Unit II

Cell Mediated Effector Response

Slides were made from YouTube

Unit I: Immunology- Fundamental concepts and anatomy of the immune system; Components of innate and acquired immunity; Phagocytosis; Complement and Inflammatory responses; Haematopoesis; Organs and cells of the immune system- primary and secondary lymphoid organs-Bone marrow, thymus, lymph nodes, spleen; Lymphatic system; Lymphocyte circulation; Lymphocyte homing; Mucosal and Cutaneous associated Lymphoid tissue (MALT and CALT); Mucosal Immunity. Toll-like receptors, inflammation. Antigens - haptens, antigenicity and immunogenicity.

Unit II: Humoral and Cell-Mediated Immune responses, primary and secondary immune modulation, Immunoglobulins: Basic structure, Classes and Subclasses of immunoglobulins, ADCC; antigenic determinants; B and T cell epitopes; B and T cell receptors; Immune responses generated by B and T lymphocytes; activation and differentiation of B and T cells, Memory B cell maturation, activation and differentiation; Cell-mediated effector functions; Functional T Cell Subsets; Cell-mediated immune responses, Cytokines-properties, receptors and therapeutic uses. Structure and function of antibody molecules; Multigene organization of immunoglobulin genes; Immunoglobulin superfamily; Generation of antibody diversity.

Unit III: Major Histocompatibility Complex - MHC genes, MHC and immune responsiveness and disease susceptibility, HLA typing; MHC molecules, antigen processing and presentation, endogenous antigens, exogenous antigens, non-peptide bacterial antigens and super-antigens.

Unit IV: Antigen-antibody interactions- Kinetics of immune response; Precipitation, agglutination and complement mediated immune reactions; Advanced immunological techniques; RIA, ELISA, Western blotting, ELISPOT assay, immunofluorescence, flow cytometry and immunoelectron microscopy; Surface plasmon resonance, Biosenor assays for assessing ligand–receptor interaction, CMI techniques- lymphoproliferation assay, Mixed lymphocyte reaction, Cell Cytotoxicity assays, Apoptosis, Microarrays.

Unit V: Clinical Immunology: Immunity to Infection Hypersensitivity – Type I-IV; Autoimmunity; Types of autoimmune diseases; Mechanism and role of CD4+ T cells; MHC and TCR in autoimmunity; Treatment of autoimmune diseases; Transplantation immunology– Immunological basis of graft rejection; congenital and acquired immunodeficiencies. Cancer: Tumor immunology; Oncogenes, Tumor Suppressor Genes; Immune response to tumors and tumor evasion of the immune system.

PAPER- III **(BCH 303)** **MAX.MARKS – 100**

IMMUNOLOGY

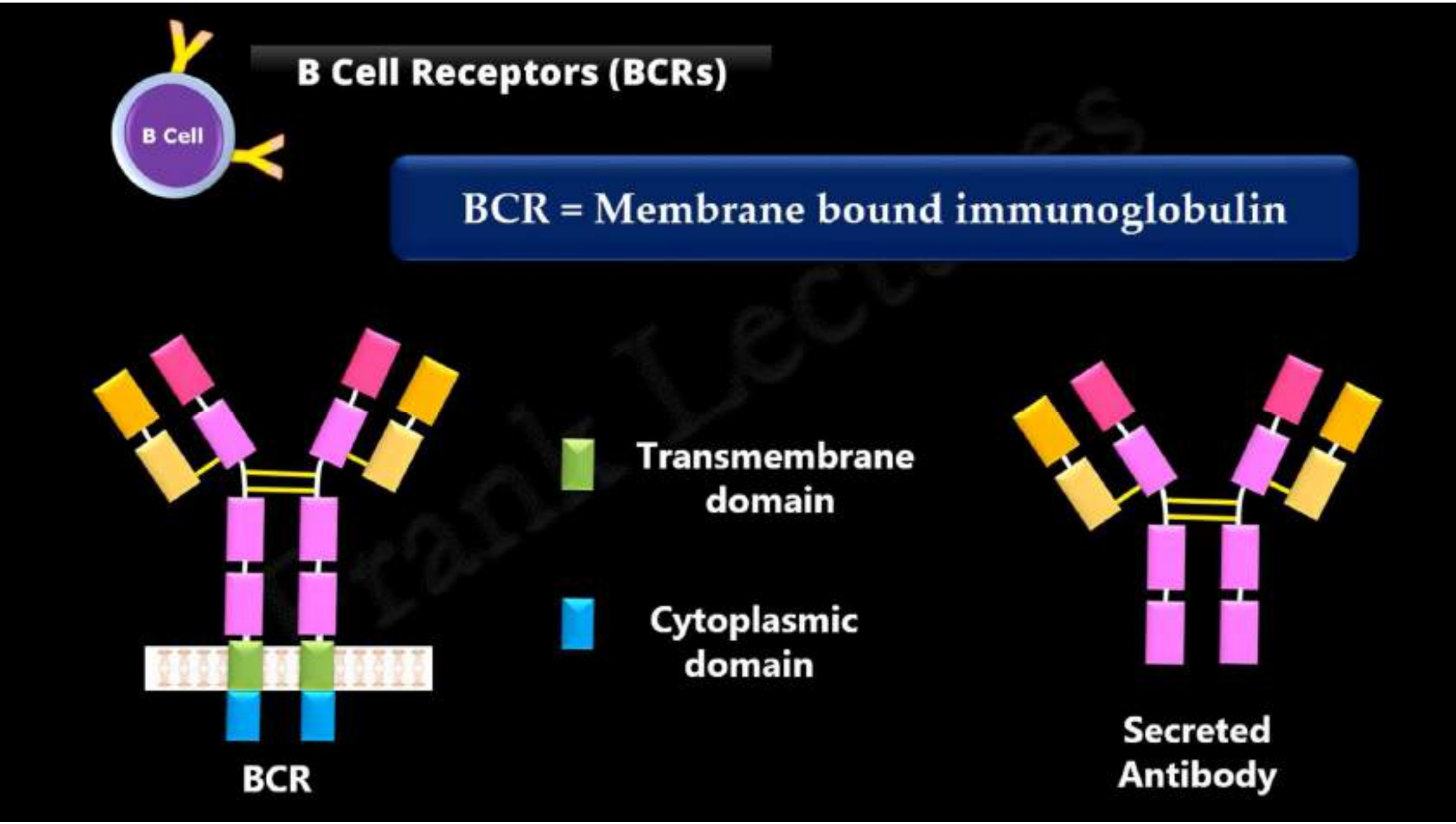
UNIT-I The biochemical basis of immunology- Innate immunity, Specific acquired immunity, Immunoglobulin Classification, structure and biochemical basis of function, variable domain bind antigen, MHC, T-cells, B-cells, receptors. Antigens haptens, recognition of antigen – primary interaction its detection and application.

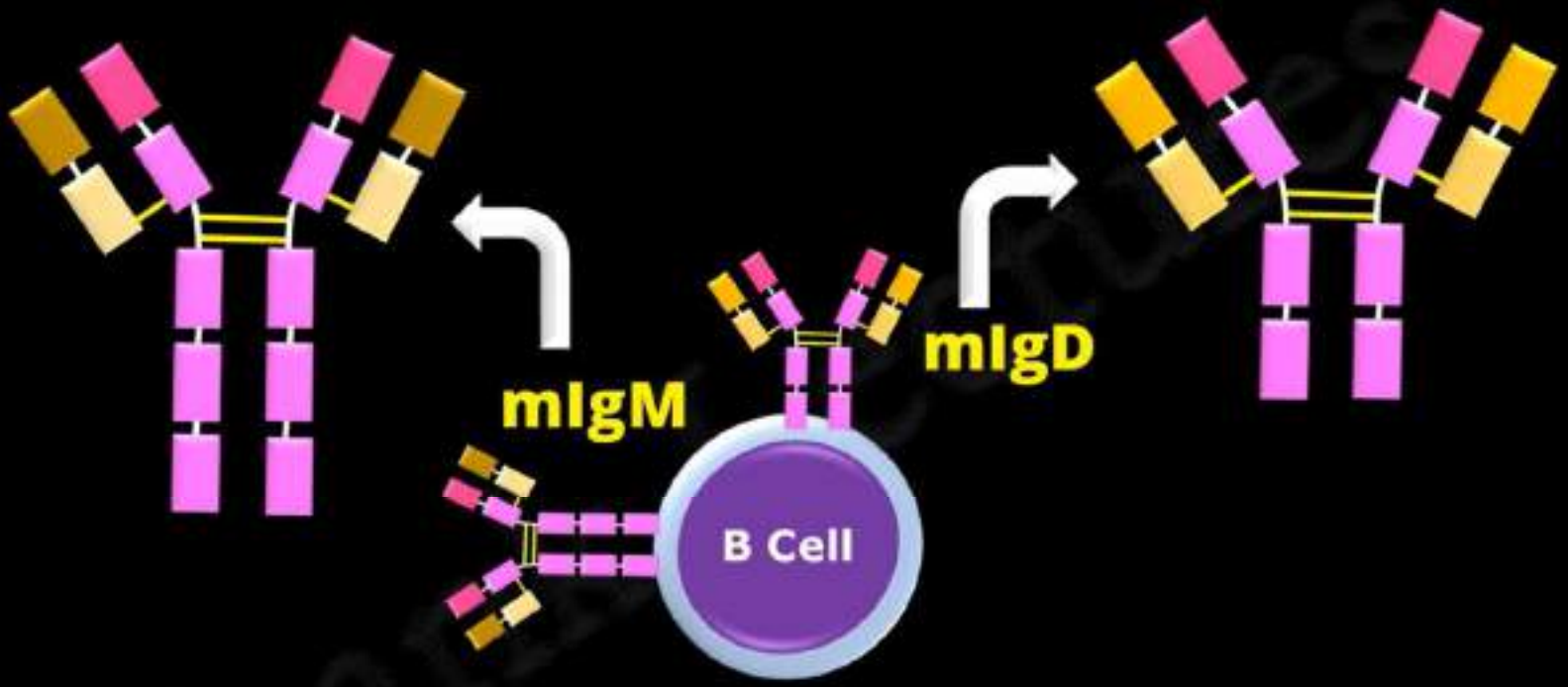
UNIT –II Major Histocompatibility Complex (MHC) Genes and product- Polymorphism of MHC genes, Role of MHC antigens in immune Reponses, MHC antigens in transplantation.

UNIT- III Measurement of antigen-antibody interactions – Production of polyclonal and monoclonal antibodies: Principles techniques and applications. Agglutination and precipitation techniques, RIA, ELISA, IRMA, immunofluorescence assays. Measurement of T cell activation.

UNIT-IV Acquired immune response: consequences of antigens recognition, product effectors and its control development, adversial strategies, and immunodeficiency. Elementary knowledge of hypersensitivity.

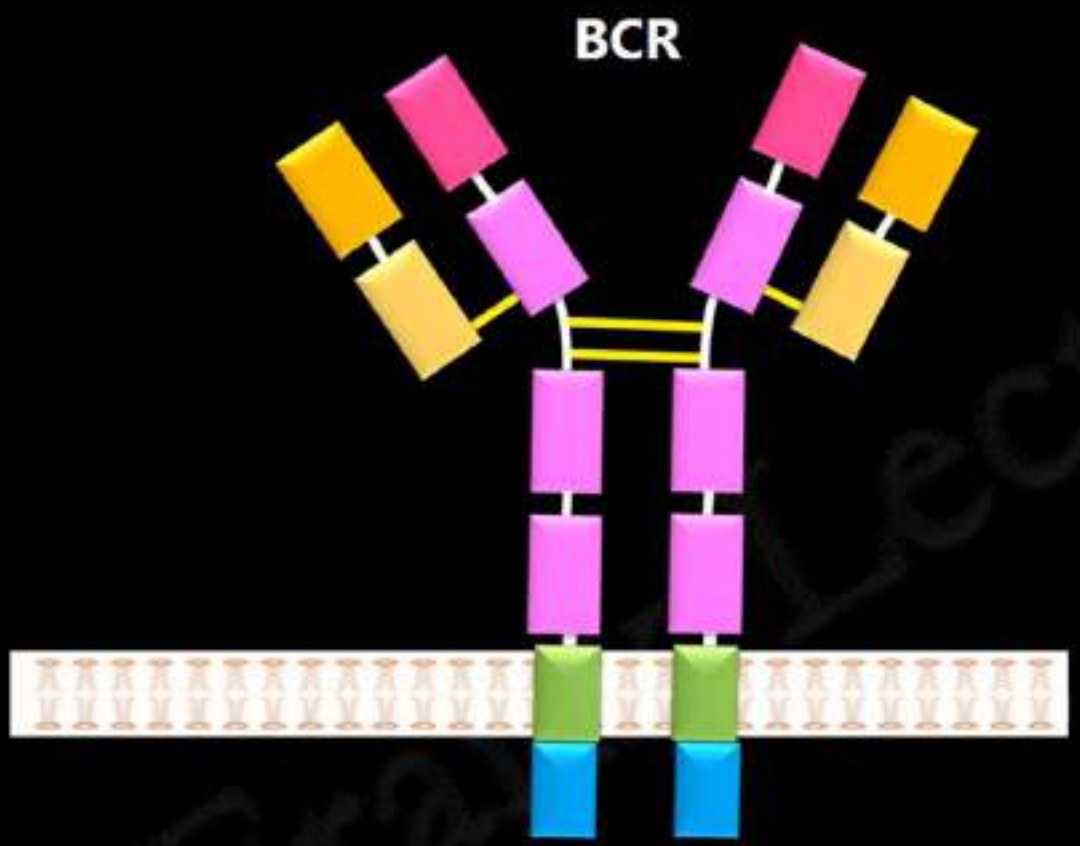
UNIT- V Disorders of immune responses – Autoimmunity, congenital immunodeficiencies, acquired immunodeficiencies, immune responses to infectious diseases, role of vaccines in the prevention of diseases.


