TCR-T CELL SIGNALLING

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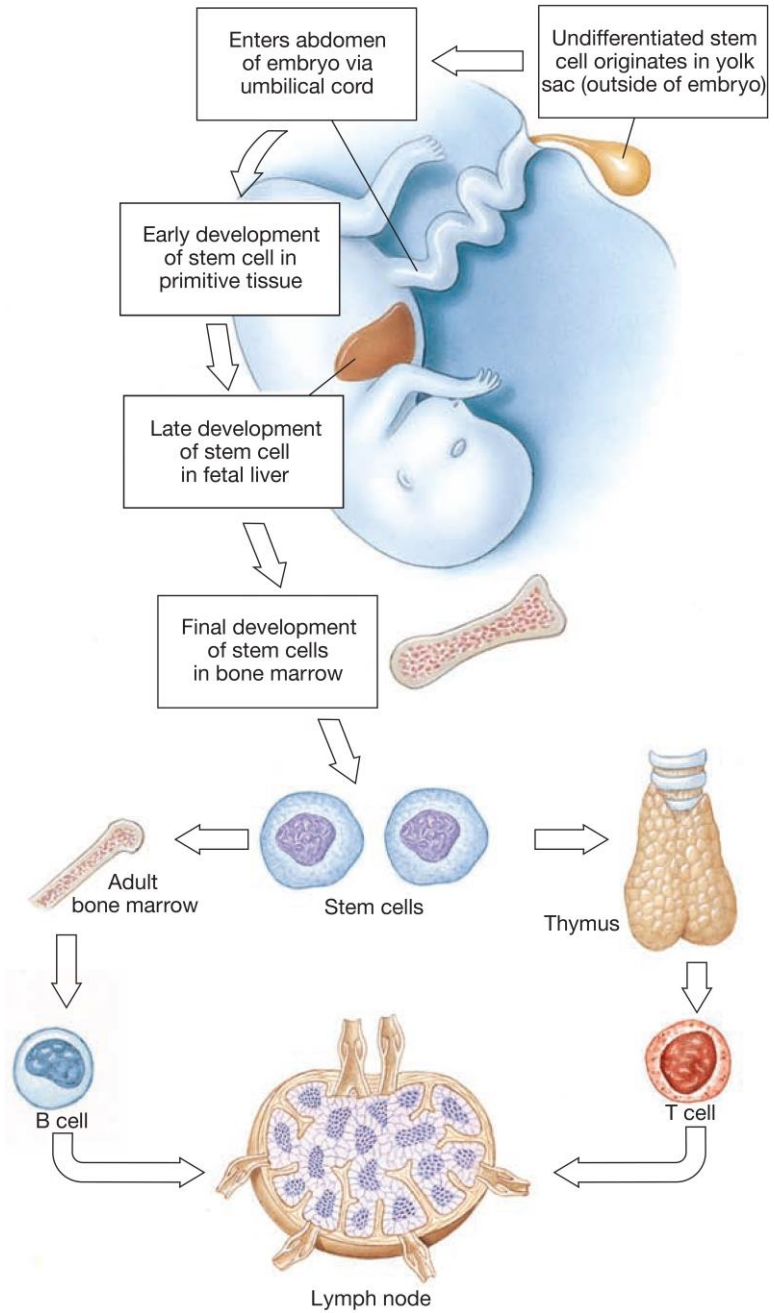
REFERENCE

1. **ROITT'S ESSENTIAL IMMUNOLOGY**
2. **KUBY IMMUNOLOGY**
3. **CELLULAR AND MOLECULAR IMMUNOLGY ABBAS**
4. **IMMUNOLGY MALE AND BROSTOFF**
5. **IMMUNOLOGY KHAN**
6. **CELL BRUCE ALBERTS**



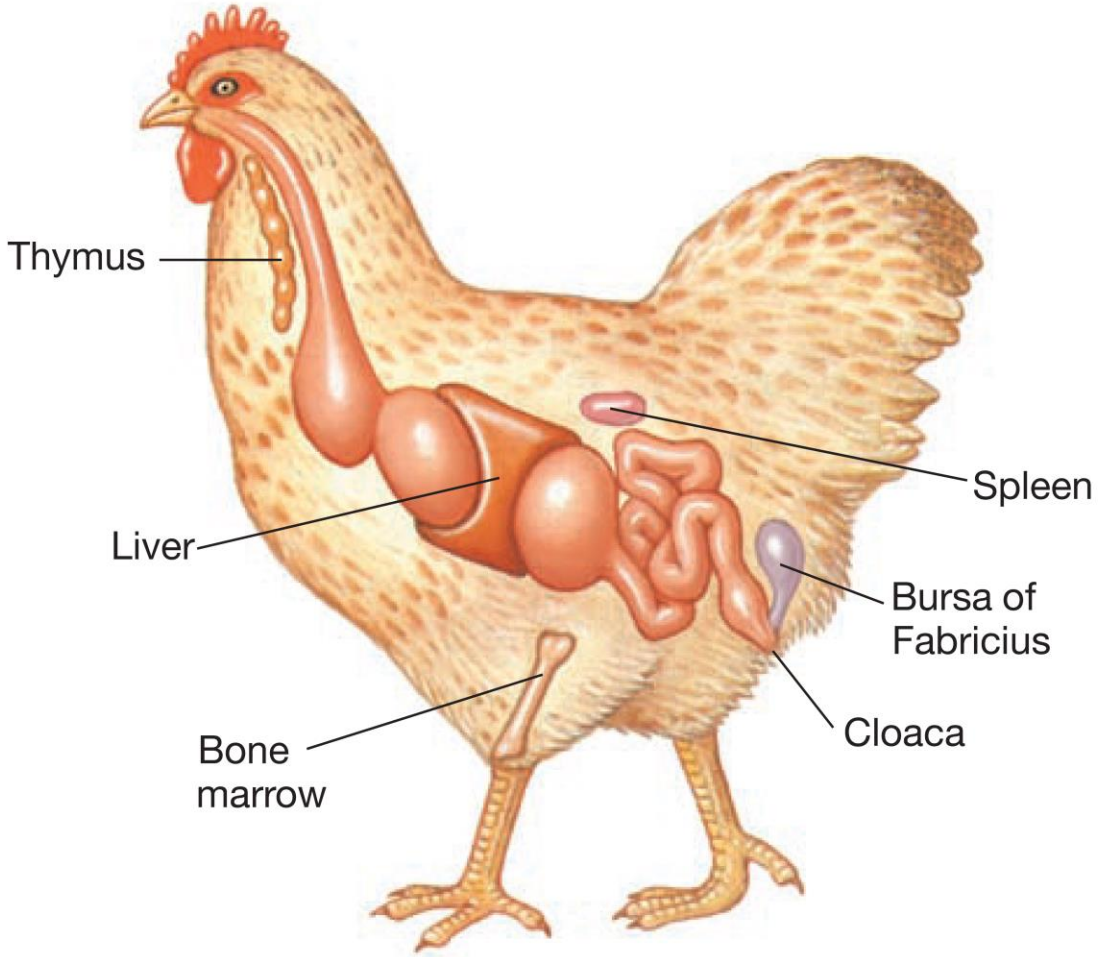
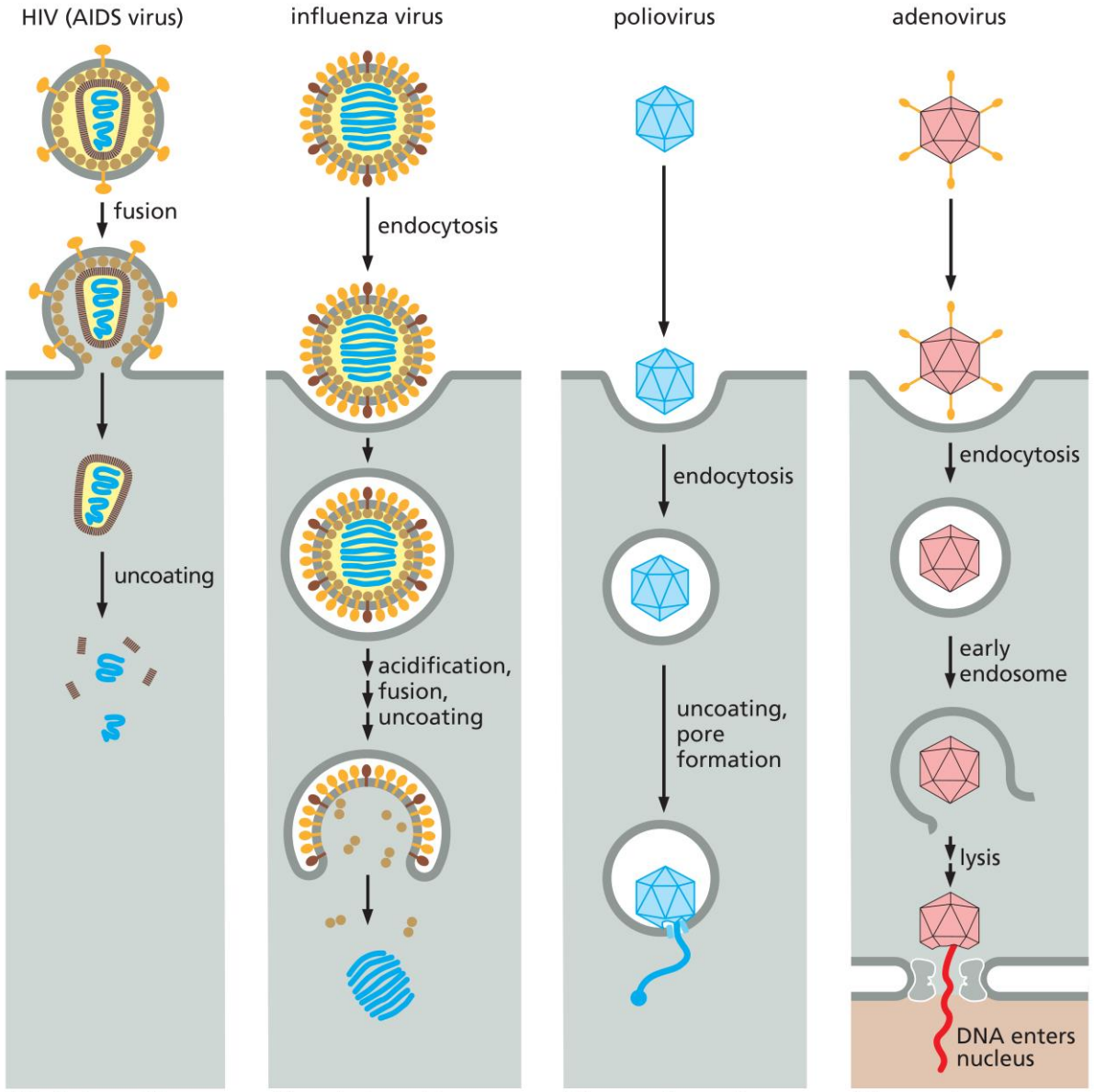
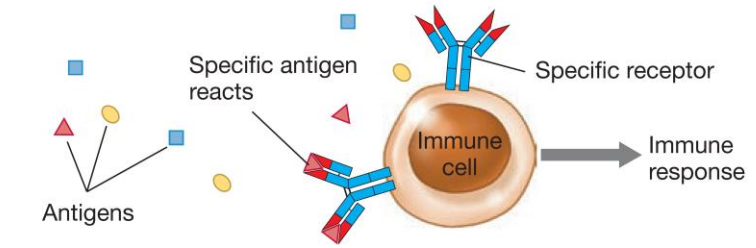


