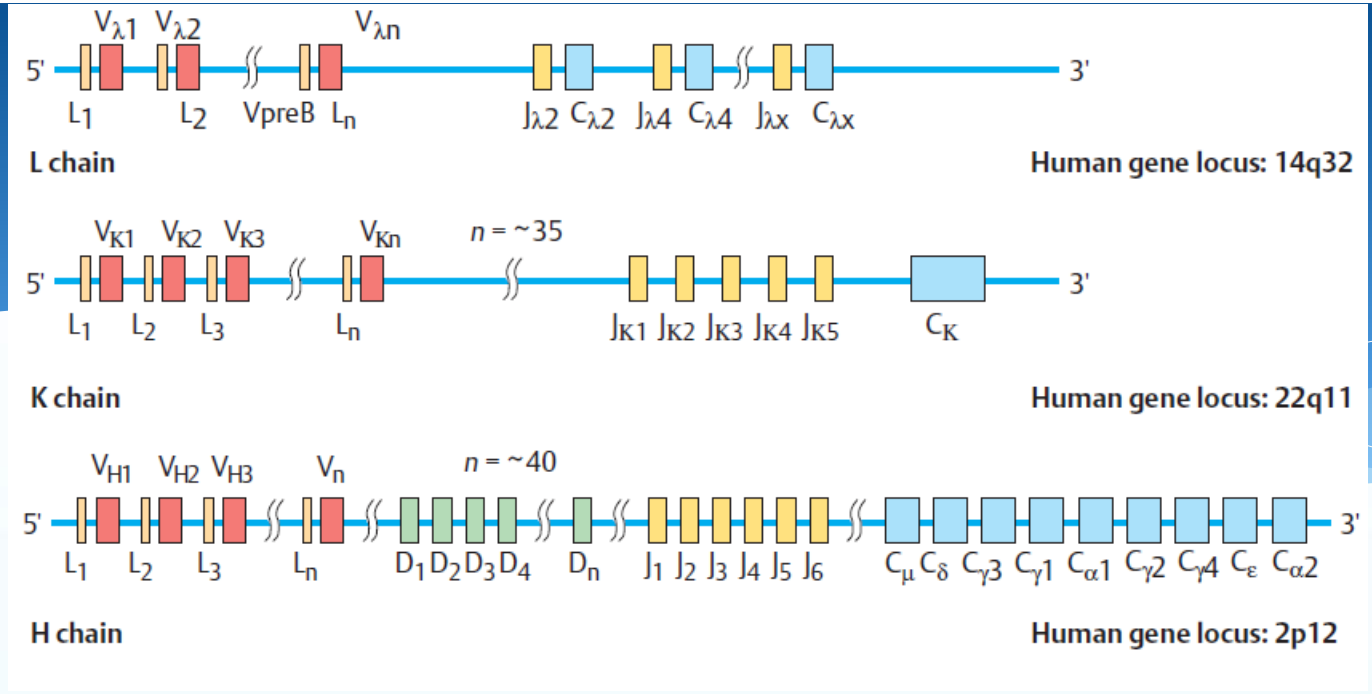
“J” - Joining segments

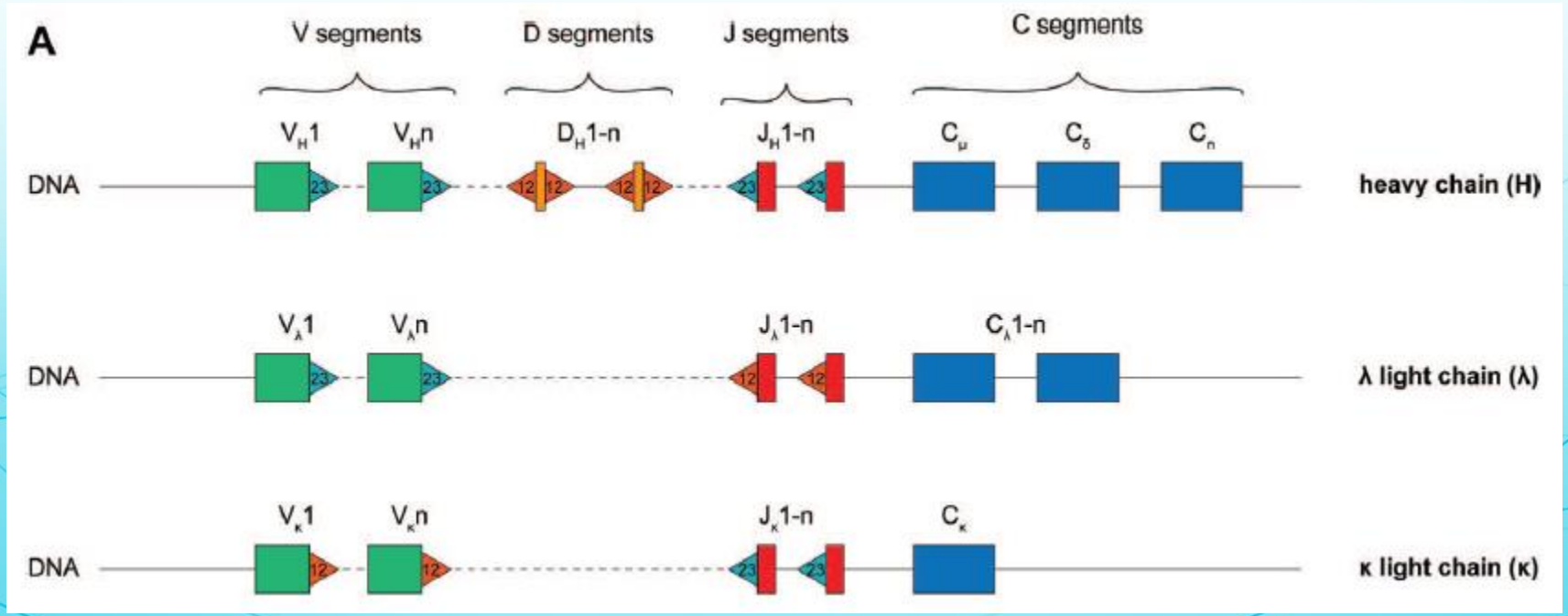


The constant regions are encoded by the same genes in all B cells.

Classes of Igs

	IgM	IgG	IgA	IgD	IgE
MW	900,000	160,000	360,000	200,000	160,000
Sediment coefficient	**19**	7	11	8	7
Carbohydrate (%)	12	8	7	12	12
Subclasses		γ_1-γ_4	A1-A2		
Serum concentration in Adult (mg/mL)	1.5	**13.5**	3.5	0.05	Trace
Half-Life (days)	5	**23**	6	2.5	3


Vλ1 Vλ2 Vλn
5'
3'
L1 L2 VpreB Ln