B Cell
B Cell Receptors (BCRs)
BCR = Membrane bound immunoglobulin
Transmembrane domain
Cytoplasmic domain
BCR
Secreted Antibody



Mature naïve B cell

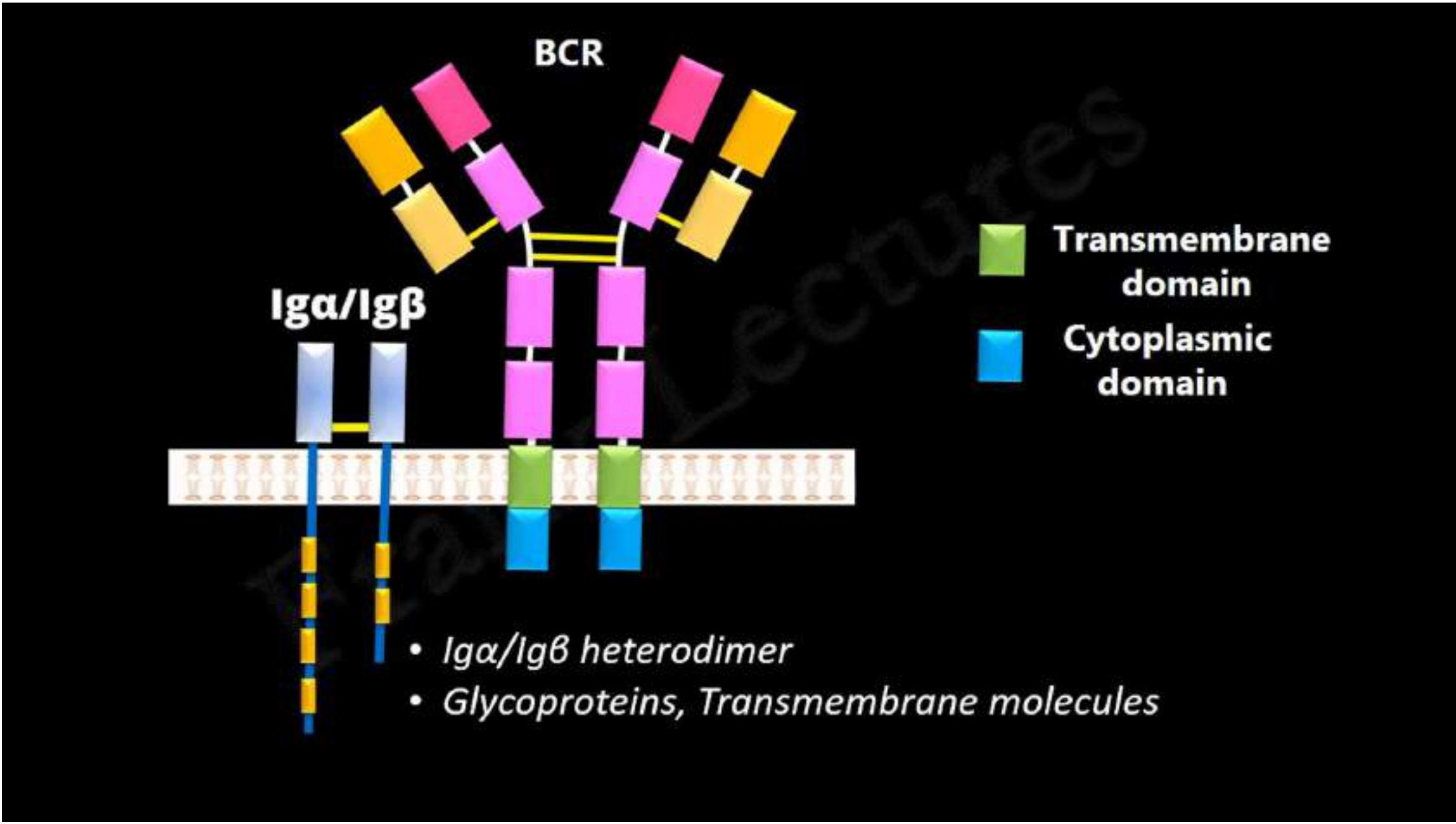
- *B cells express mIgM and mIgD as BCRs*
- *Both are of same antigenic specificity*

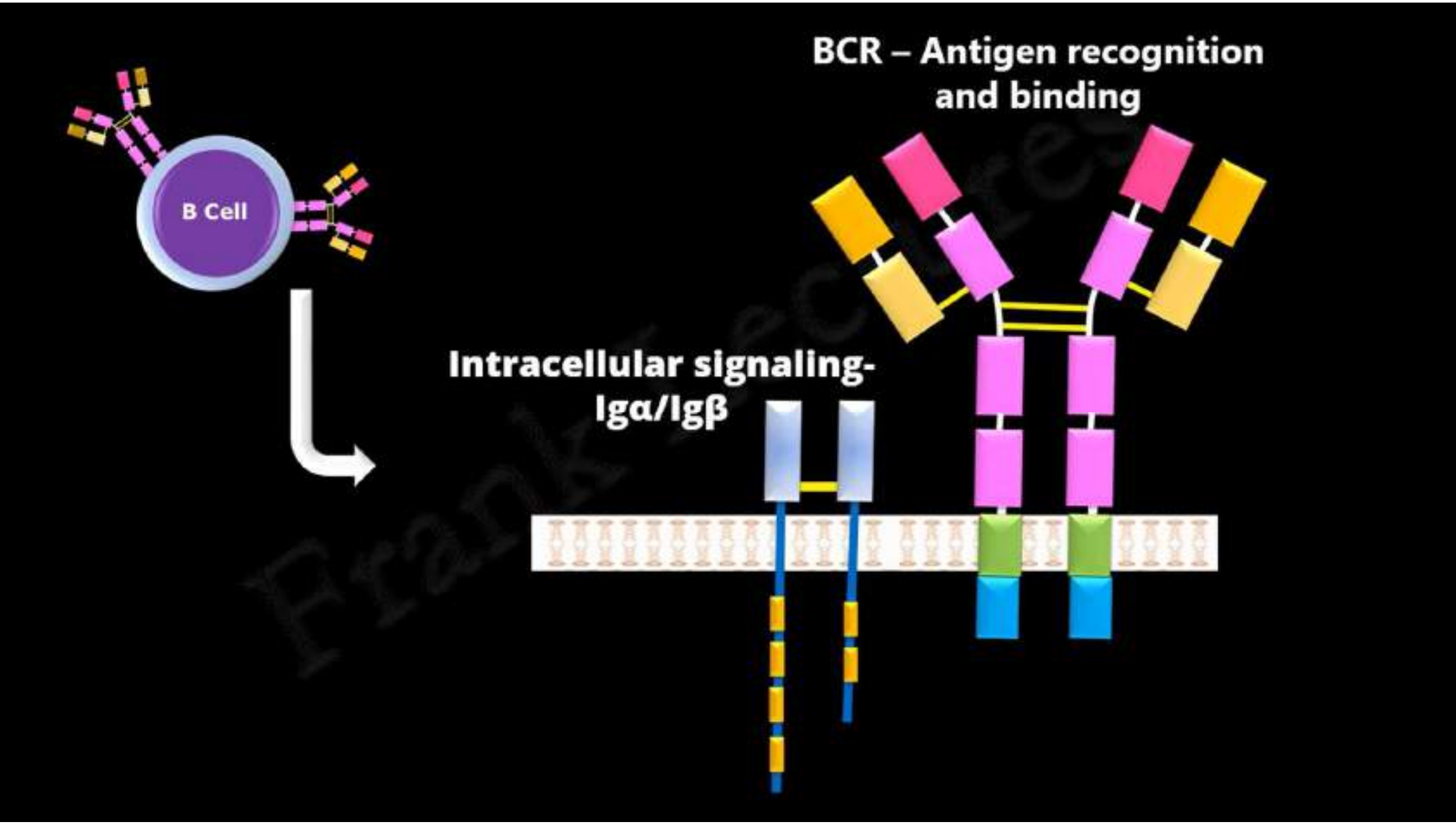


Transmembrane domain

Cytoplasmic domain

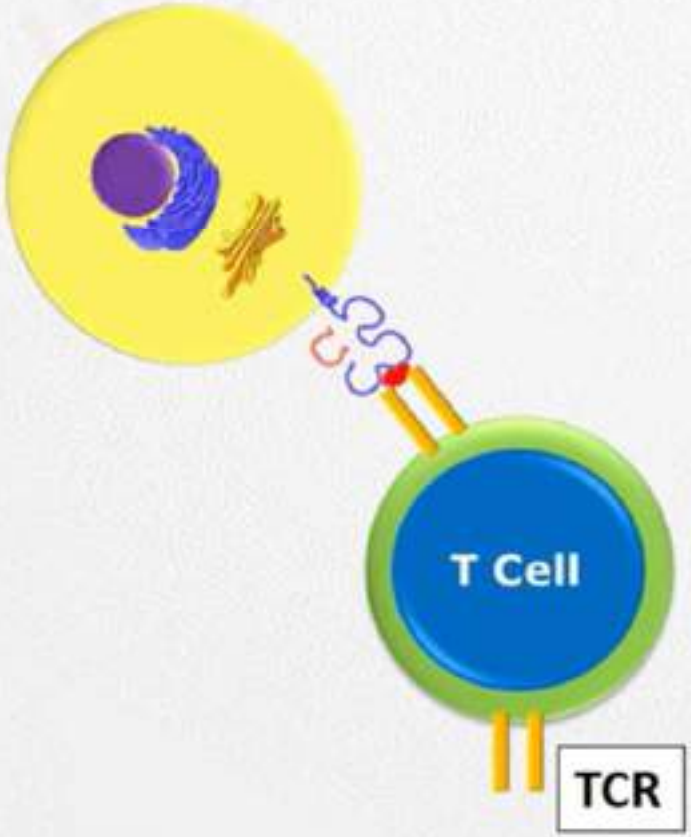
- *Cytoplasmic tails of BCRs are very short.*
- *Cannot convey antigen recognition signal to the nucleus*


BCR
Igα/Igβ
Transmembrane domain
Cytoplasmic domain
• Igα/Igβ heterodimer
• Glycoproteins, Transmembrane molecules


BCR – Antigen recognition and binding
B Cell
Intracellular signaling-
Igα/Igβ

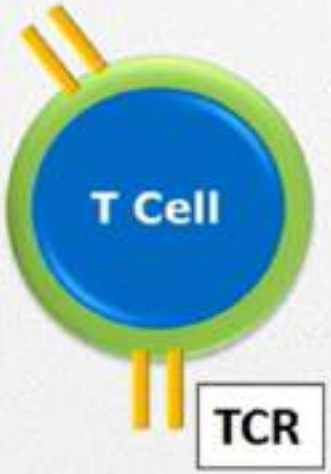
T Cell Receptor (TCR)

TCR interacts with MHC-peptide complex on the surface of Antigen Presenting Cells or target cells.

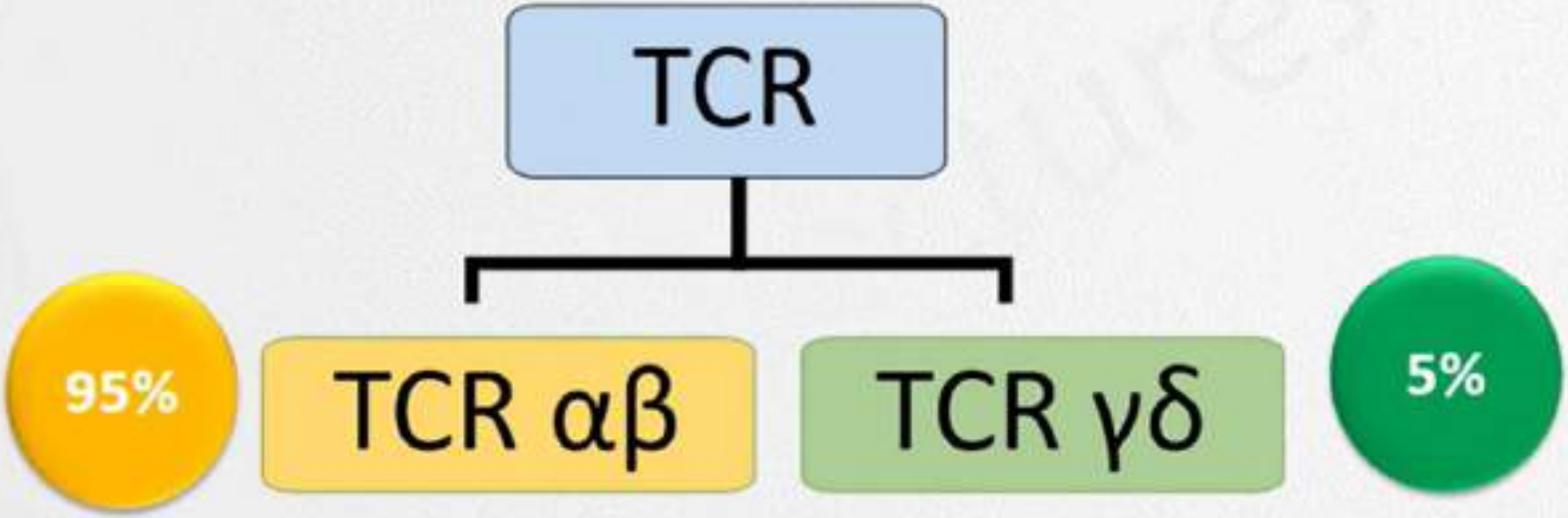


T Cell Receptor (TCR)

An individual T cell generally carries between 10,000 and 30,000 identical copies of a single TCR.



T Cell Receptor (TCR)



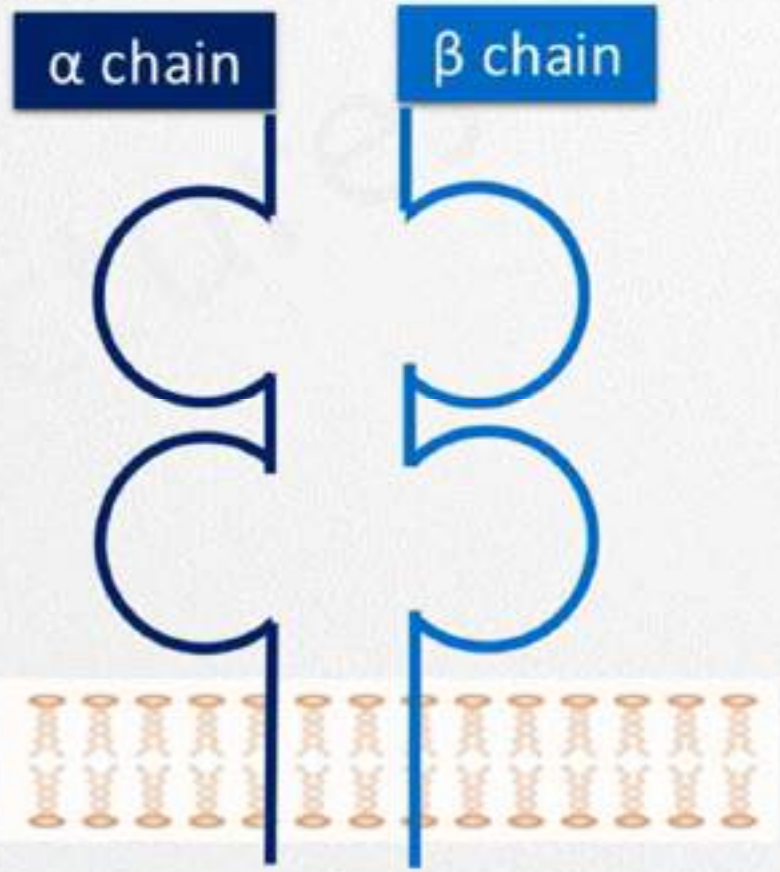
T cell express either an αβ or a γδ receptor, but not both.