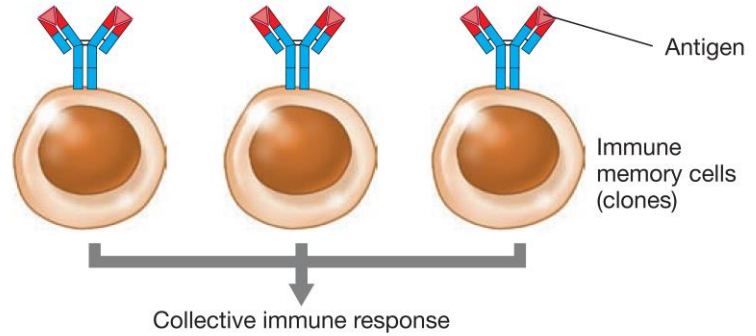
FIGURE 17.4 The bursa of Fabricius. In chickens this is where B cells develop. It is a pouch located off the cloaca, a chamber into which waste and reproductive materials empty.





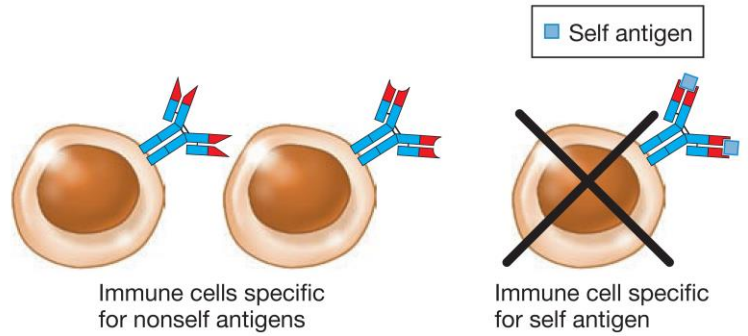
Specificity: Immune cells have surface receptors that interact with individual antigens.

(a)

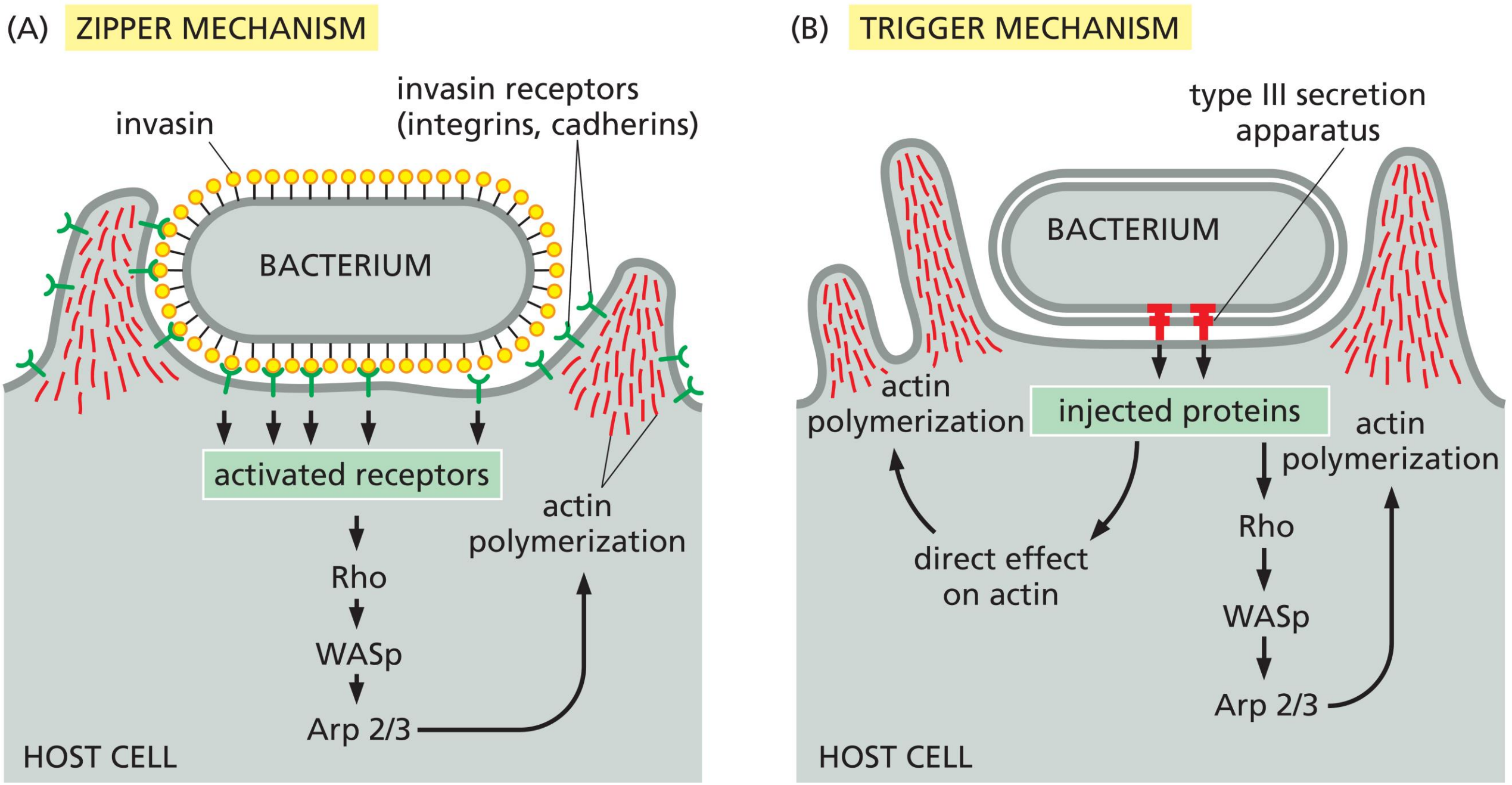


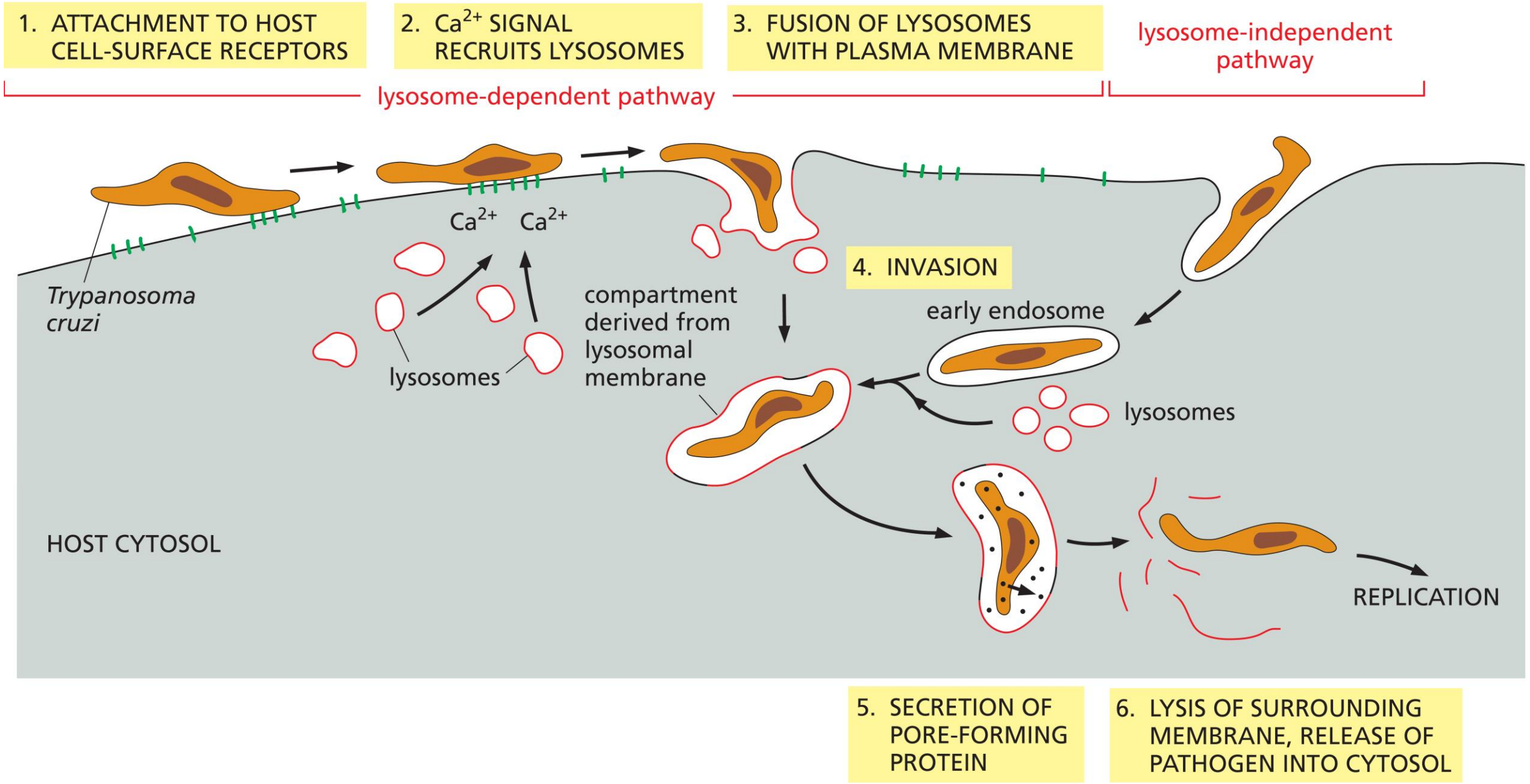
Memory: The first antigen exposure induces multiplication of antigen-reactive cells, resulting in multiple copies, or *clones*. After a subsequent exposure to the same antigen, the immune response is faster and stronger due to the large number of responding cells.