Jλ2 Cλ2 Jλ4 Cλ4 Jλx Cλx
L chain
Human gene locus: 14q32
VK1 VK2 VK3 VKn
n = ~35
L1 L2 L3 Ln
JK1 JK2 JK3 JK4 JK5 CK
K chain
Human gene locus: 22q11
VH1 VH2 VH3 Vn
n = ~40
L1 L2 L3 Ln
D1 D2 D3 D4 Dn
J1 J2 J3 J4 J5 J6
Cμ Cδ Cγ3 Cγ1 Cα1 Cγ2 Cγ4 Cε Cα2
H chain
Human gene locus: 2p12

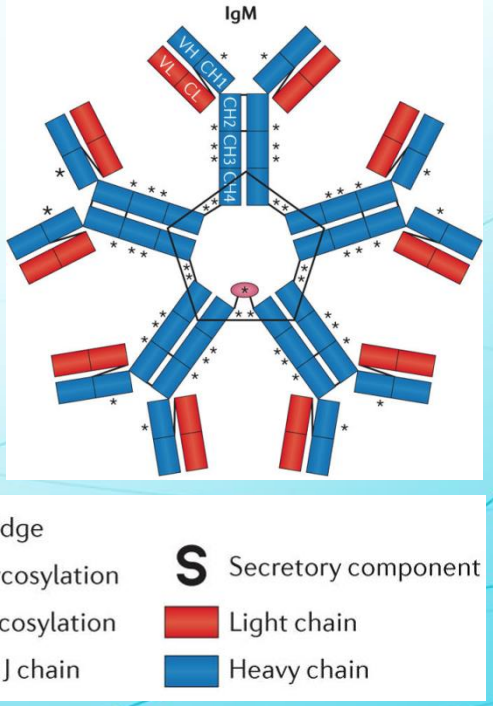

A
V segments
D segments
J segments
C segments
VH1 VHn
DH1-n
JH1-n
Cμ Cδ Cn
DNA
heavy chain (H)
Vλ1 Vλn
Jλ1-n
Cλ1-n
DNA
λ light chain (λ)
Vκ1 Vκn
Jκ1-n
Cκ
DNA
κ light chain (κ)