TCR αβ

Composed of two polypeptides

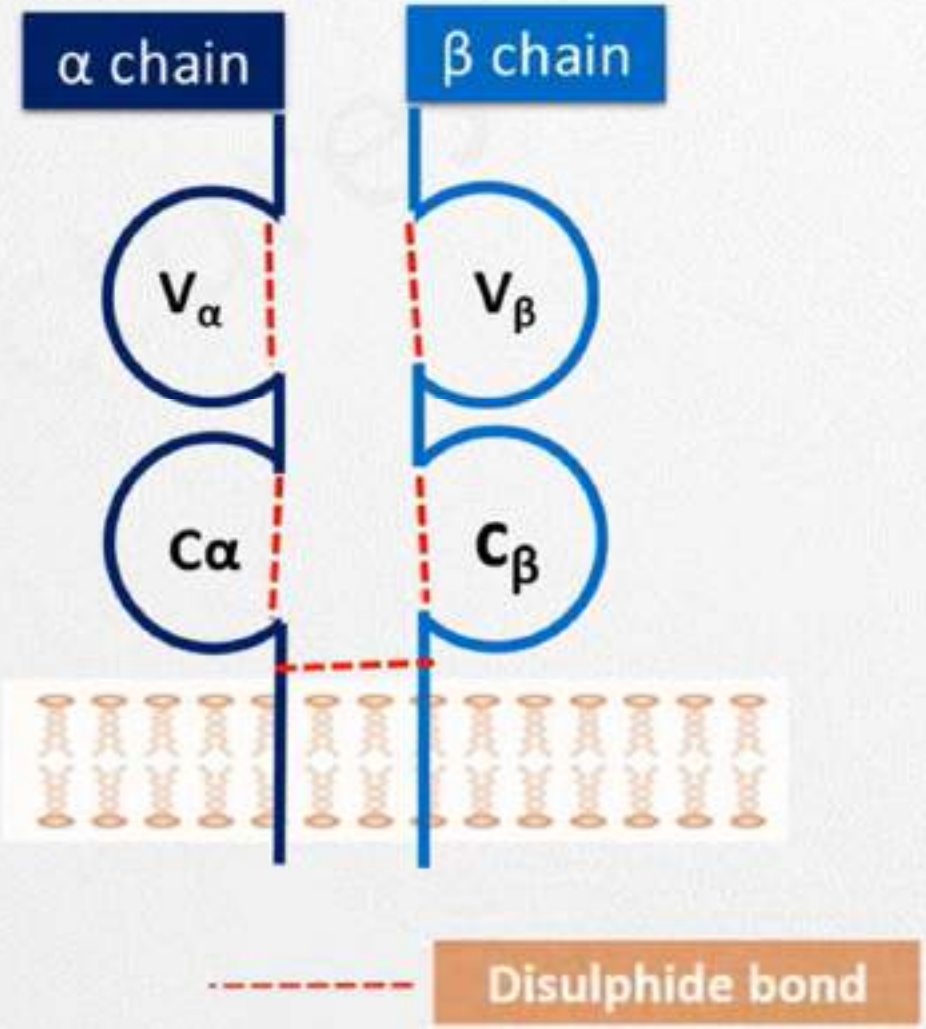
α chain (49kDa)

β chain (43kDa)



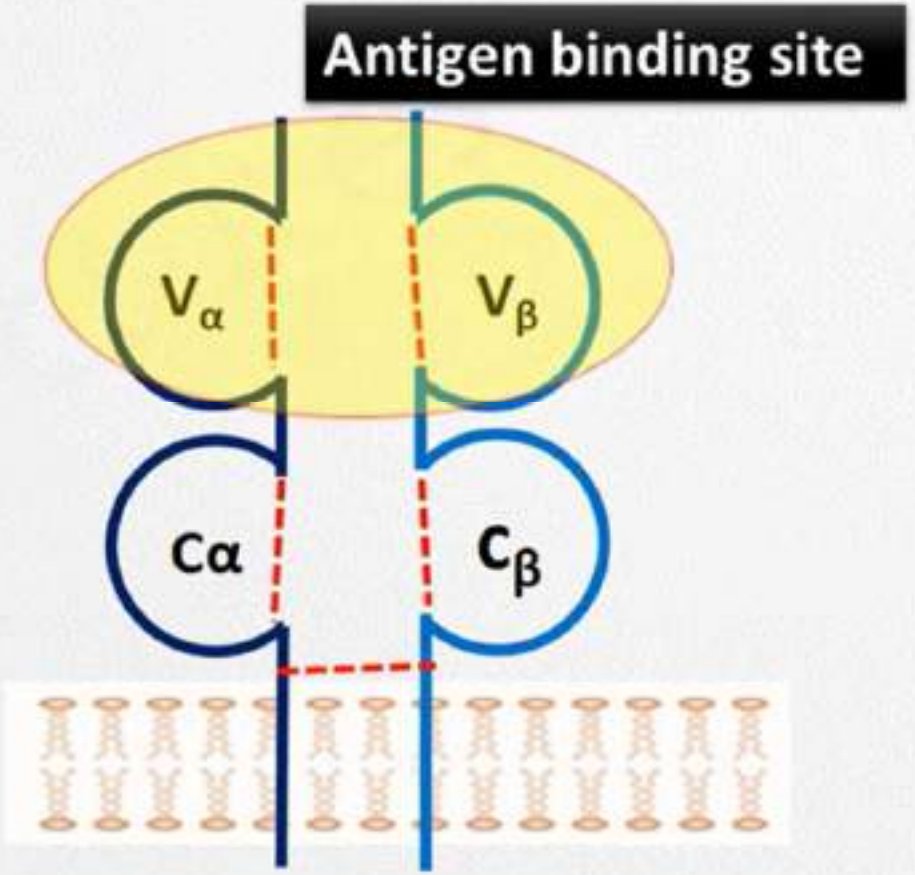
TCR αβ

Each chain has a Variable (V) domain and a Constant (C) domain.



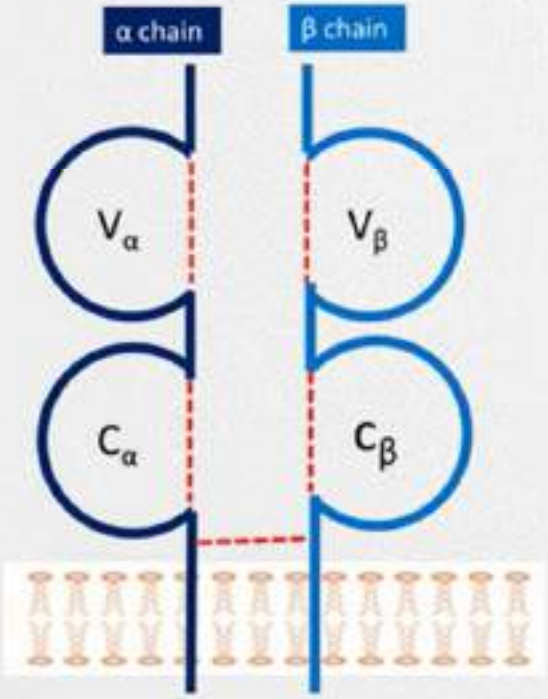
TCR αβ

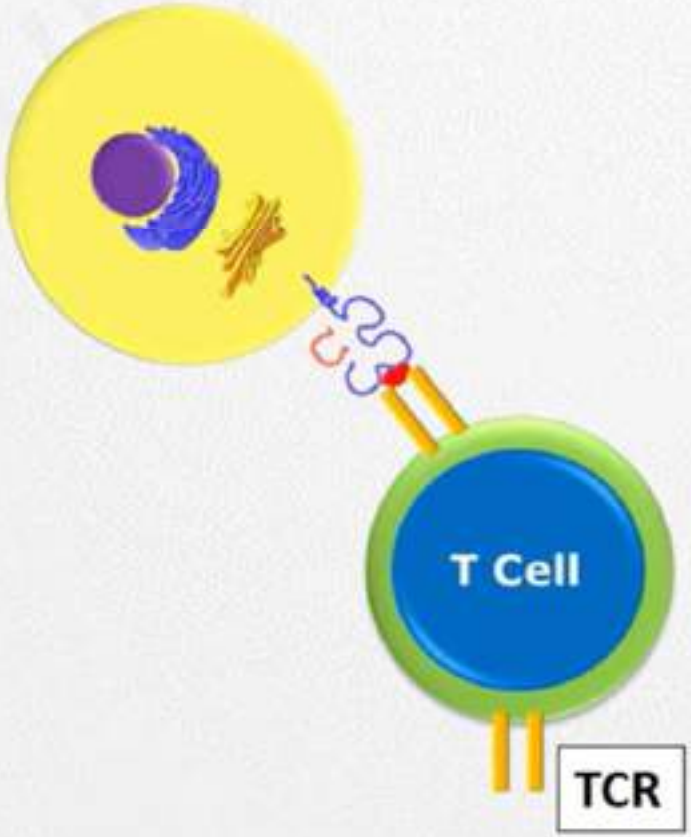
Variable domain of both chains form the **antigen-binding site.**

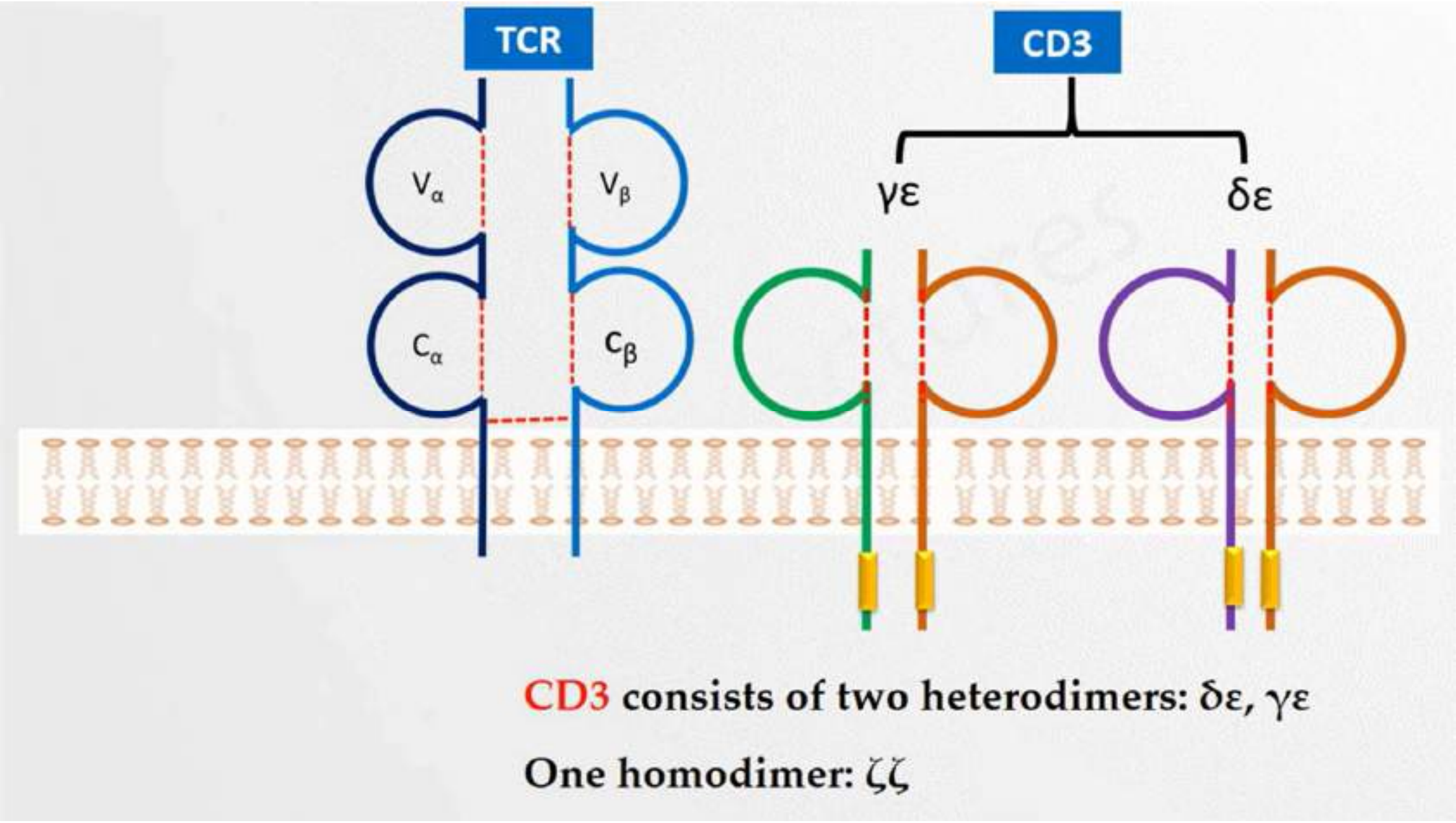


The cytoplasmic tail of the TCR is extremely short.