(b)



Tolerance: Immune cells are not able to react with self antigen. Self-reactive cells are destroyed during development of the immune response.





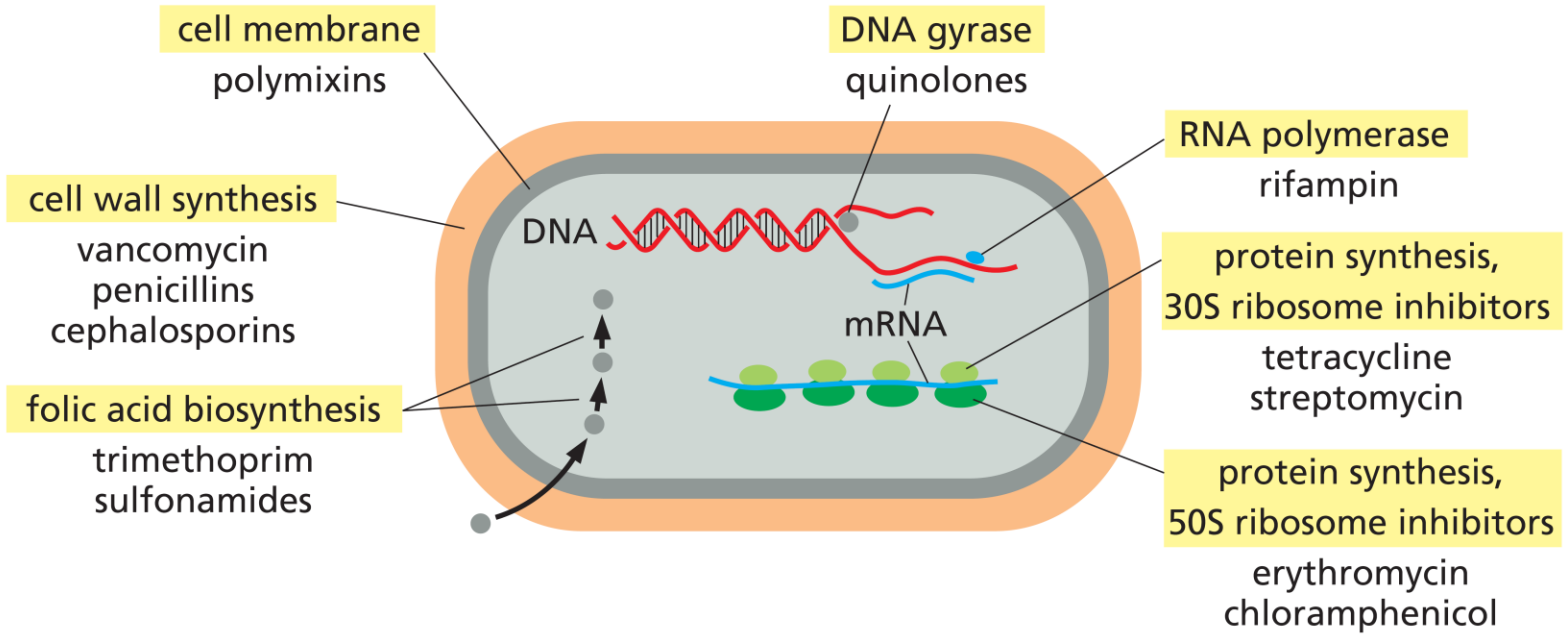
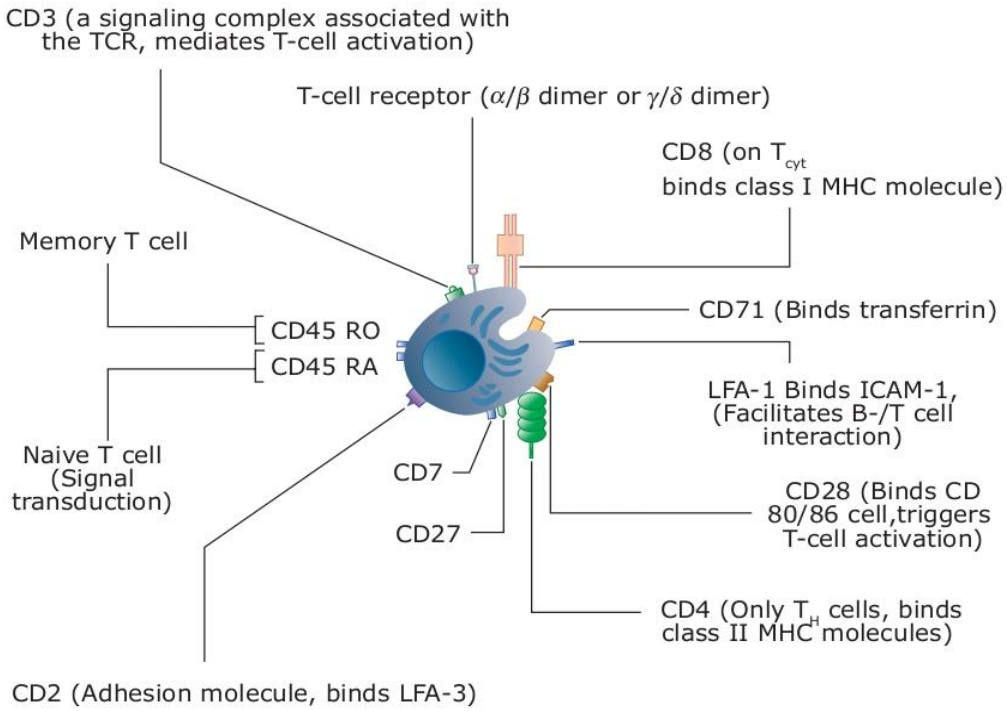


Figure 23–33 Antibiotic targets. Although there are many antibiotics in clinical use, they have a narrow range of targets, which are highlighted in *yellow*. A few representative antibiotics in each class are listed. Nearly all antibiotics used to treat human infections fall into one of these categories. The vast majority inhibit either bacterial protein synthesis or bacterial cell wall synthesis.