Immunoglobulin types

* **1.** Circulating Ig
* **2.** Membrane-bound Ig
* **3.** Secretory Ig
* **4.** Cell-bound Ig

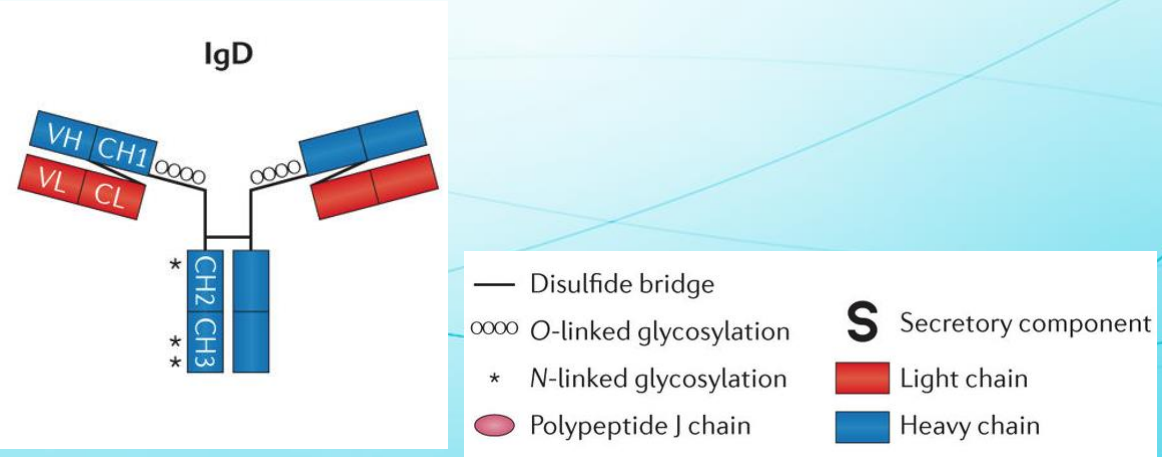
IgM

* Monomer, IgM associates with transmembrane invariant accessory chains, forming the B cell receptor.
* IgM is secreted as a pentamer, which is linked by disulfide bonds and a single J chain.
* Multimerization enhances avidity via multi-site binding and complement binding via a central crystallizable fragment (Fc) bulge.
* IgM possesses five N-linked glycoslation sites.



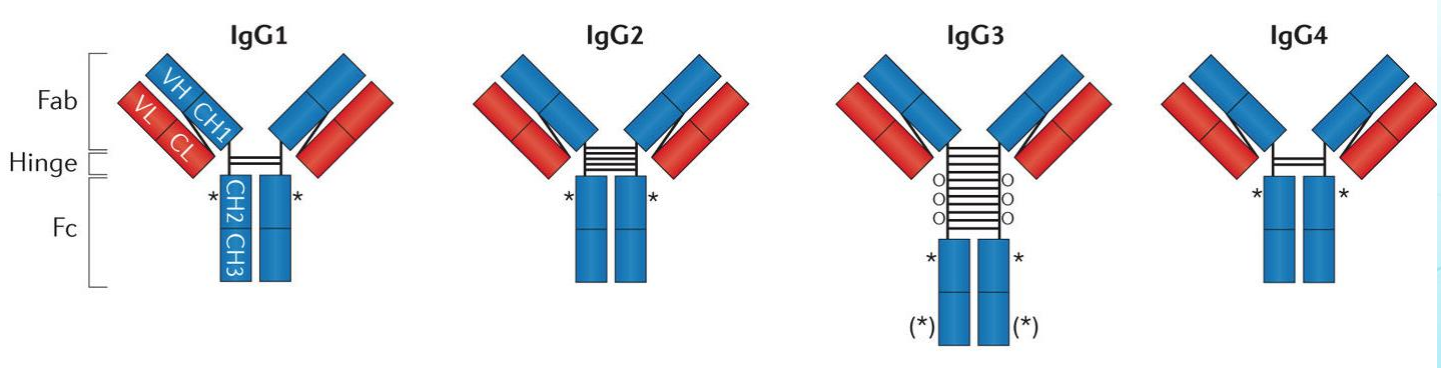
IgD

* Increased hinge flexibility and forms a ‘T’ shape due to heavy glycosylation, which allows for greater epitope binding and synergy with IgM early in infection, particularly within mucosal tissues where it is localized