(about 3 amino acid long)

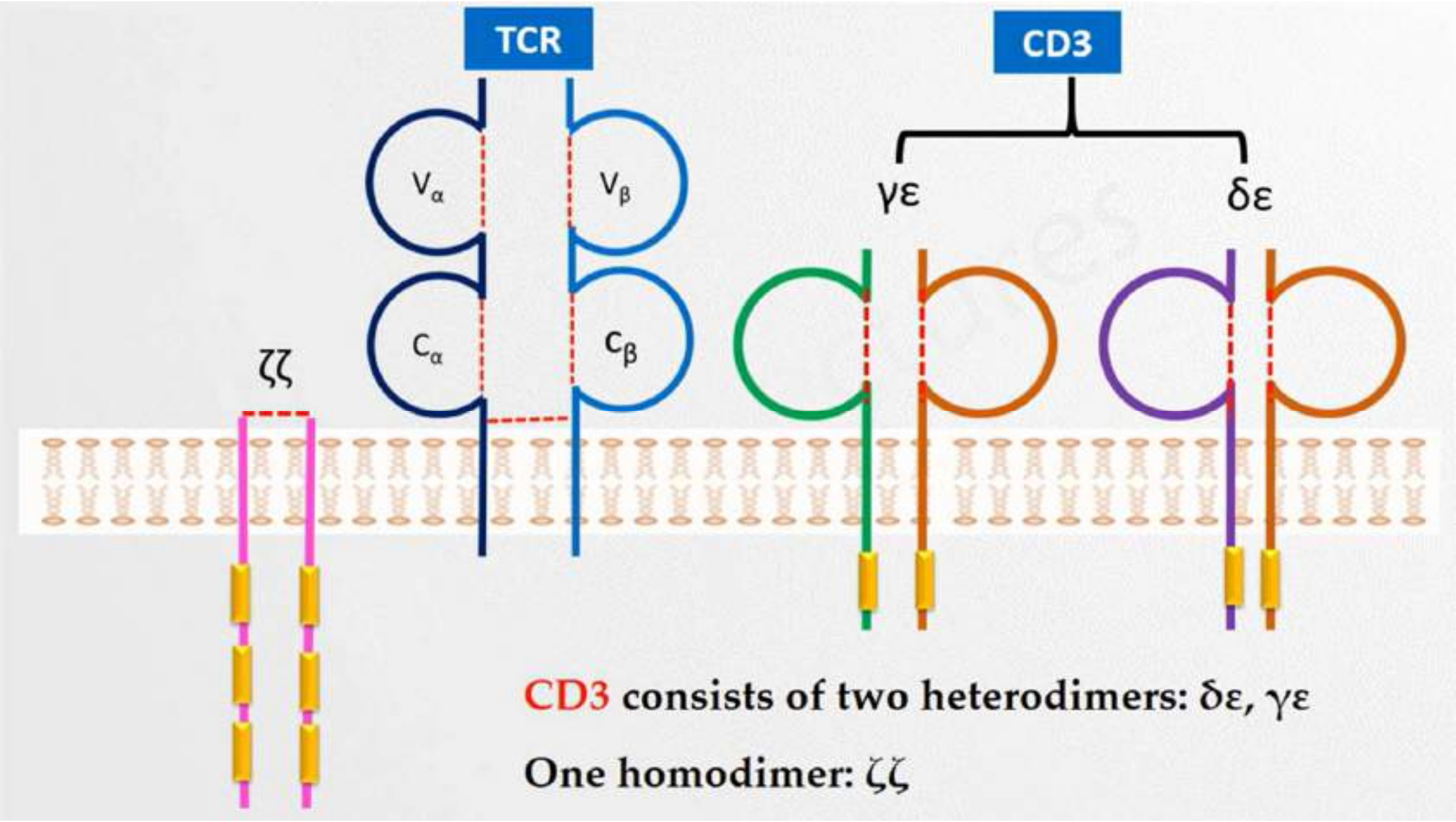






CD3 consists of two heterodimers: δε, γε

One homodimer: ζζ


TCR
CD3
V_α
V_β
C_α
C_β
γε
δε
ζζ
CD3 consists of two heterodimers: δε, γε
One homodimer: ζζ

T CELL RECEPTOR (TCR):

The figure shows a schematic diagram of a T cell receptor (TCR). Which is expressed on the surface of T cells as a heterodimer. The three dimensional structure of the TCR has been determined by X-ray crystallography.

The mature T cells display **thousands of heterodimer surface receptors** known as T cell receptor (TCR).

In the plasma membrane, the TCReceptor chains **α and β** are associated with **six additional adaptor proteins** to form an octameric complex.

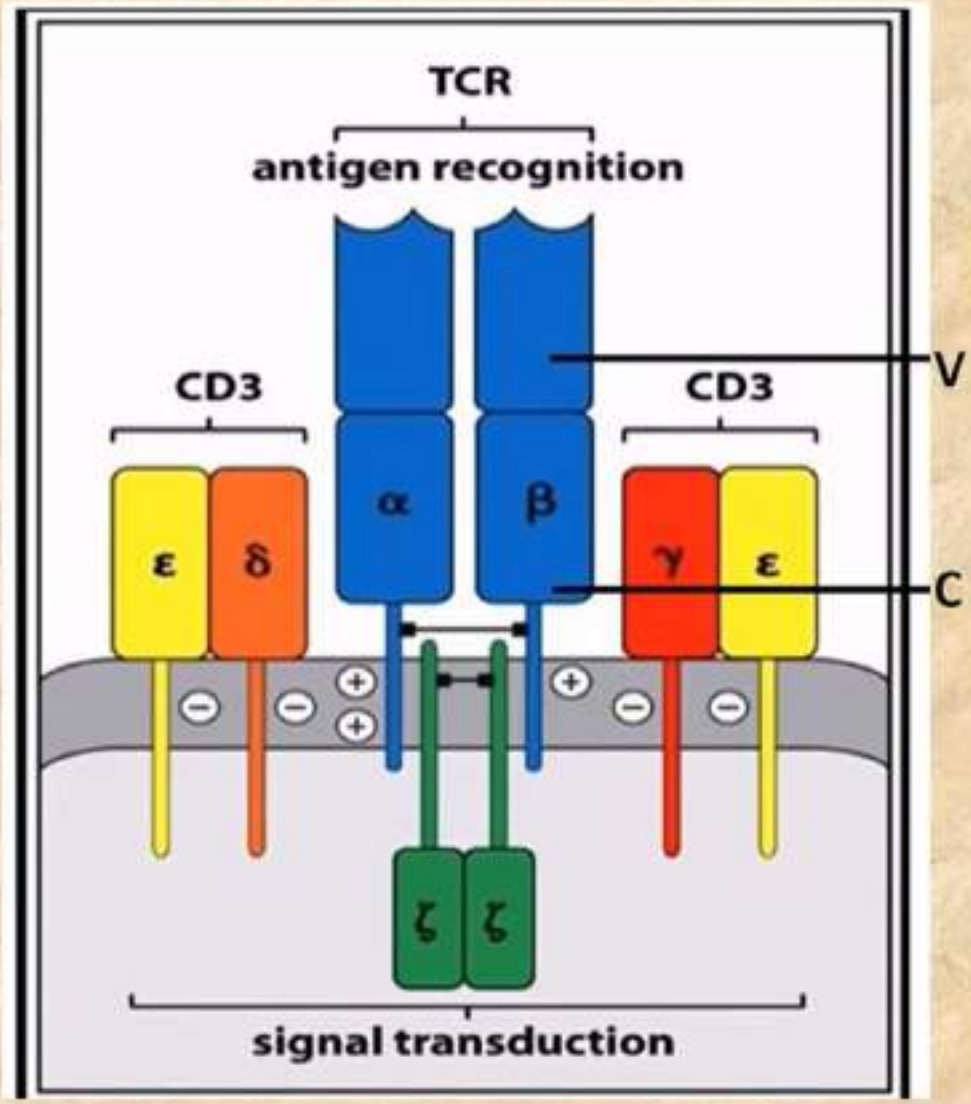


Fig. TCR-CD3 Complex

STRUCTURE OF T CELL RECEPTOR (TCR) :

It is a heterodimer of two polypeptide chains, alpha (40-50kDa) and beta (35-47 kDa), covalently linked by a **disulfide bond**. Both alpha and beta chains are similar to immunoglobulin, each consisting of a variable (**V**) and constant (**C**) region. Both α and β chains contribute to the **receptor formed by the V regions** and are also associated non-covalently with four different complex of proteins: gamma (γ), delta (δ),epsilon (ε) known as **CD3 molecule** along with zeta chain (ζ), to form an **octameric complex**.

The **variable regions** in both the α and β chains together forms **the Antigen binding site** and contributes to the **diversity of the T Cell Receptor**.

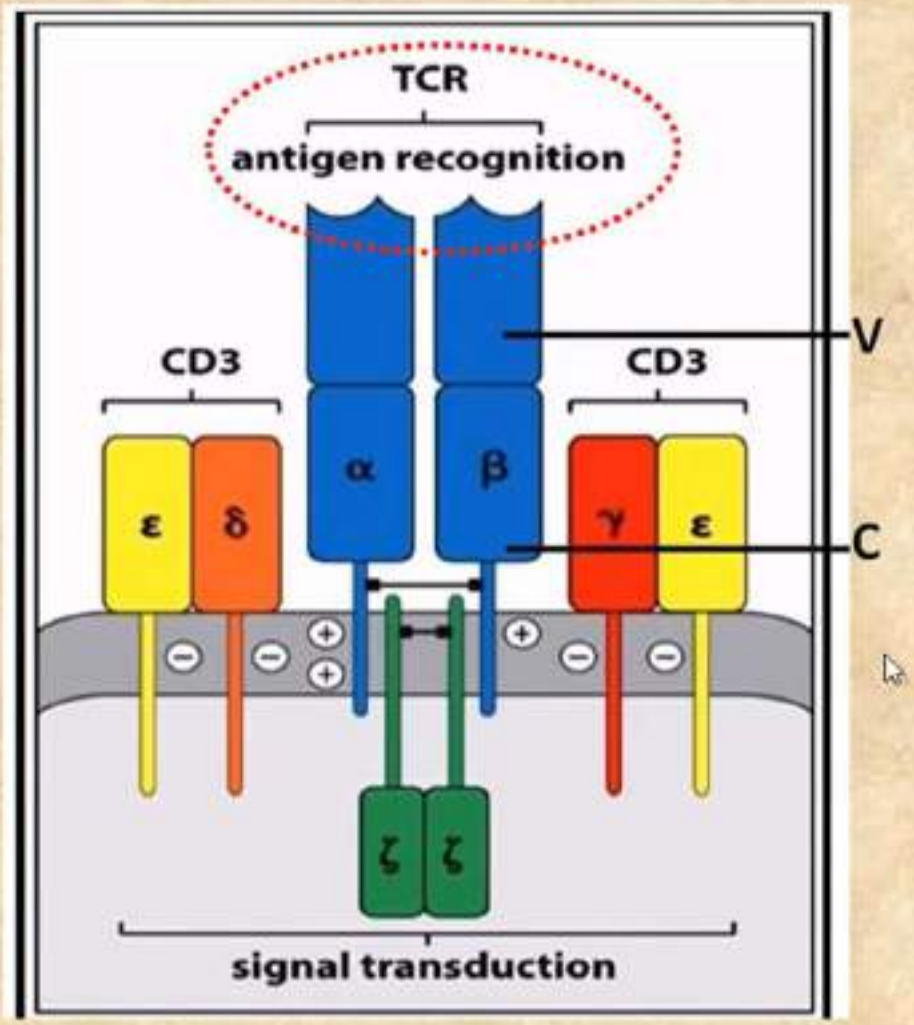
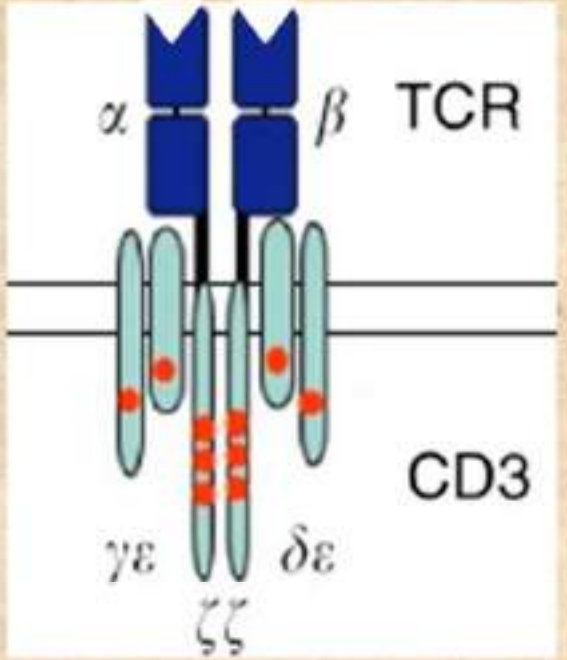


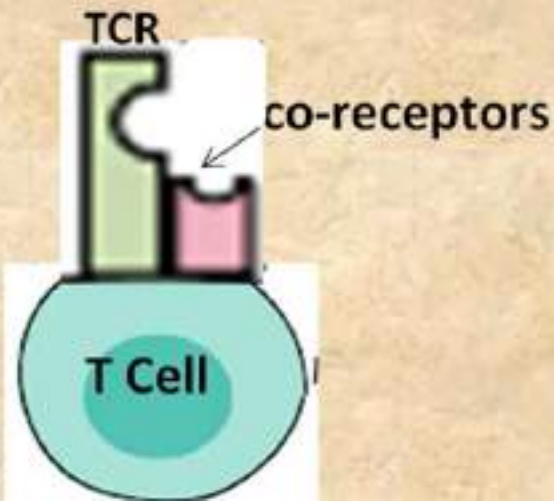
Fig. T cell Receptor-CD3 Complex

So, a TCR is a actually complex of proteins i.e. Alpha (α) and beta (β) proteins together forming the **antigen recognition sites** along with invariant CD3 proteins and the zeta proteins as **signaling molecules** .

The cytoplasmic tail of the TCR is extremely short, hence the **CD3 adaptor proteins contain the signalling motifs** needed for propagating the signal from the triggered TCR into the cell.



The **T Cell Receptor** present on all T cells**,** is a complex of polypeptides along with presence of **specific** membrane molecules called as **co-receptors.**



Cell-Mediated Effector Response

- The principal role of cell-mediated immunity is to detect and eliminate cells that harbor intracellular pathogens.
- Cell-mediated immunity also can recognize and eliminate cells, such as tumor cells, that have undergone genetic modifications so that they express antigens not typical of normal cells.
- The cell-mediated branch of the immune system involves two types of effector cells:

1) **antigen-specific effector cells**:
   - CD8+cytotoxic T lymphocytes (TC cells or CTLs) and
   - Cytokine-secreting CD4+ TH cells

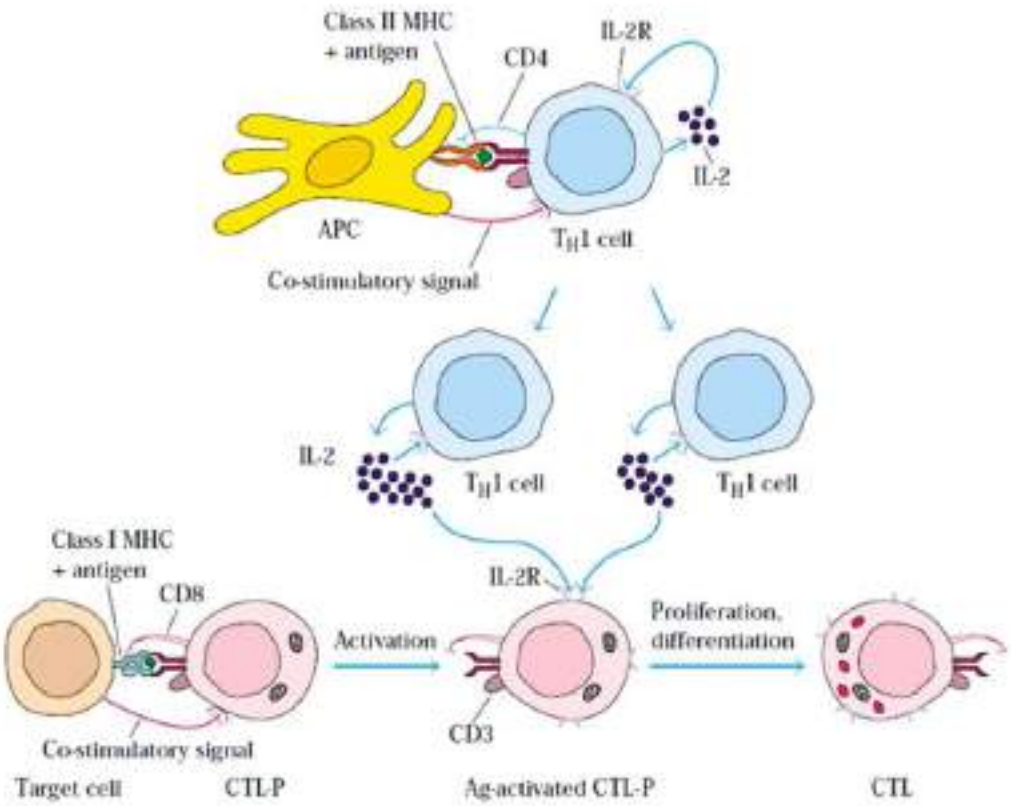
2) Nonspecific cells include NK cells and nonlymphoid cell types such as macrophages.