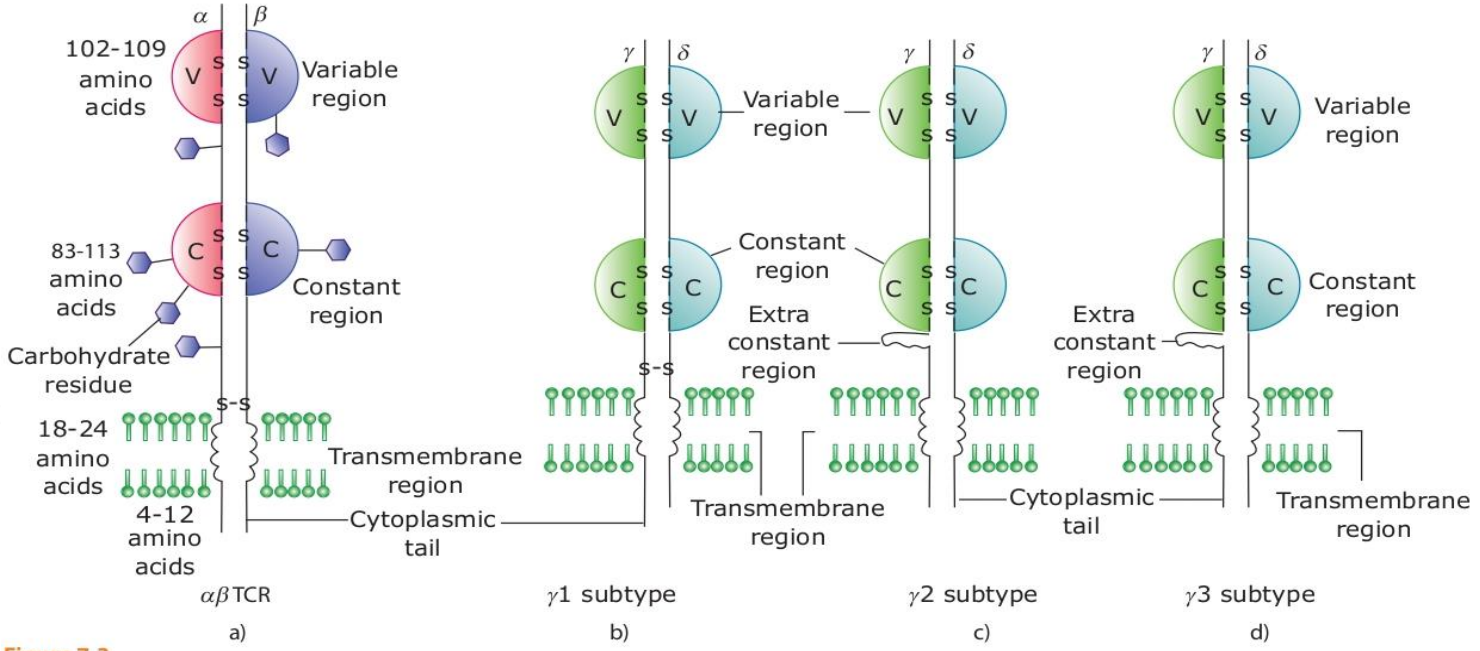
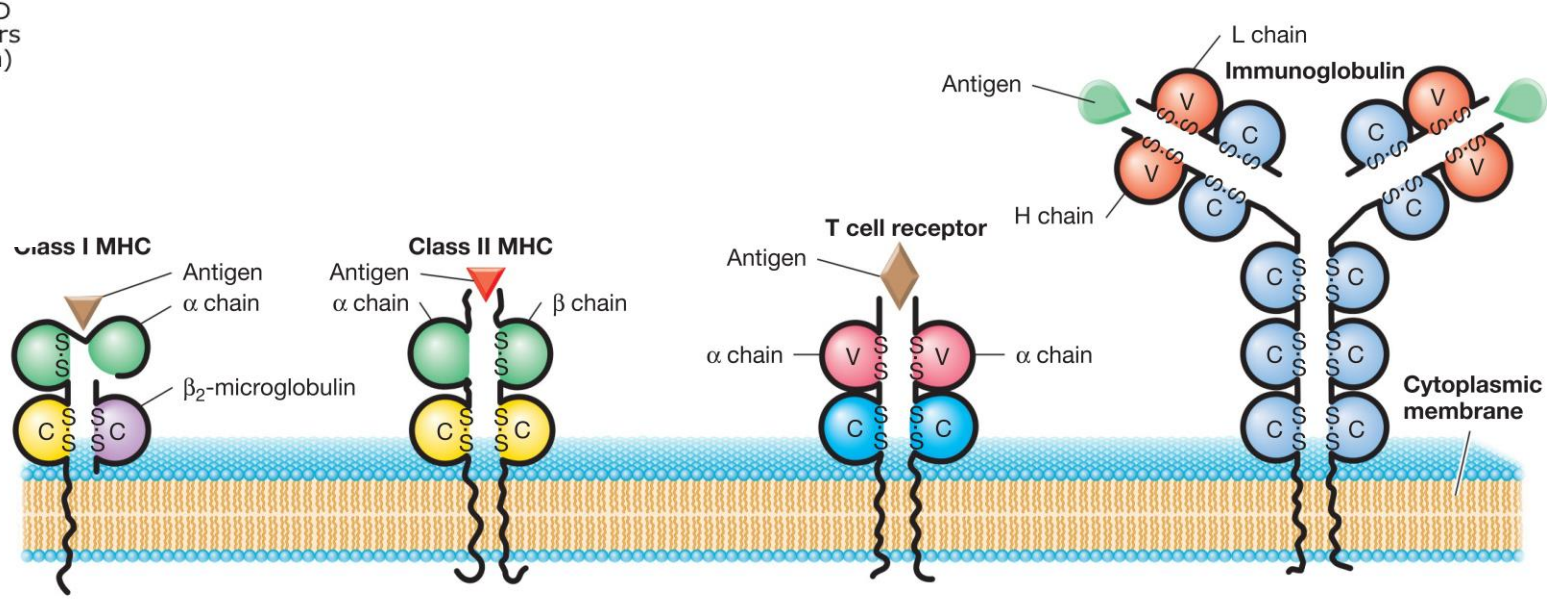
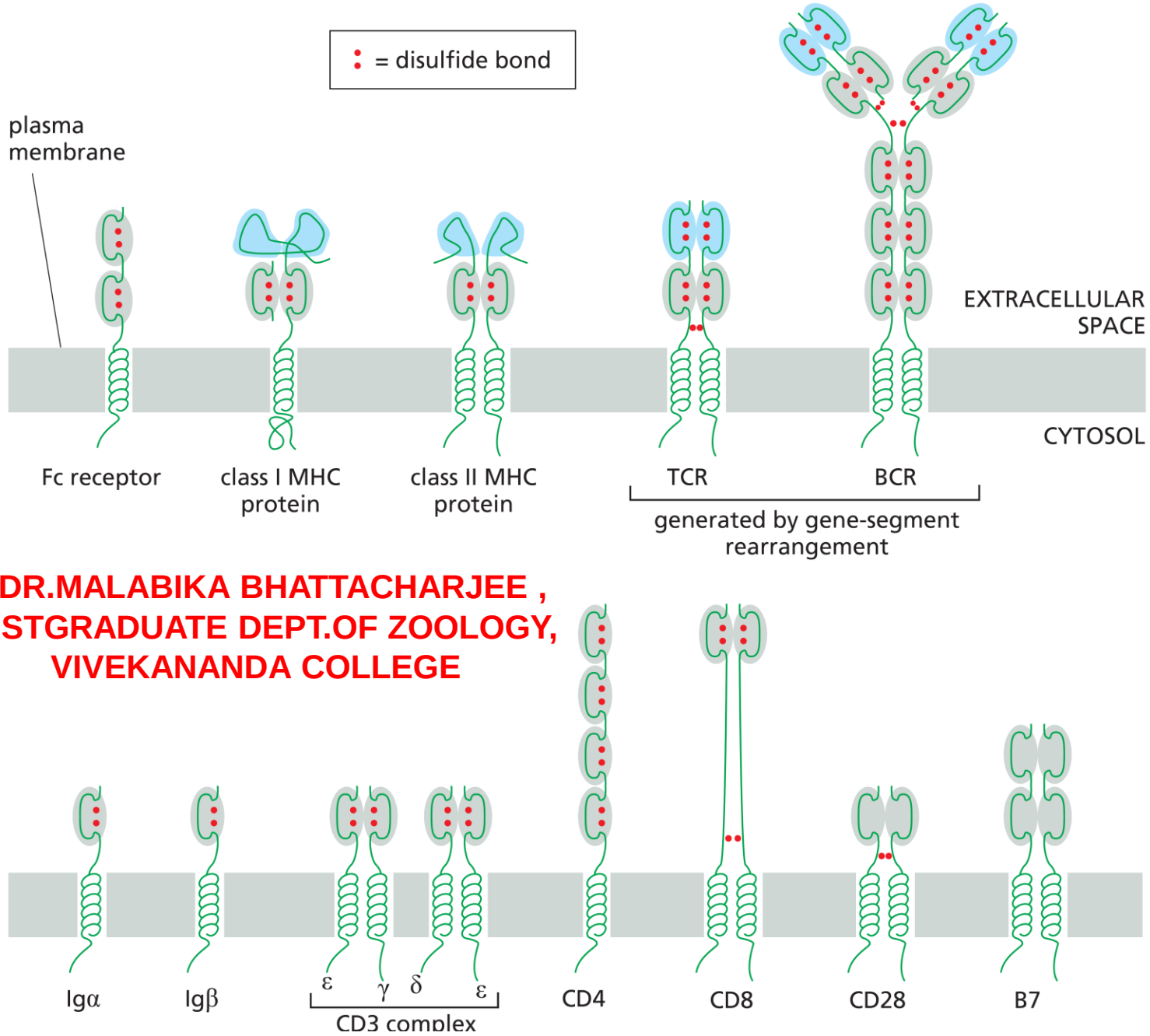