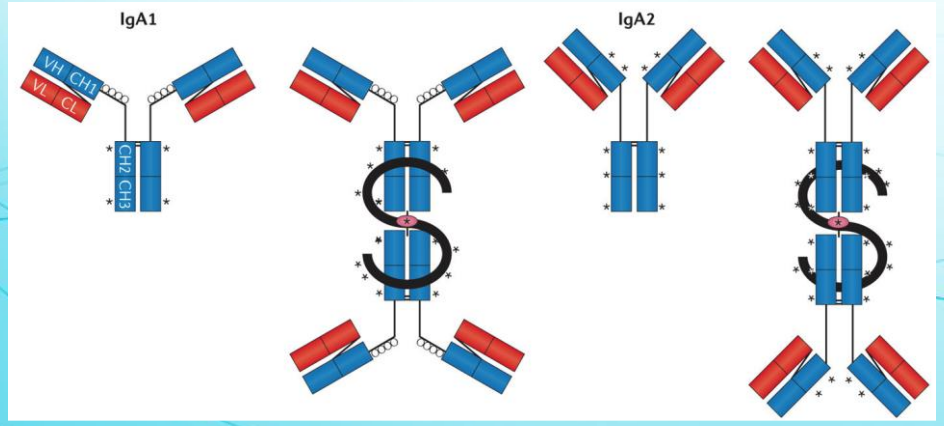
IgG

* principal isotype utilized in monoclonal therapeutics - because of its high serum abundance, long half-life, critical role in anti pathogen control and destruction, extensive available structural and functional data and amenability for protein engineering and production



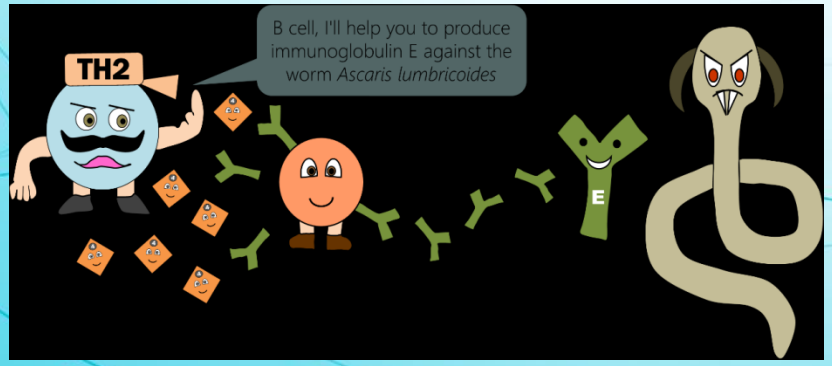
IgA (Secretary form)

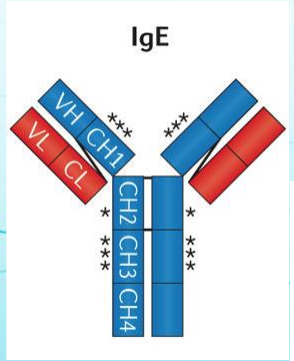
* IgA1 has a flexible, heavily O-glycosylated hinge that induces a ‘T’ shape, which is vulnerable to pathogen cleavage, whereas IgA2 has a more rigid ‘Y’-shaped hinge.
* Monomeric IgA is present in the serum.
* By contrast, dimeric IgA, which is linked by disulfide bridges to a J chain and complexed to a glycosylated polypeptide chain (secretory component) that is derived from the polymeric immunoglobulin receptor, is secreted into the mucosa.
* IgA1 possesses two N-linked and four O-linked glycan sites, and IgA2 possesses five N-linked glycan sites.

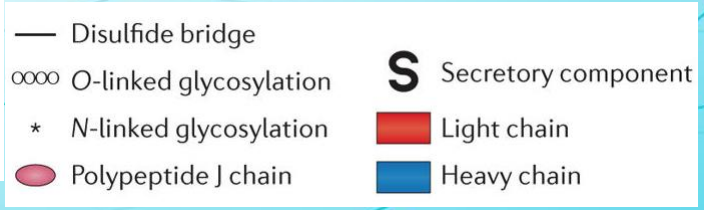


IgE

* is involved in the response to helminths, where substantial structural rigidity must be overcome to enable binding to its cognate Fc receptor (FcR) and drive persistent antibody effector function for weeks to months against parasites and allergens







Roles…

* IgG plays a major role in elimination of microbes by facilitating:
* (i) Opsonization by phagocytes;
* (ii) Antibody-Dependent Cell mediated Cytotoxicity (ADCC) by **natural killer cells**;
* (iii) Complement activation; and
* (iv) Neutralization of viruses and toxins.