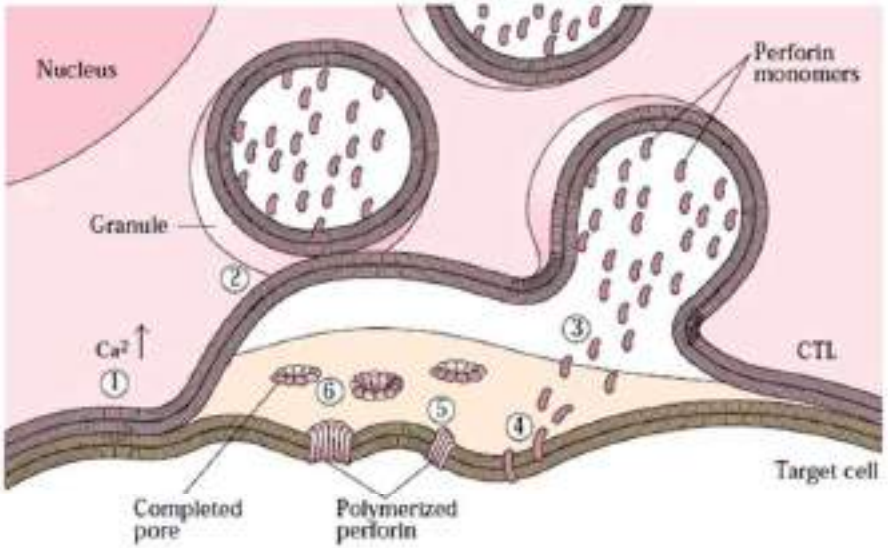
- The activity of both **specific** and **nonspecific** components usually depends on effective local concentrations of various cytokines.

Cytotoxic T Cells

- Cytotoxic T lymphocytes, or CTLs, are generated by immune activation of T cytotoxic (TC) cells.
- These effector cells have lytic capability and are critical in the recognition and elimination of altered self-cells (e.g., virus-infected cells and tumor cells).
- In general, CTLs are CD8+ and are therefore class I MHC restricted
- Two steps for TC cells mediated effector response:
  1) Generation of CTLs
  2) Killing of Target Cell by CTLs

- **Generation of CTLs:**
  - Upon interaction with antigen–class I MHC complexes on appropriate target cells, CTL-Ps begin to express IL-2 receptors (IL-2R) and lesser amounts of IL-2.
  - Proliferation and differentiation of antigen-activated CTL-Ps generally require additional IL-2 secreted by TH1 cells resulting from antigen activation and proliferation of CD4+ T cells.
  - In the subsequent effector phase, CTLs destroy specific target cells.

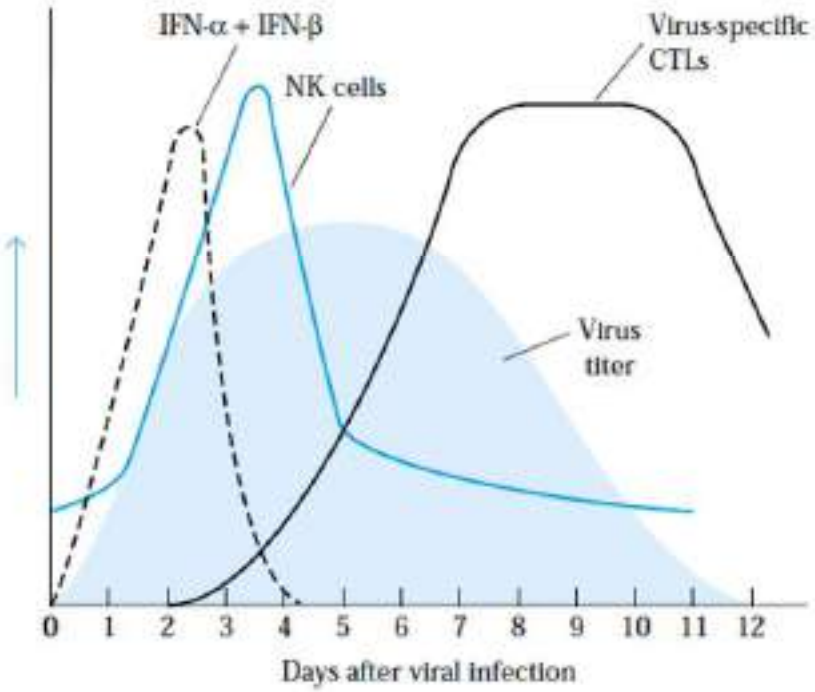




- CTL-mediated pore formation in target-cell membrane:
  - A rise in intracellular Ca^{2+}triggered by CTL target cell interaction (1) induces exocytosis, in which the granules fuse with the CTL cell membrane (2) and release monomeric perforin into the small space between the two cells (3). The released perforin monomers undergo a Ca^{2+}-induced conformational change that allows them to insert into the target-cell membrane (4). In the presence of $Ca^{2+}$the monomers polymerize within the membrane (5), forming cylindrical pores which leads to the cell death by apoptois

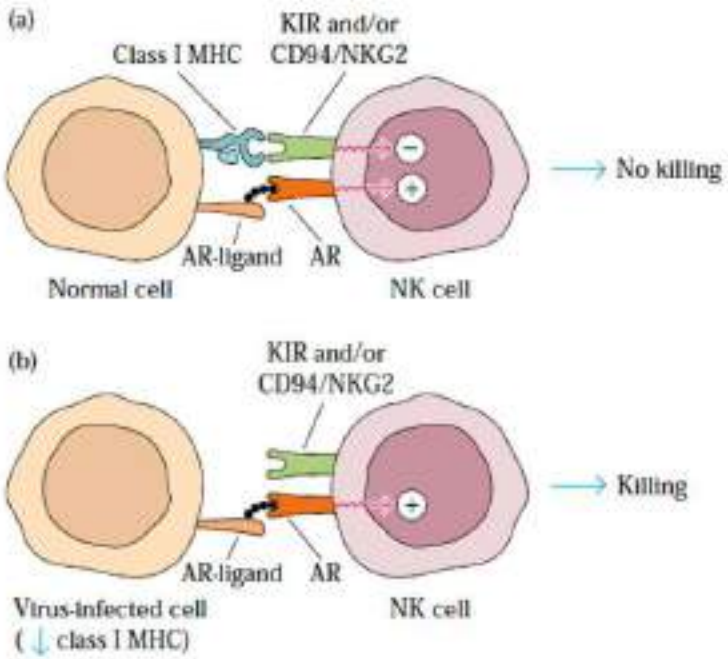
Natural Killer Cells

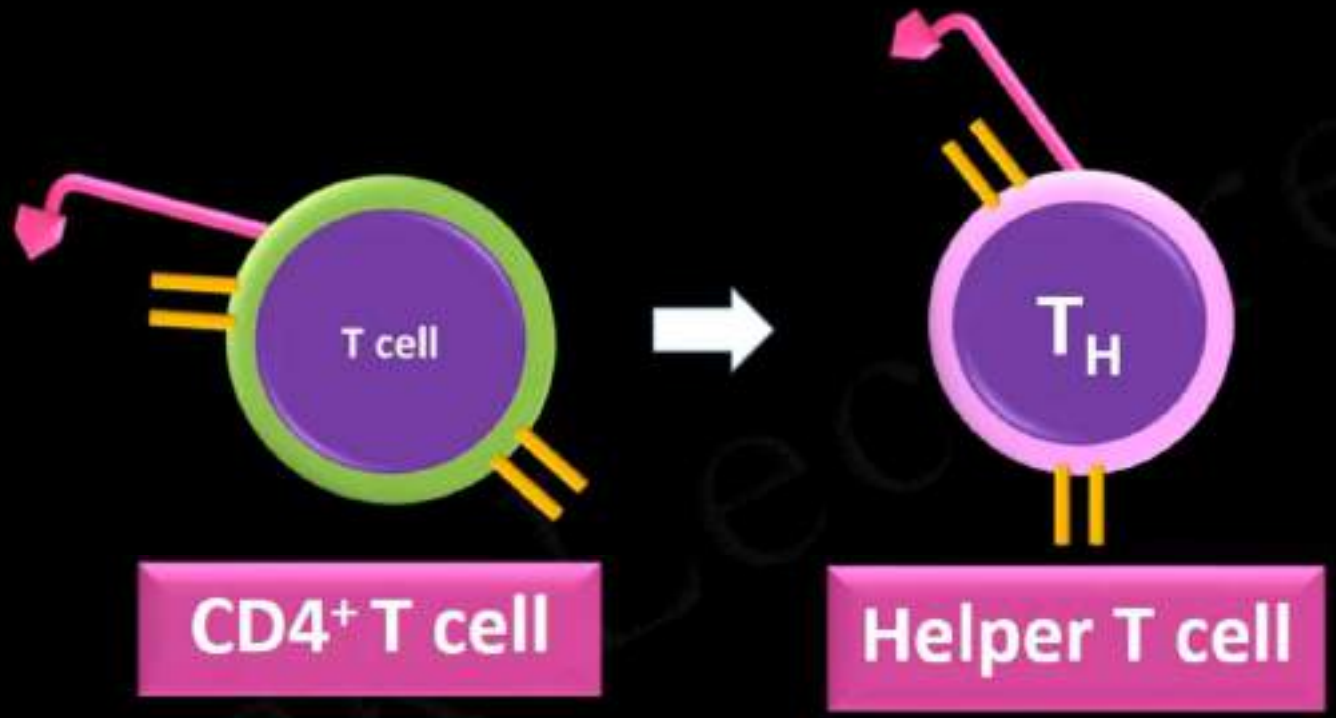
- NK cells are involved in the early response to infection with certain viruses and intracellular bacteria.
- NK activity is stimulated by IFN-α IFN-β and IL-12.
- In the course of a viral infection, the level of these cytokines rapidly rises, followed closely by a wave of NK cells that peaks in about 3 days



Natural Killer Cells

- **How cytotoxic activity of NK cells is restricted to altered self-cells?**
- An activation receptor (AR) on NK cells interacts with its ligand on normal and altered self-cells, inducing an activation signal that results in killing.
- However, engagement of inhibitory NK cell receptors such as KIR and CD94/NKG2 by class I MHC molecules delivers an inhibitory signal that counteracts the activation signal.
- Expression of class I molecules on normal cells thus prevents their destruction by NK cells. Because class I expression is often decreased on altered self-cells, the killing signal predominates, leading to their destruction.





Helper T cells help other cells of the immune system to eliminate the pathogens.

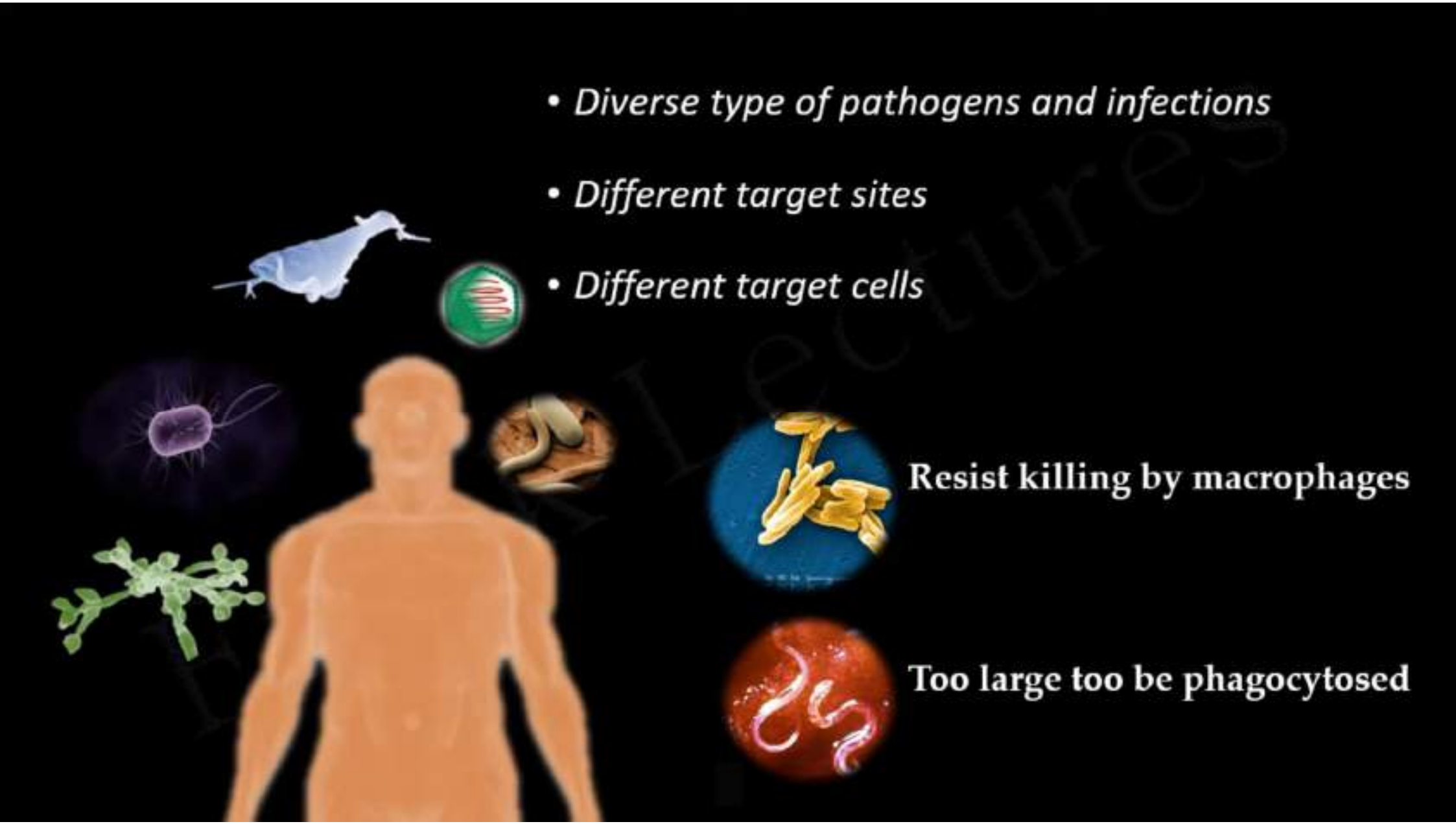
Helper T cell Subsets

1. T_H1 cells
2. T_H2 cells
3. T_H17 cells
4. T_{FH} cells
5. T_{reg} cells

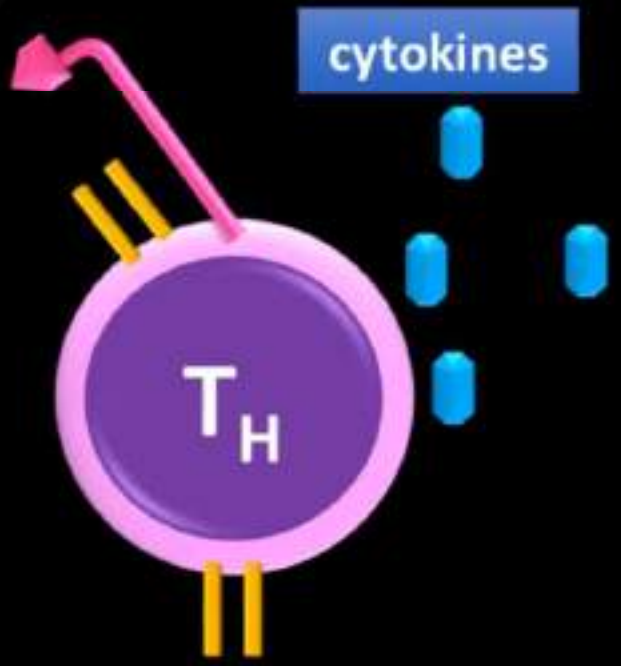
Basis of this classification:

- *Cytokines that induce their differentiation*
- *Master transcriptional regulator*
- *Cytokines they produce and secrete*

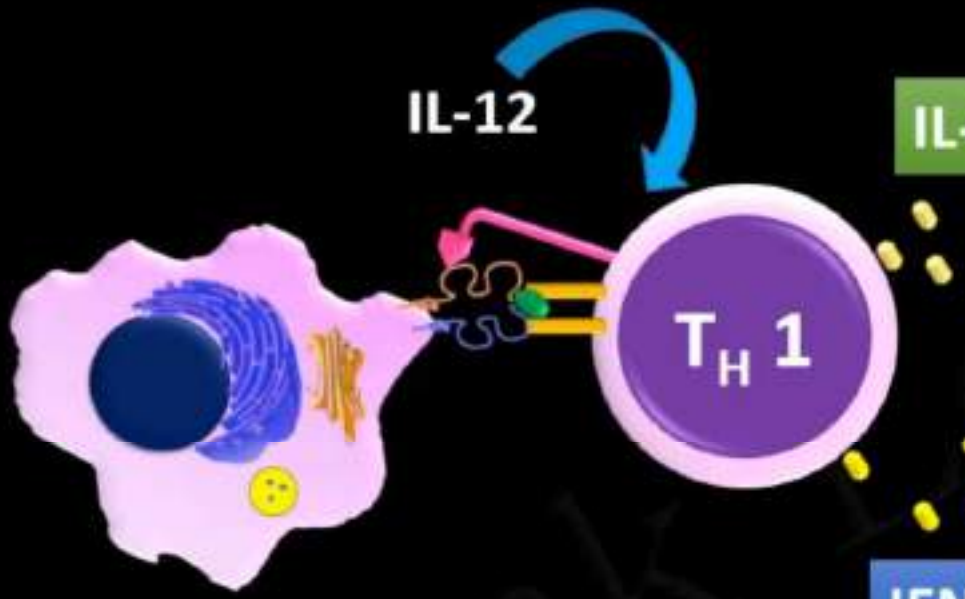
Why such diverse types of Helper T cells needed by our immune system?


• Diverse type of pathogens and infections
• Different target sites
• Different target cells
Resist killing by macrophages
Too large too be phagocytosed

Helper T cells works **by secreting cytokines which communicate with the other cells of the immune system** and activate them to eliminate the pathogens by appropriate immune response.



When there is an intracellular infection



IL-2

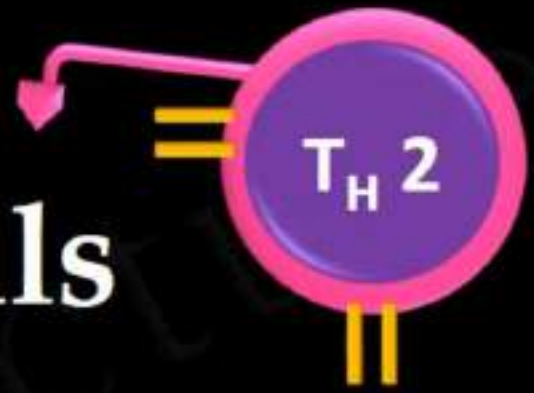
- Promotes growth and differentiation of other T cells

IFN-γ

- Activates the macrophages

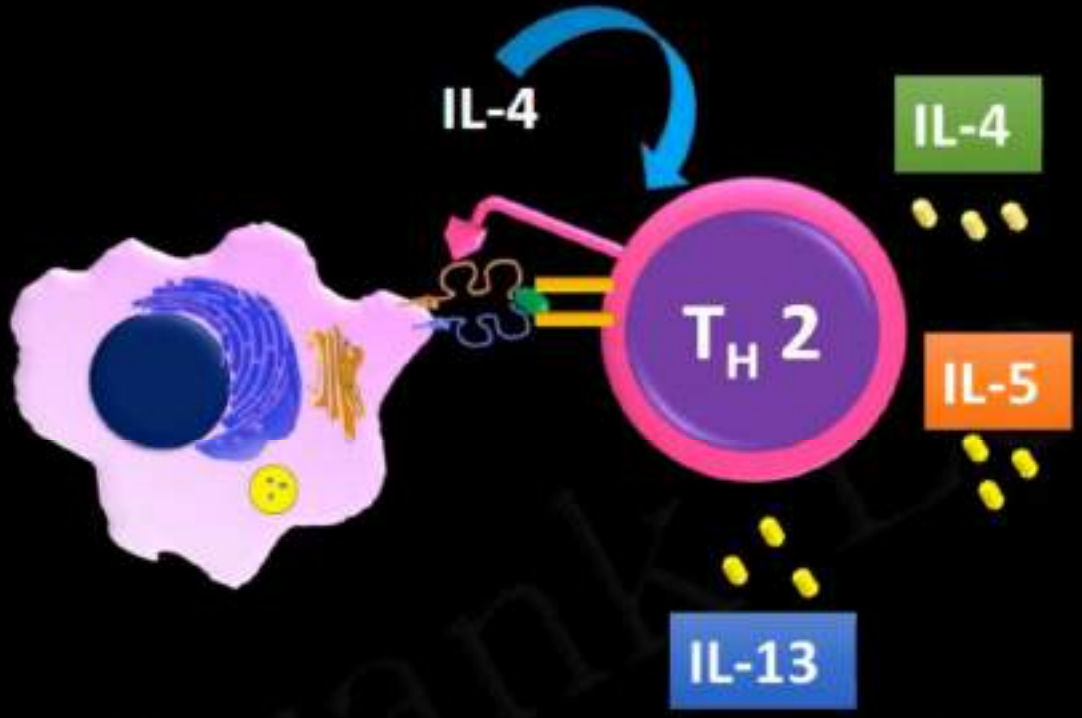
- Also stimulates production of antibodies

T_H2 cells

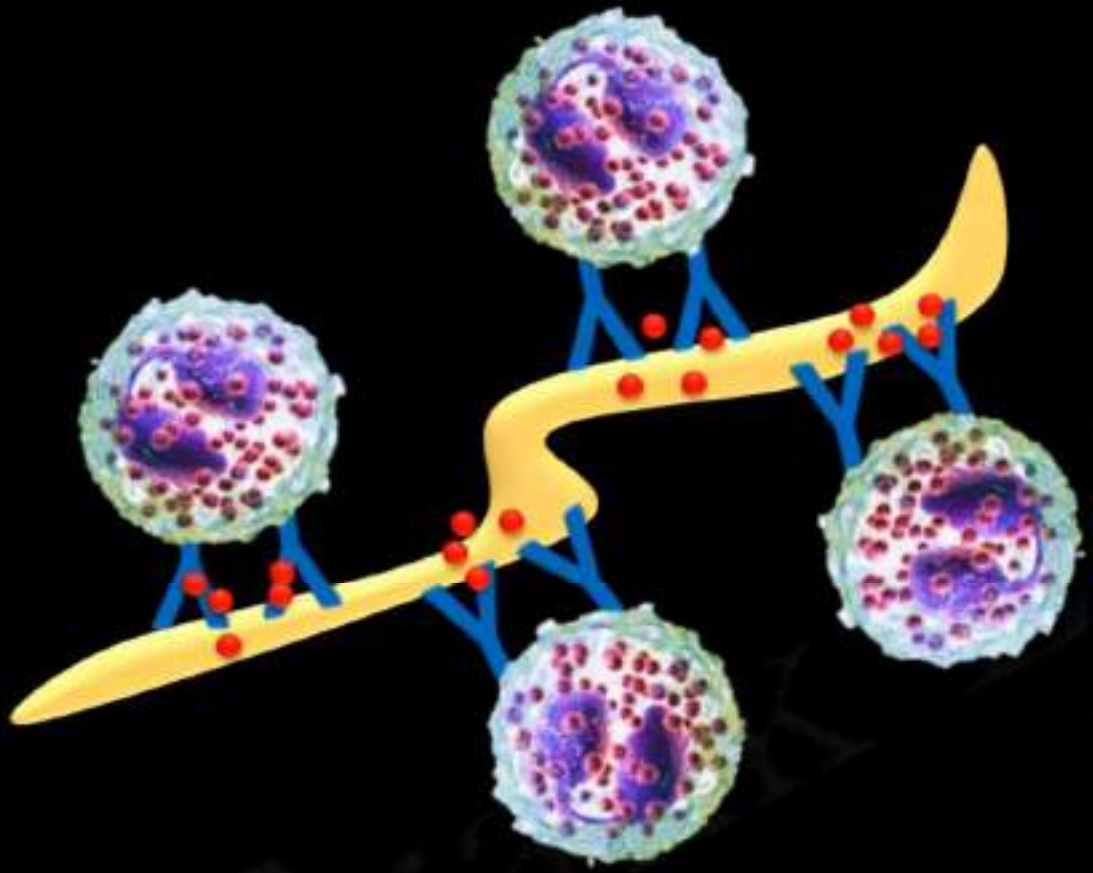


T helper Type 2 cells or Type 2 T Helper cells

When there is a infection by parasites



- Stimulates B cells to produce IgE antibodies
- Activates mast cells and eosinophils
- Induces production of mucus in the intestines

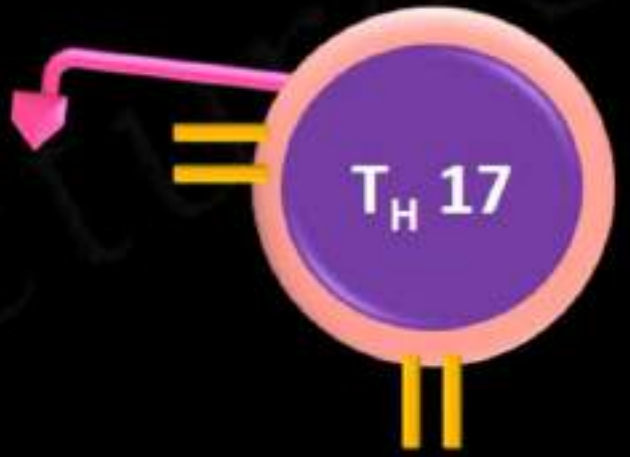


1. IgE antibodies coat the surface of the parasite

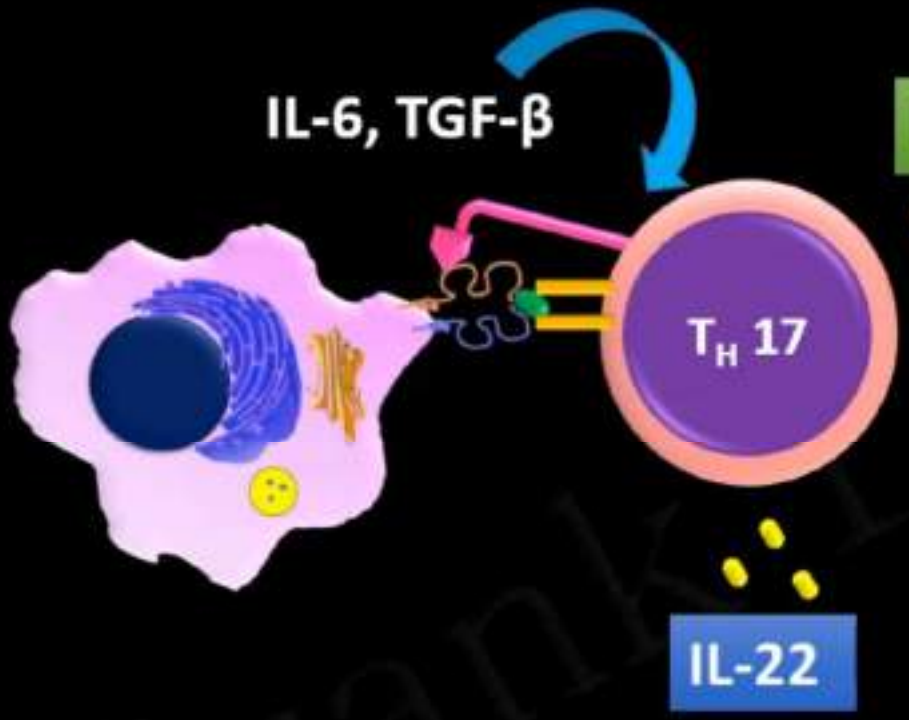
2. Mast cells and eosinophils bind to the Fc region of these bound antibodies.