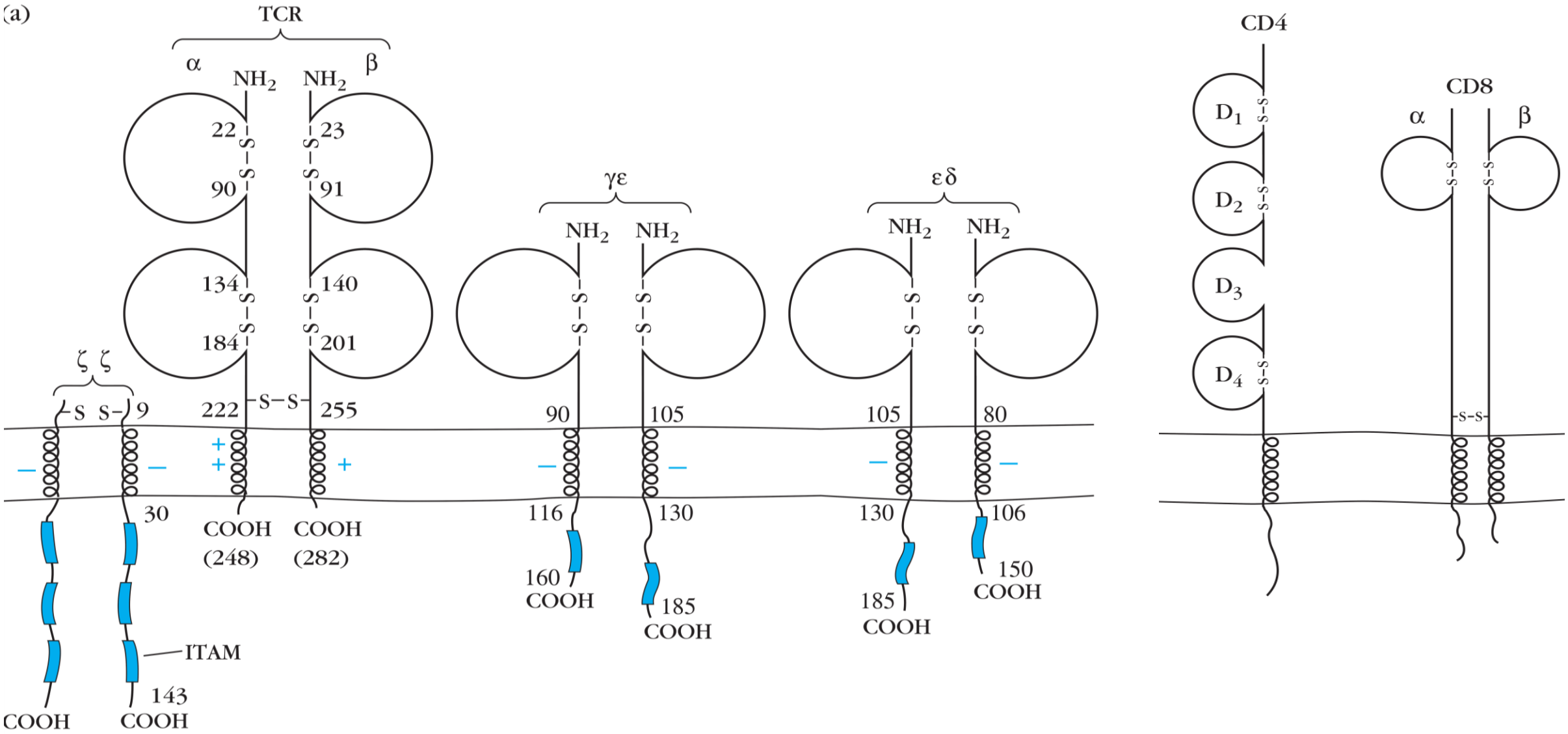
Figure 7.3
(a) Schematic diagram of TCR of αβ cell; (b), (c) and (d) Schematic diagram of TCRs of the three subtypes of γδ cells—γ1, γ2 and γ3 respectively.

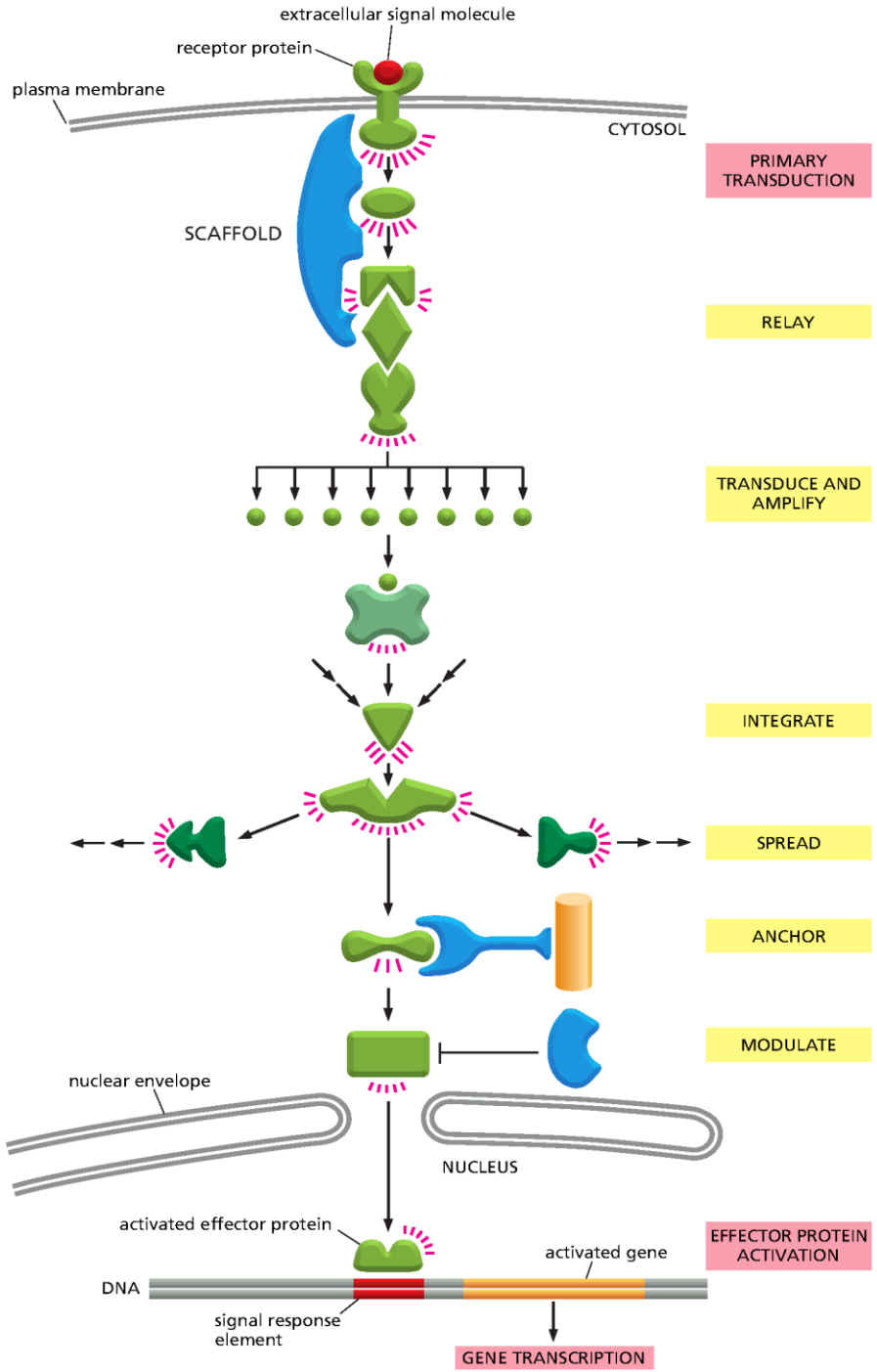




Many Cell-Surface Proteins Belong to the Ig Superfamily

1. Most of the proteins that mediate antigen recognition and cell–cell recognition in the immune system contain one or more Ig or Ig-like domains, suggesting that the proteins have a common evolutionary history.
2. Included in this very large **Ig superfamily are antibodies, TCRs, MHC proteins, the CD4, CD8, and CD28 co-receptors,** the ***B7 co-stimulatory proteins***, and most of the ***invariant polypeptide chains associated with TCRs and BCRs, as well as the various Fc receptors on lymphocytes and other leukocytes***.
3. Many of these proteins are dimers or higher oligomers, in which Ig or Ig-like domains of one chain interact with those in another

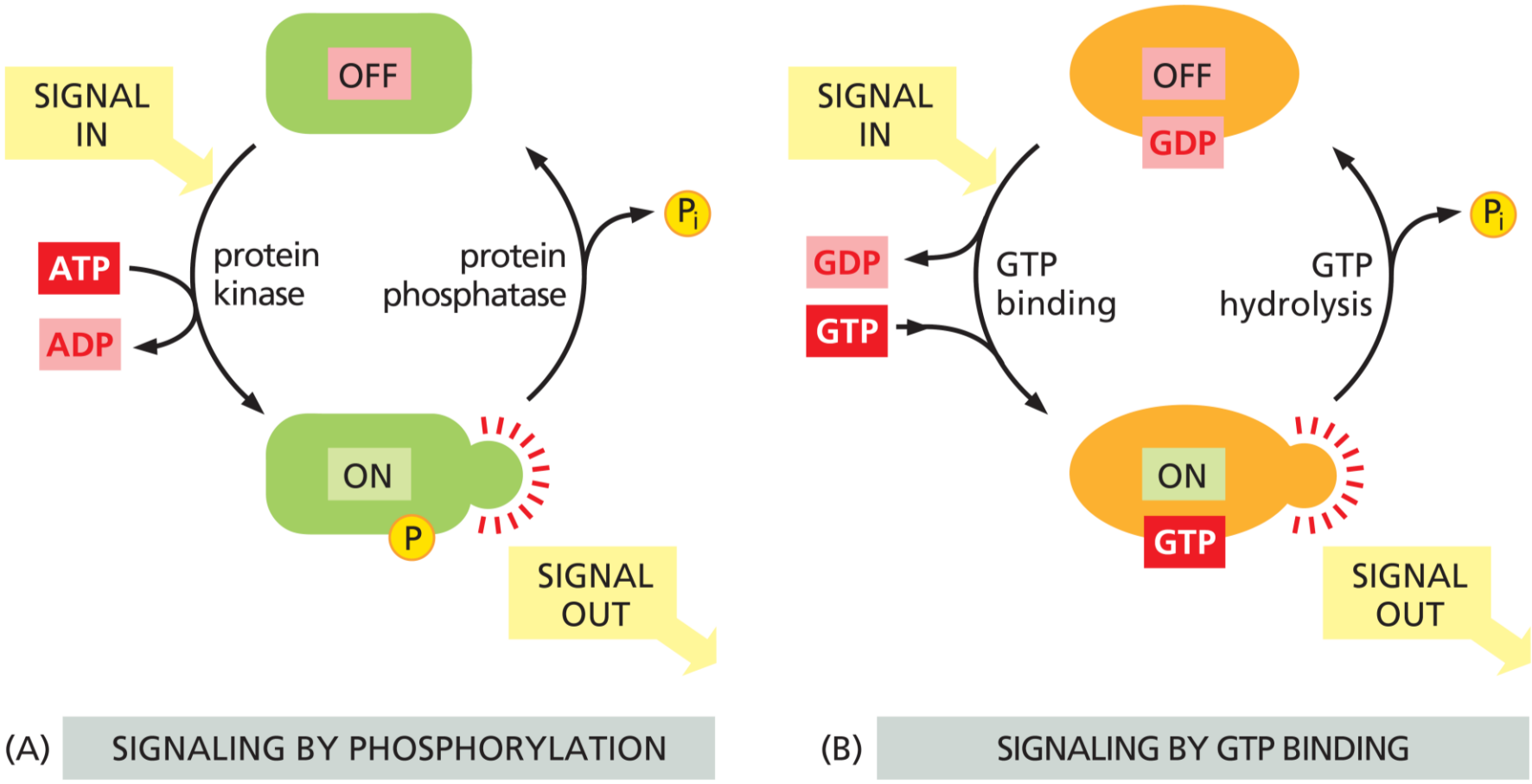




The large intracellular signalling molecules are intracellular signalling proteins which help relay signal into the cell by either generating small intracellular mediators or activating the next signalling or effector protein in the pathway.

1. The protein may simply relay the signal to the next signalling component in the chain.
2. It may act as a scaffold to bring two or more signalling proteins together
3. It may transform, or transduce, the signal into a different form, which is suitable for either passing the signal along or stimulating a cell response.
4. It may amplify the signal it receives, either by producing large amounts of a small intracellular mediator or by activating many copies of a down-stream signalling protein.
5. It may receive signals from two or more signalling pathways and integrate them before relaying a signal onward.
6. It may spread the signal from one signalling pathway to another, creating branches in the signalling stream, thereby increasing the complexity of the response.
7. It may anchor one or more signalling proteins in a pathway to a particular structure in the cell where the signalling proteins are needed.
8. It may modulate the activity of other signalling proteins and thereby regulate the strength of signalling along a pathway.

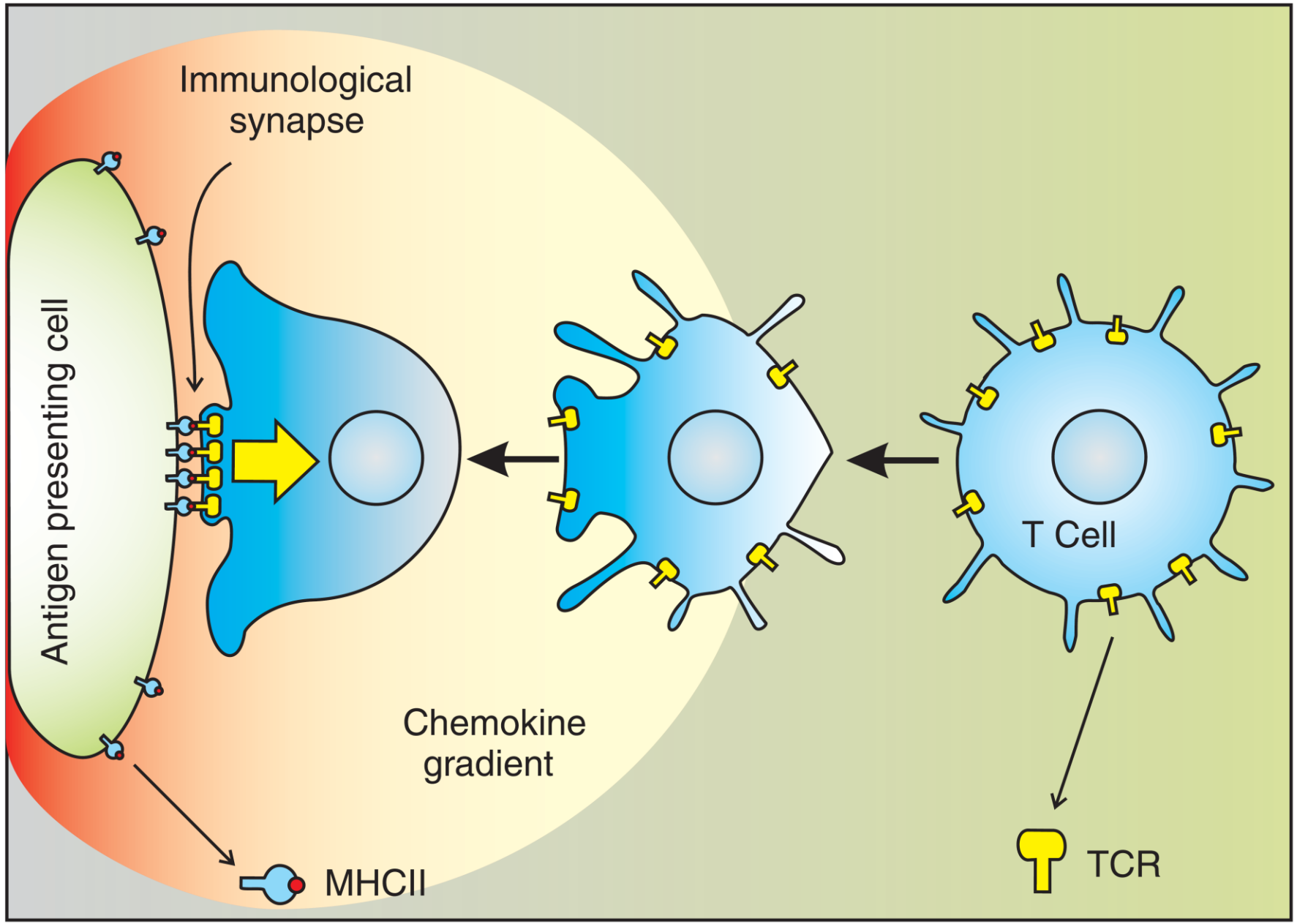
1. Some **intracellular signaling molecules are small chemicals**, which are often called **second messengers** (the "first messengers" being the extracellular signals).
    a. They are generated in large amounts in response to receptor activation and diffuse away from their source, spreading the signal to other parts of the cell.
    b. Some, such as ***cyclic AMP*** and ***Ca^{2+}*** are ***water-soluble and diffuse*** in the ***cytosol***,while others, such as ***diacylglycerol***, are lipid-***soluble and diffuse in the plane of the plasma membrane***.
    c. In either case, they pass the signal on by binding to and altering the behavior of selected signaling or effector proteins.
2. Most intracellular signaling molecules are proteins, which help relay the signal into the cell by either generating second messengers or activating the next signaling or effector protein in the pathway.
3. Many of these proteins behave like *molecular switches.* The largest class of molecular switches consists of proteins that are activated or inactivated by phosphorylation in.
4. For these proteins, the ***switch is thrown in one direction by a protein kinase***, ***which covalently adds one or more phosphate groups to specific amino acids on the signaling protein***, and ***in the other direction by a protein phosphatase, which removes the phosphate groups***



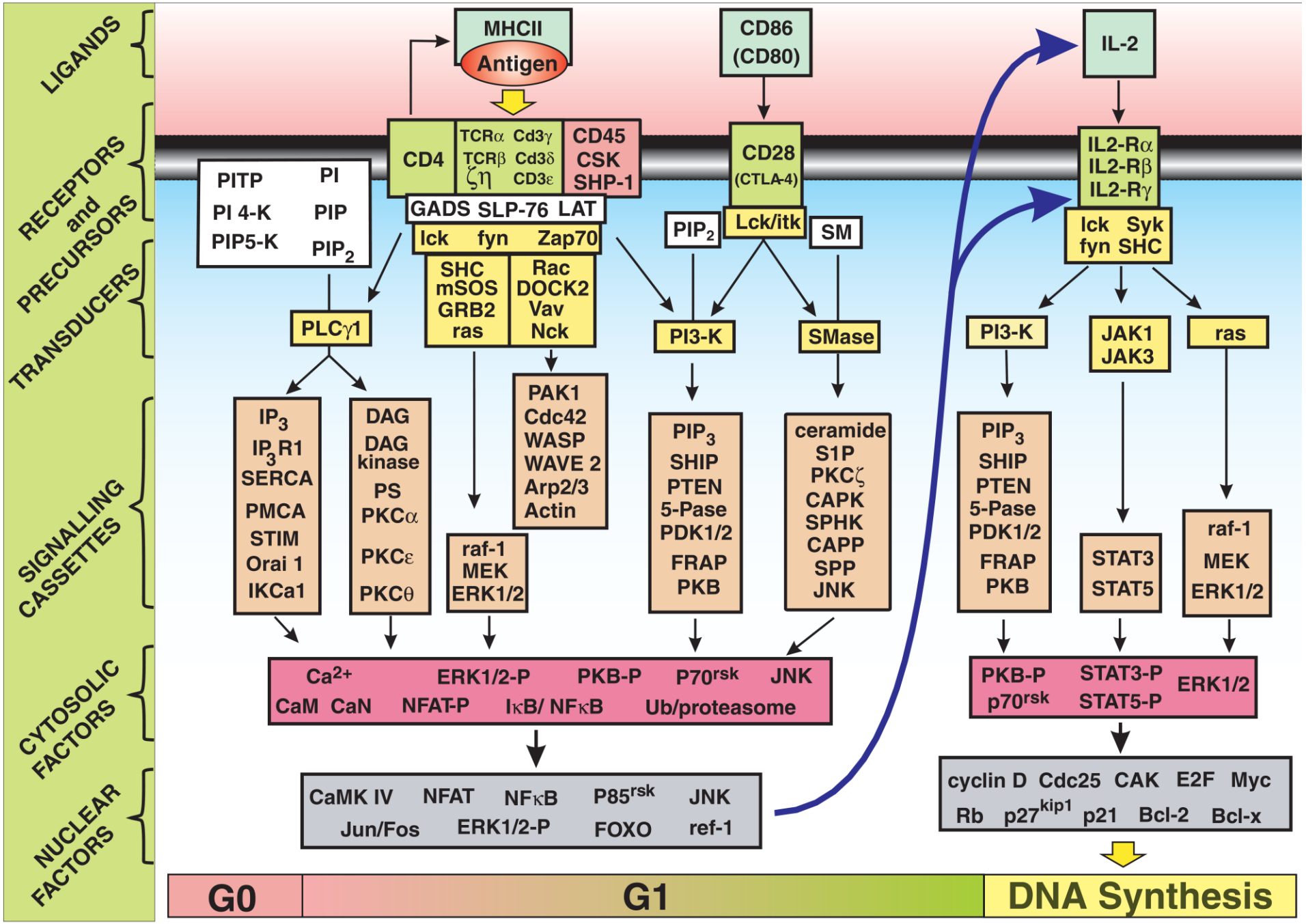
Two types of intracellular signaling proteins that act as molecular switches.