3. The enzymes released by degranulation of these cells result in the destruction of parasite.

T_H17 cells



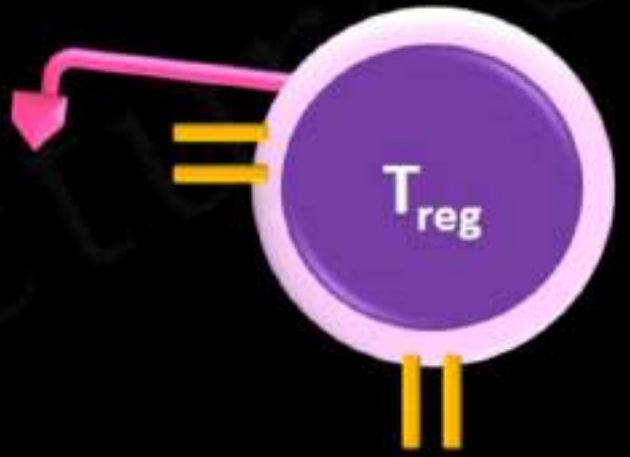
When there is a infection by fungi or extracellular bacteria



- Recruit neutrophils to the site of infection

- Stimulate epithelial cells to produce antimicrobial peptides

T_{reg} cells

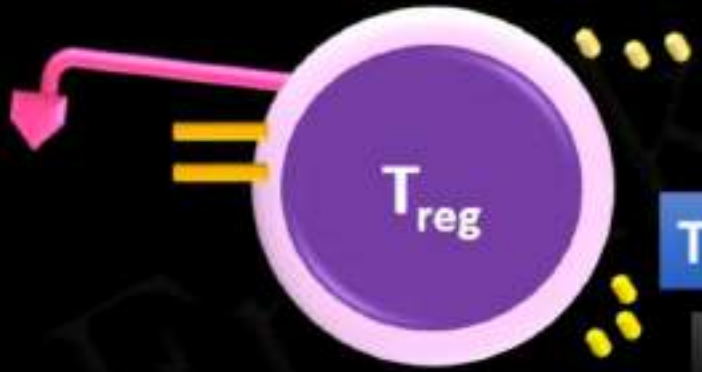


Regulatory T cells

(earlier known as Suppressor T cells)

Once a pathogen is eradicated

- Suppress T cell responses and limit immune response
- Prevent Autoimmunity



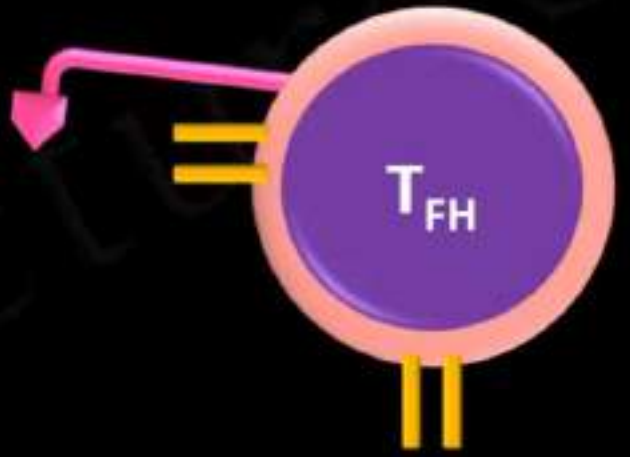
IL-10

- Potent suppressor of macrophage funtions

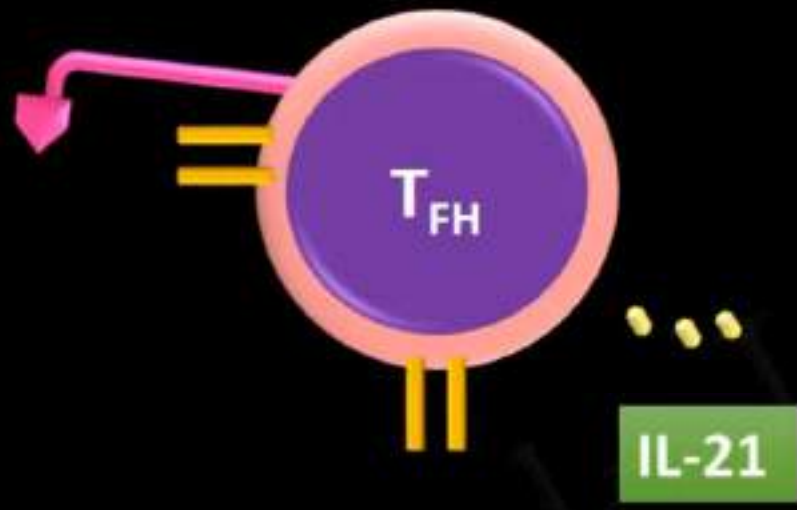
TGF-β

- Induces generation of more T_{reg} cells

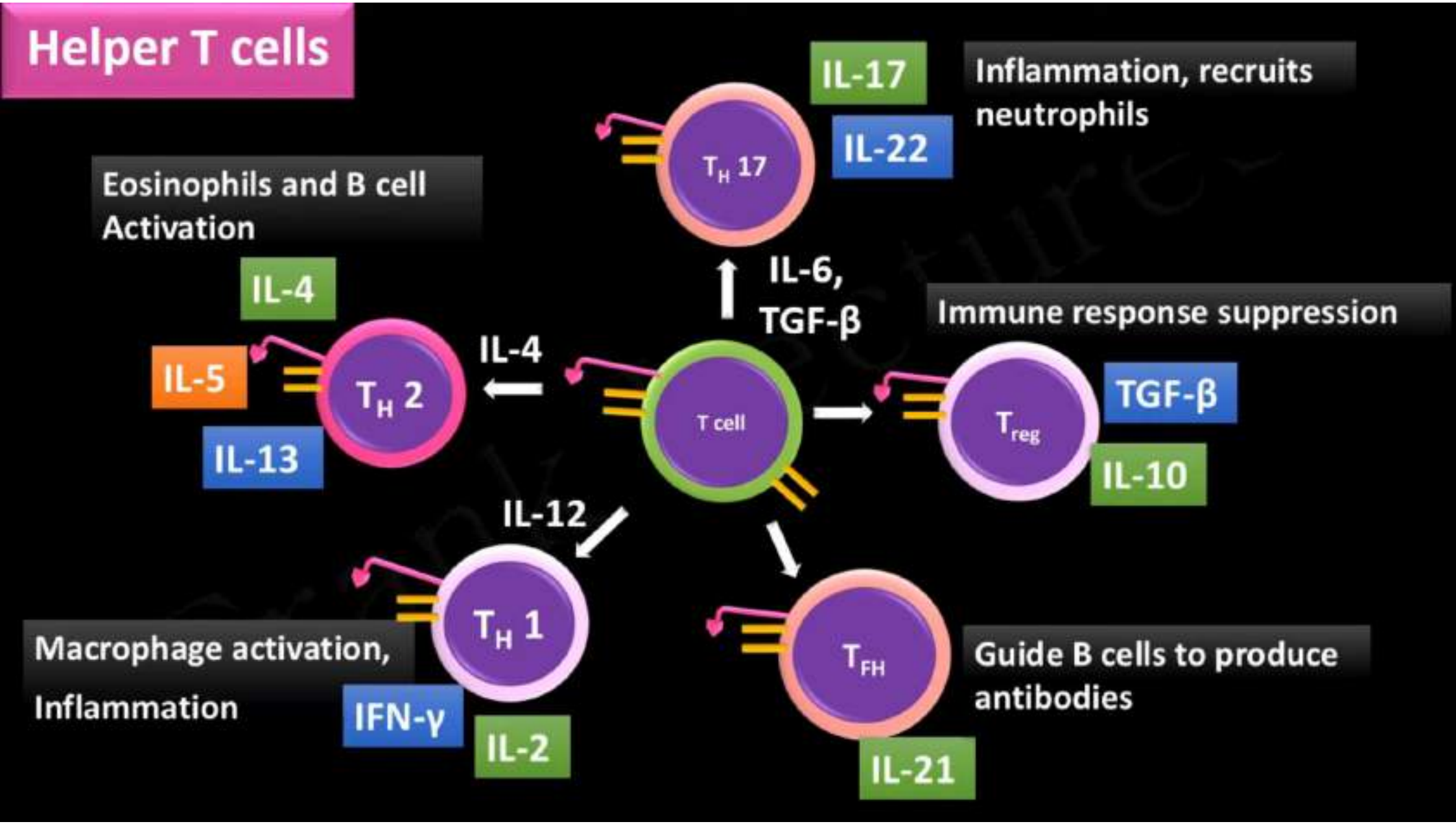
T_{FH} cells



Follicular Helper T cells

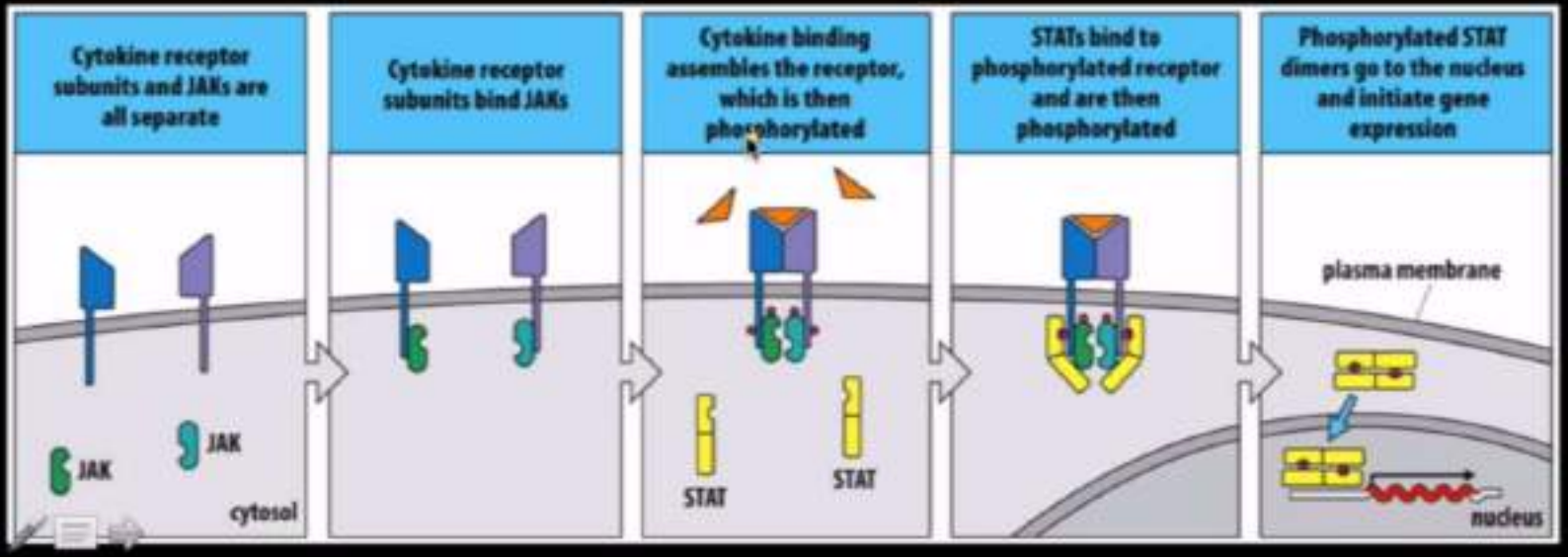


- Guide B cells to make appropriate antibodies to clear particular infection


Helper T cells
IL-17
IL-22
Inflammation, recruits neutrophils
T_H 17
Eosinophils and B cell Activation
IL-4
IL-5
IL-13
T_H 2
IL-4
IL-6, TGF-β
T cell
Immune response suppression
T_{reg}
TGF-β
IL-10
IL-12
T_H 1
Macrophage activation, Inflammation
IFN-γ
IL-2
T_{FH}
Guide B cells to produce antibodies
IL-21

Effector T-cell functions are mediated by cytokines and cytotoxins and cytokines change the pattern of gene expression in the cells targeted by effector T cells

CD8 T cells		CD4 T cells				
Cytotoxic T cells		T_H1 cells	T_H2 cells	T_{FH} cells	T_H17 cells	T regulatory cells (T_{reg})
Cytotoxins	Cytokines	Cytokines	Cytokines	Cytokines	Cytokines	Cytokines
perforin granzymes granulysin serglycin	IFN-γ LT IL-2	IFN-γ GM-CSF TNF-α LT IL-2	IL-4 IL-5 IL-10 IL-13 TGF-β	IL-21 IL-4 IFN-γ	IL-17 IL-21 IL-22 IL-26	TGF-β IL-10 IL-35
Kill virus-infected cells		Help macrophages to suppress intracellular infections	Help basophils, mast cells, eosinophils, and B cells respond to parasite infections	Help B cells become activated, switch isotype, and increase antibody affinity	Enhance the neutrophil response to fungal and extracellular bacterial infections	Suppress the activities of other effector T-cell populations



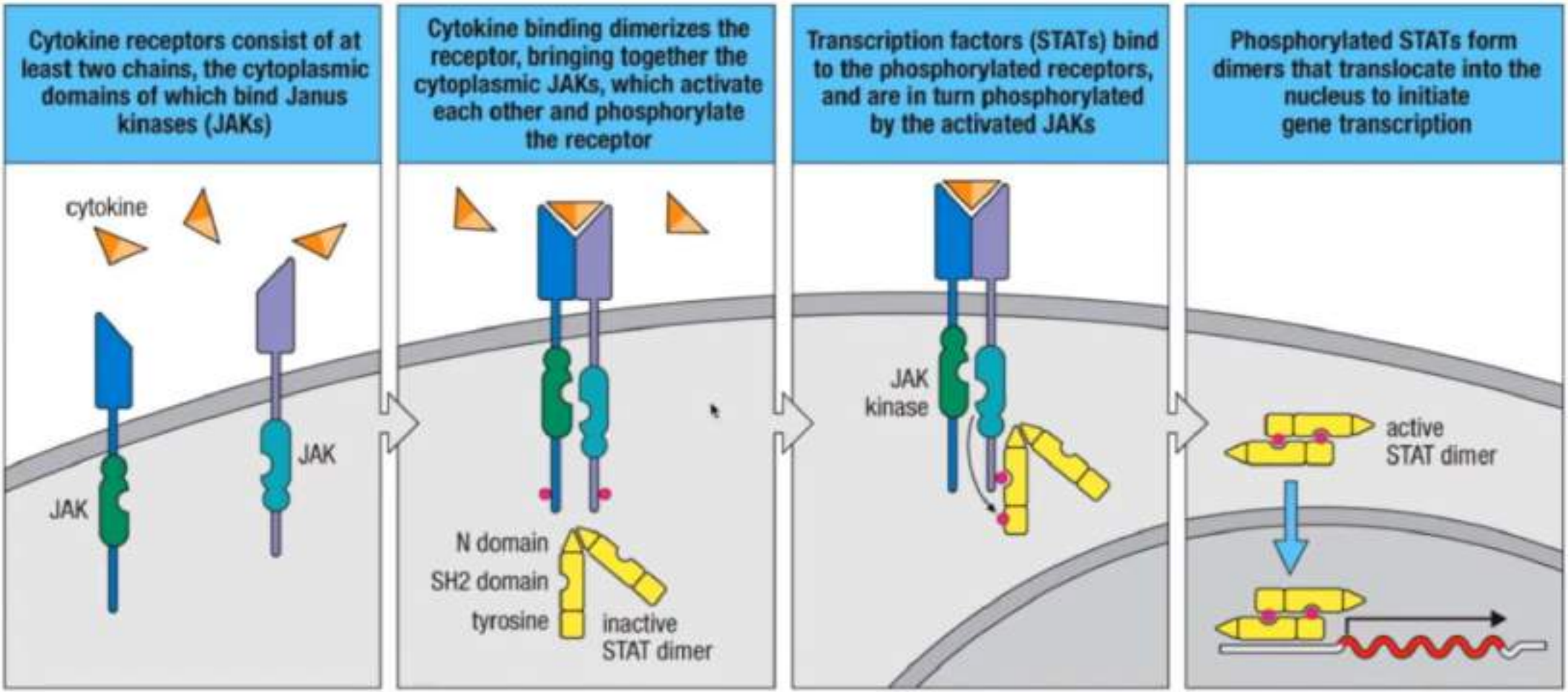
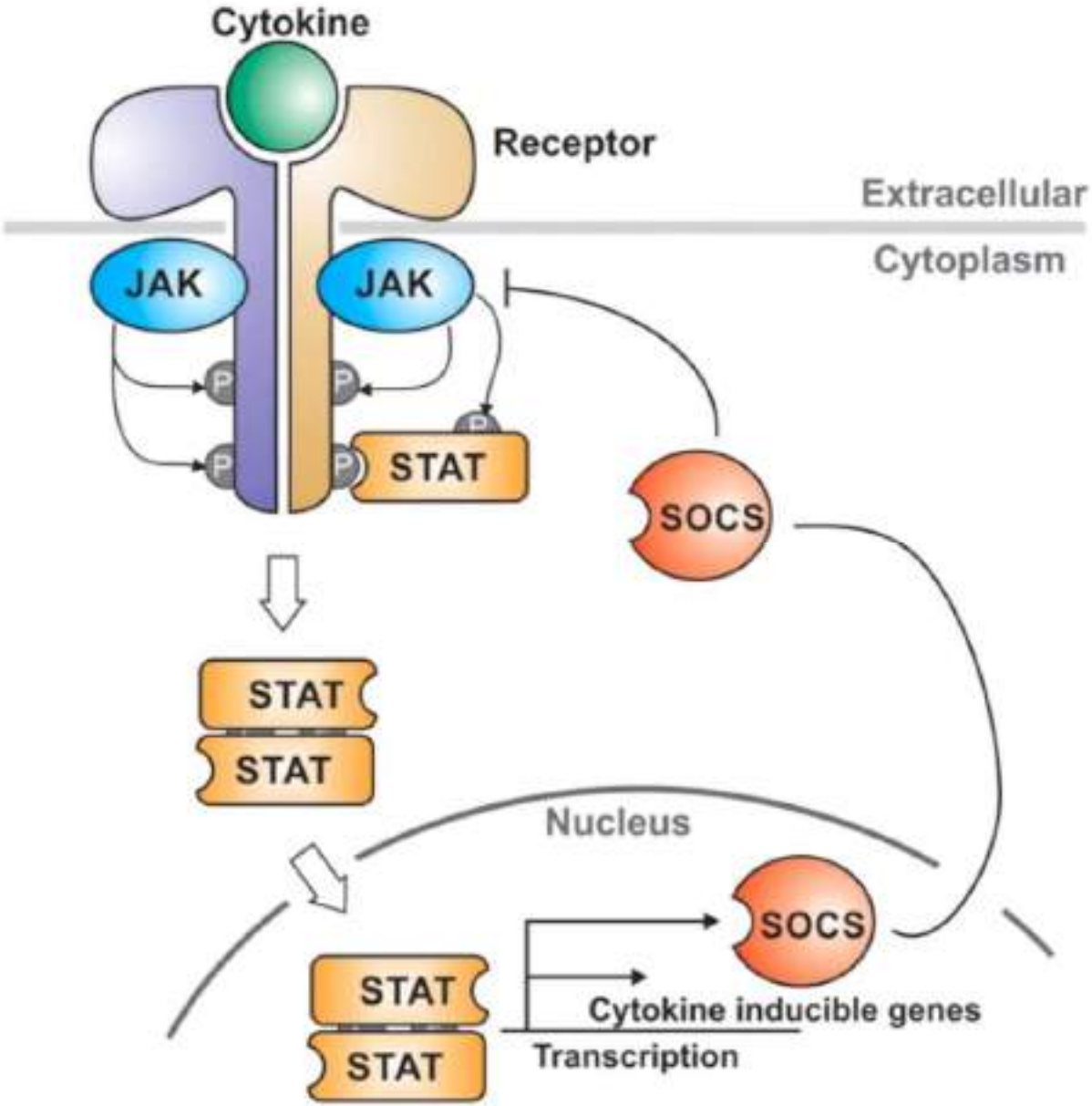
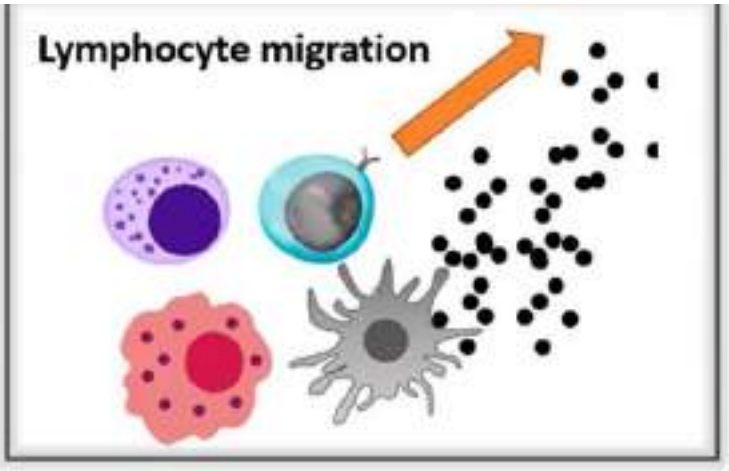
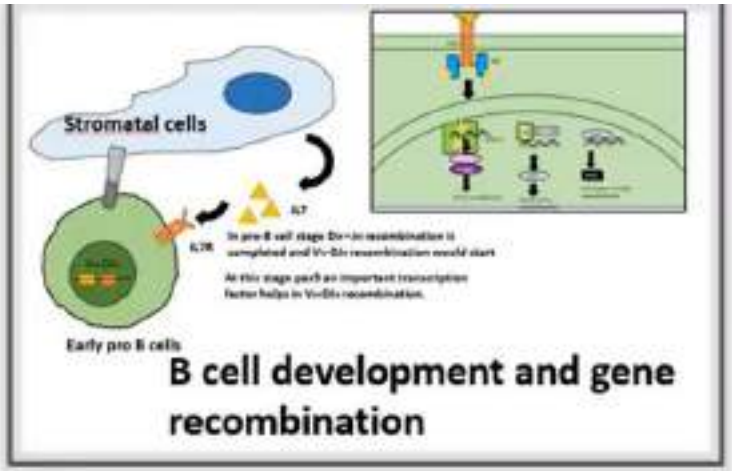


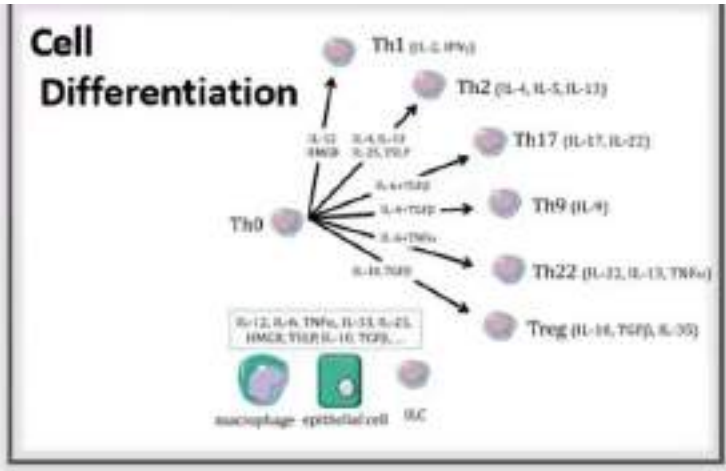
Figure 3.26 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)



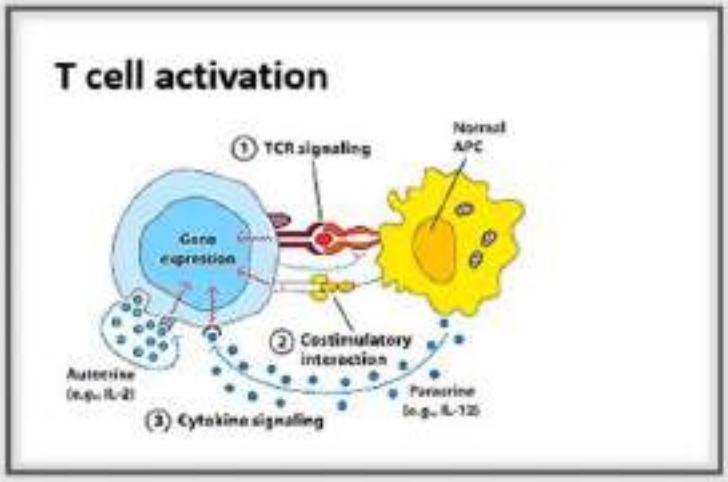
Cytokine signals can self-limit by inducing expression of **SOCS** (suppressor of cytokine signaling)

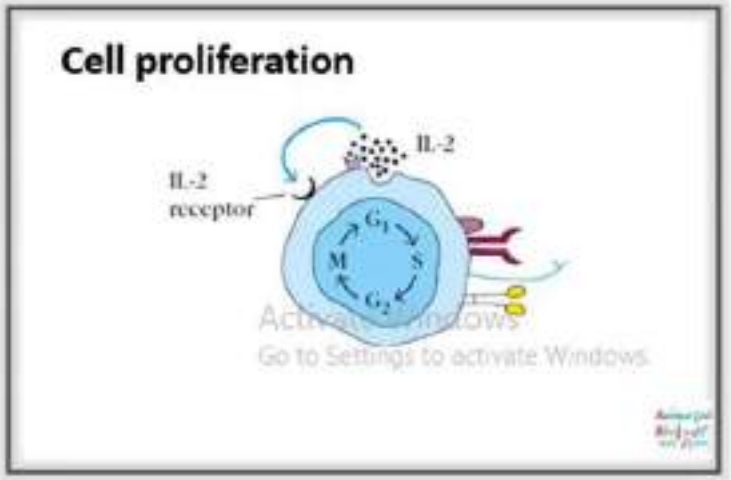


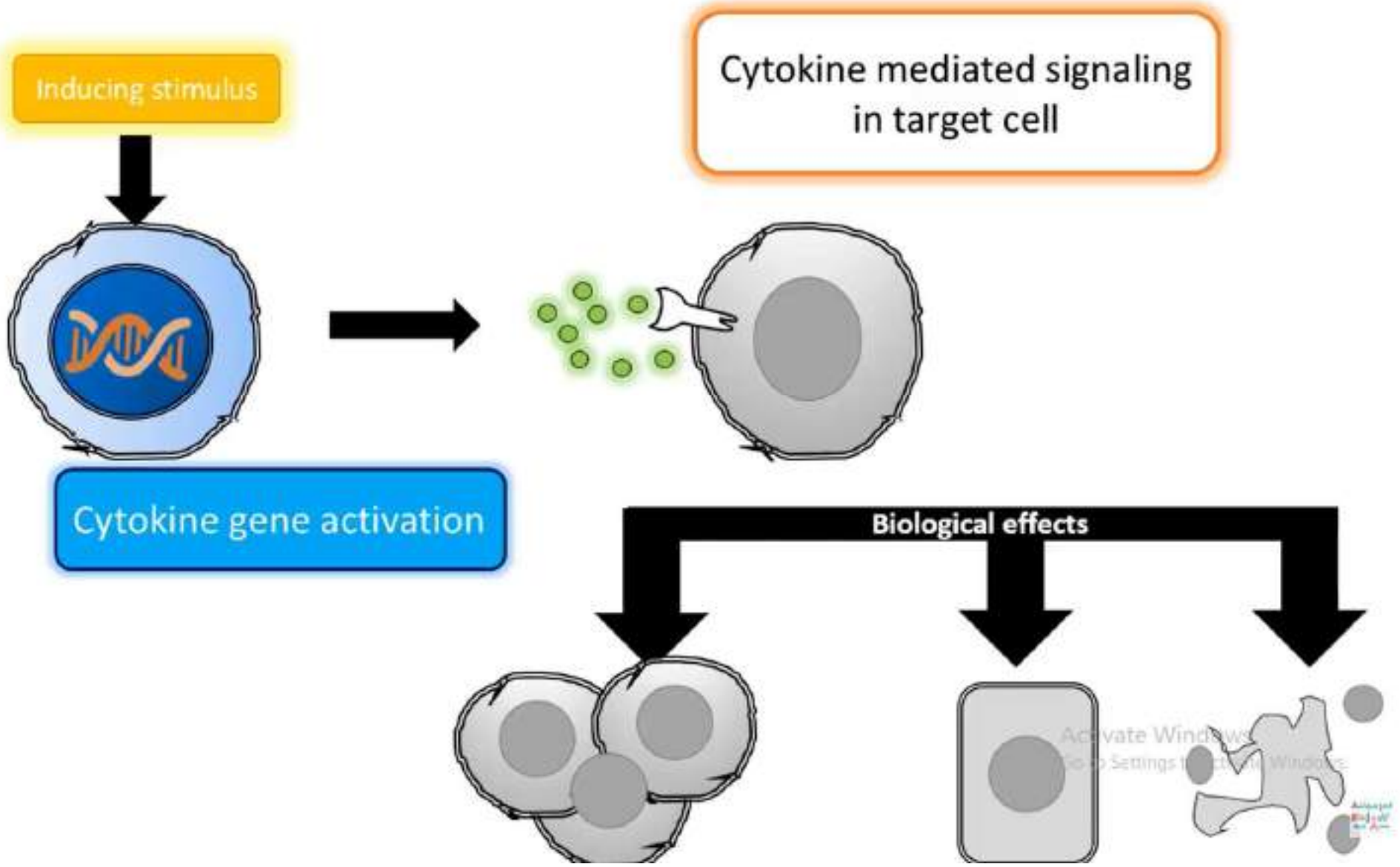




Function of Cytokine






Inducing stimulus
Cytokine mediated signaling in target cell
Cytokine gene activation
Biological effects

Communication modes used by the immune system