A. A protein kinase covalently adds a phosphate from ATP to the signaling protein, and a protein phosphatase removes the phosphate.Although not shown, many signaling proteins are activated by dephosphorylation rather than by phosphorylation.

B. A GTP binding protein is induced to exchange its bound GDP for GTP, which activates the protein; the protein then inactivates itself by hydrolyzing its bound GTP to GDP.

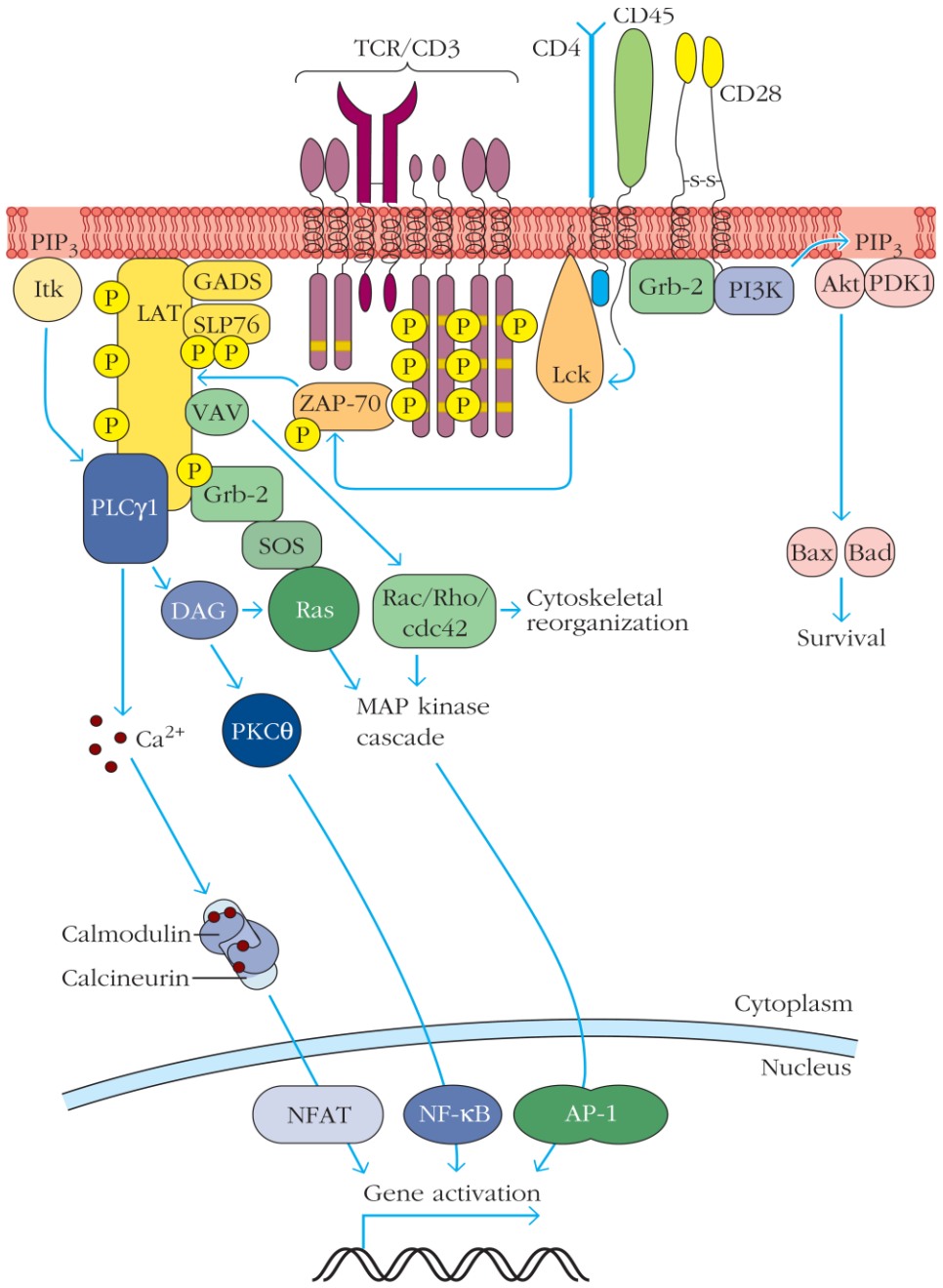


T cell migration towards antigen-presenting cells through a process of chemotaxis.
Antigen-presenting cells release cytokines that attract T cells. When they reach the antigen-presenting cell, they form the immunological synapse
where the T cell receptor (TCR) on the T cell binds to the major histocompatibility complex II (MHCII) molecules on the antigen-presenting cell. The antigenic peptide (shown in red) is held on the surface of the MHCII molecules. Details of the synapse are shown in Module 9: Figure immunological synapse.



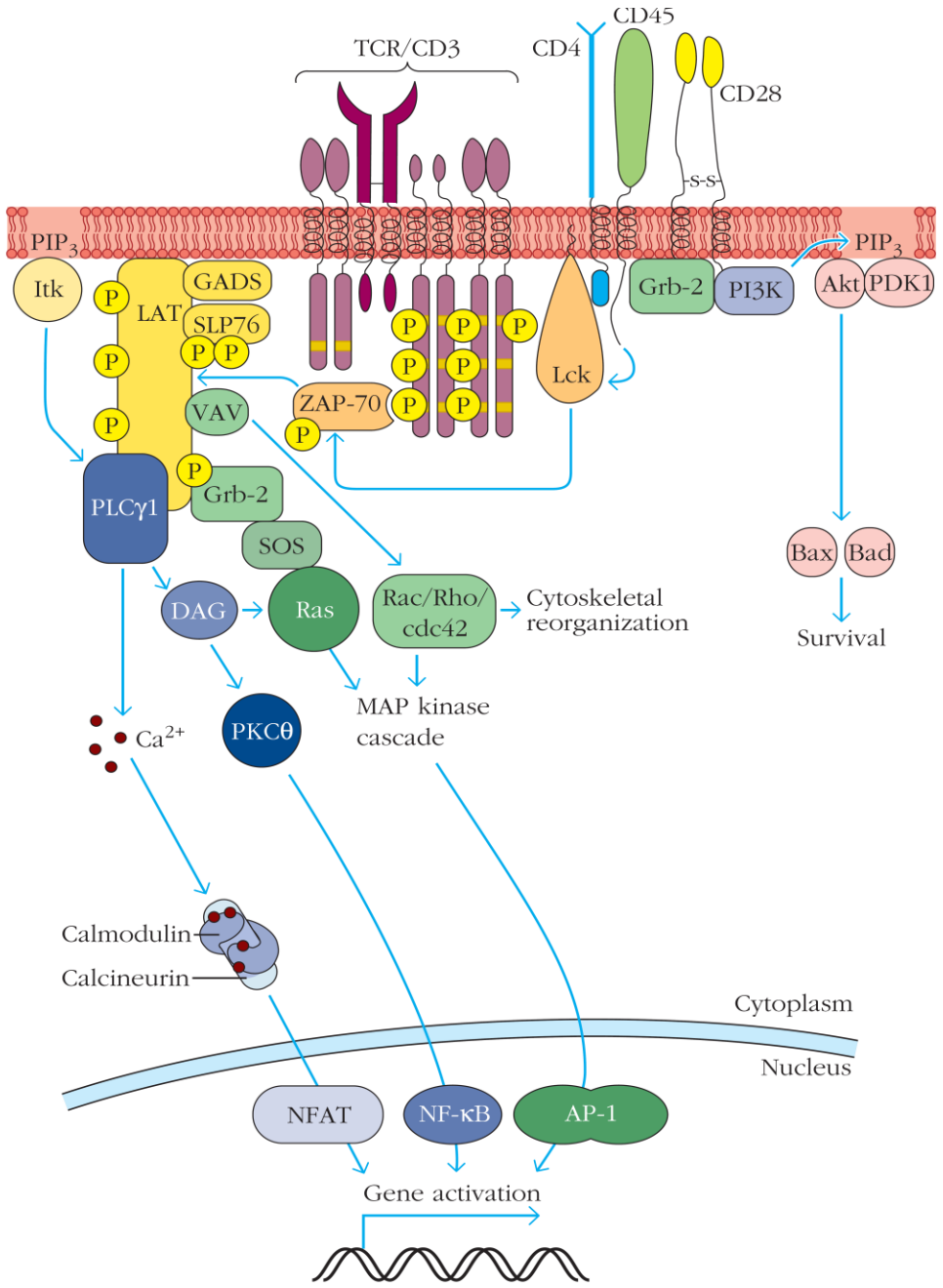
A spatiotemporal map of T cell activation.

1. Signalling begins at the top left with the major histocompatibility complex II (MHCII) presenting the antigen (red) to the T cell receptor (TCR) complex, which then initiates a sequence of events summarized in the green panel on the left of the figure.
2. The sequence begins with the TCR interacting through various transducers to activate signalling cassettes, which relay information into the nucleus through cytosolic messengers to induce gene transcription.
3. Activation of these early gene products sets up an autocrine loop to put in place the interleukin-2 (IL-2) signalling system that activates additional signalling cassettes to complete the signalling cascade by inducing DNA synthesis.



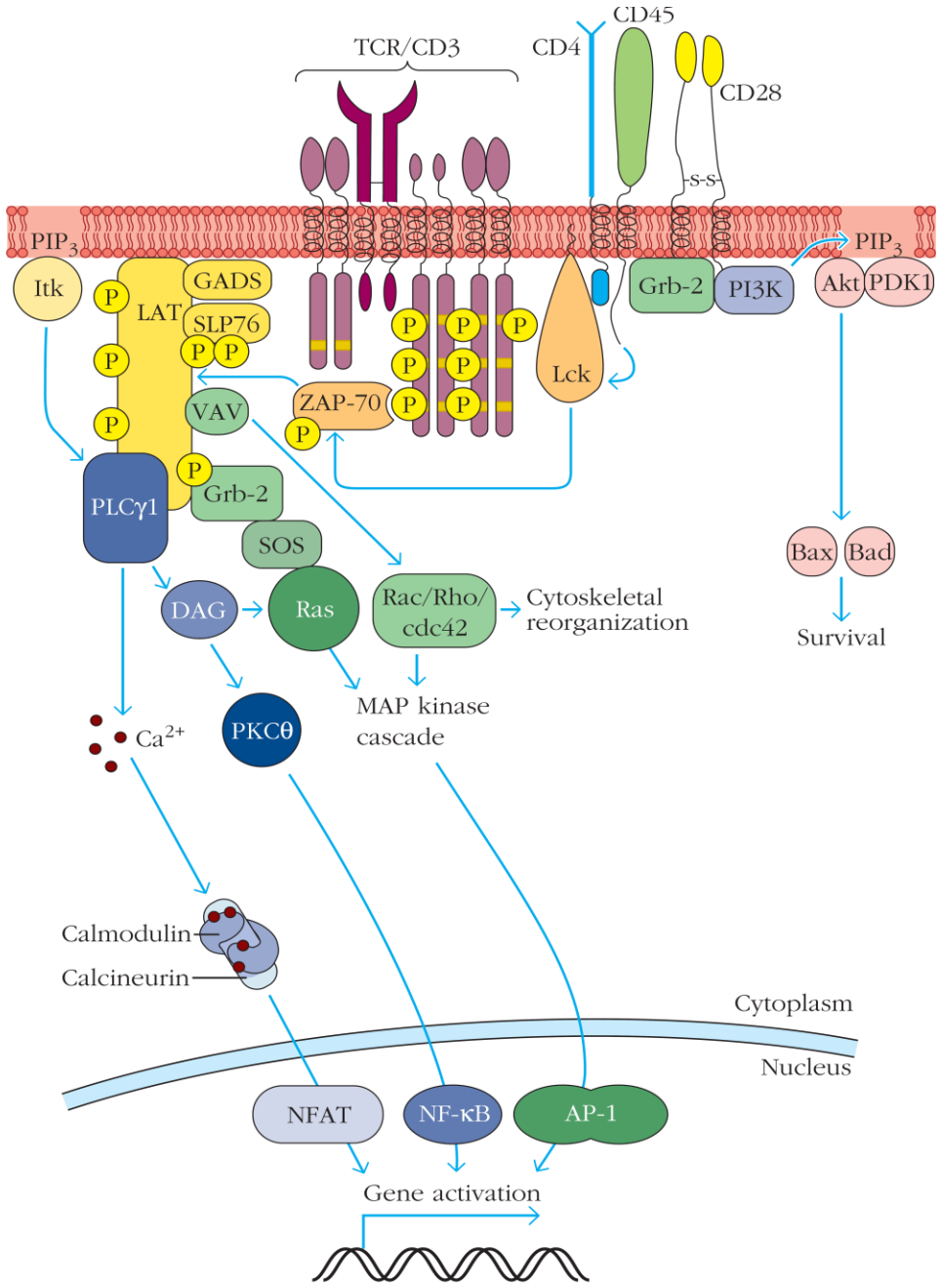
LCK IS THE FIRST TYROSINE KINASE ACTIVATED IN T CELL SIGNALING

1. When the T-cell receptor interacts with its cell-bound antigen, receptors, co-receptors, and signaling molecules cluster into the cholesterol-rich lipid rafts of the plasma membrane .
2. The ***Src-family tyrosine kinase Lck*** is normally found associated with CD4 and CD8, and the association between Lck and CD4 is particularly close. Antigen-induced clustering of the receptor–co-receptor complex brings Lck into the vicinity of the membrane-associated tyrosine phosphatase, ***CD45***, which removes the inhibitory phosphate group on Lck.
3. Reciprocal phosphorylation by nearby Lck molecules at their activating tyrosine sites then induces Lck to phosphorylate ***CD3 ITAM residues.***
4. Once the CD3 ITAMs are phosphorylated, a second tyrosine kinase, **ZAP-70,** docks at the phosphorylated tyrosine

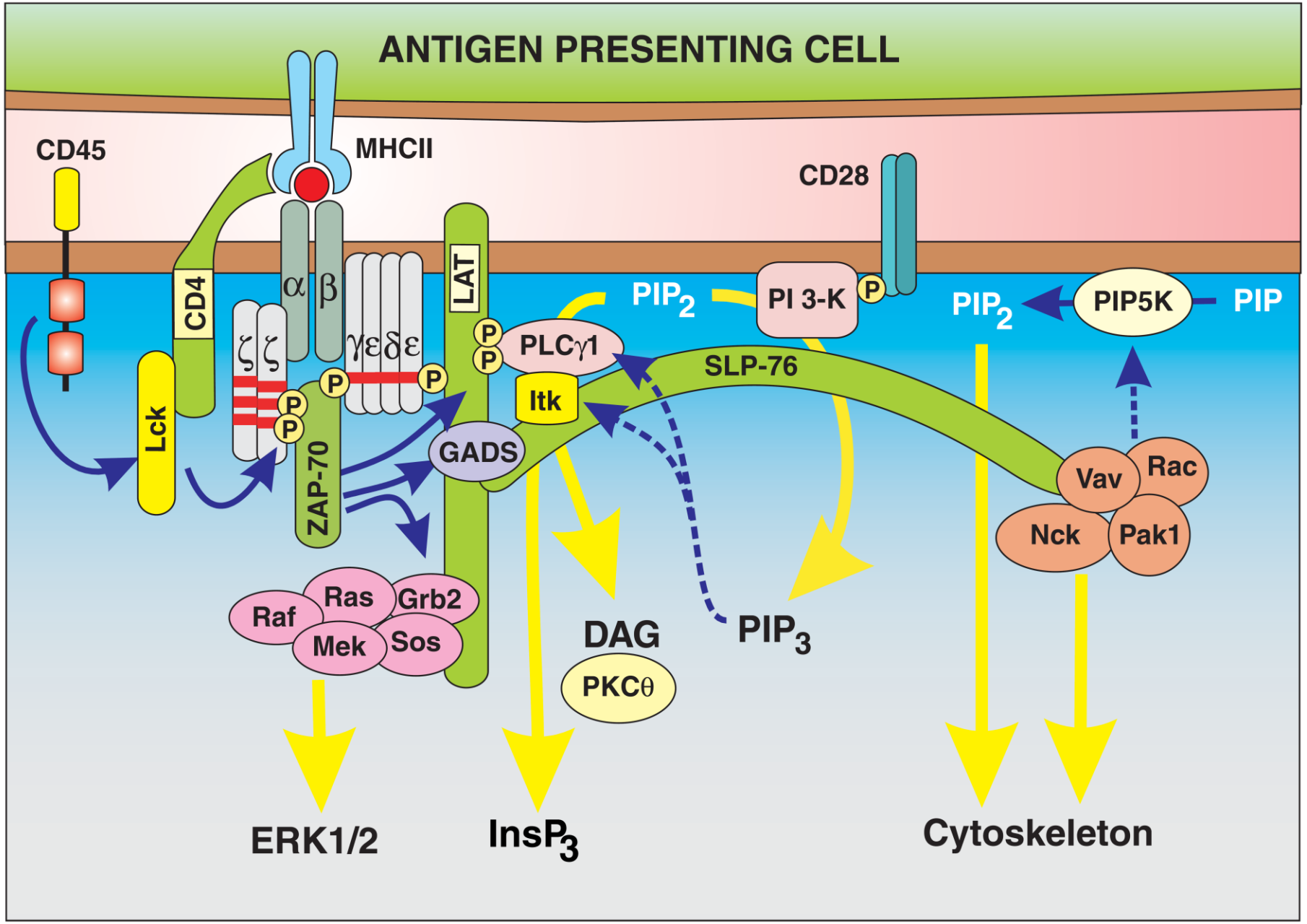


T CELLS USE DOWNSTREAM SIGNALING STRATEGIES SIMILAR TO THOSE OF B CELLS

1. In T cells, one of the earliest adapter molecules to be incorporated into the signaling complex is **LAT (*Linker protein of Activated T* cells)**, a transmembrane protein associated with lipid raft s in the plasma membrane.
2. Following TCR ligation, ***LAT is phosphorylated*** on multiple residues by ***ZAP-70***, and these phosphorylated residues now provide docking sites for several important enzymes bearing SH2 domains, including **PLCγ1** ***Phosphorylated LAT*** also binds to the ***adapter protein GADS***, which is constitutively associated with the ***adapter SLP-76***. This combination of adapter proteins is critical to T-cell receptor signaling, providing the structural framework for most downstream signaling events.
3. **PLCγ1** , ***localized to the plasma membrane*** by binding to LAT, is further activated by tyrosine phosphorylation, mediated by the **kinase Itk** (which belongs to a family of kinases referred to as Tec kinases).



4. PLCγ1 breaks down PIP_2, releasing **IP3**, which induces the release of calcium and the **activation of NFAT** via calcineurin activation. The **DAG** created by PIP_2 hydrolysis ***binds***, in T cells, to a specialized form of PKC called PKC θ (theta). The signaling cascade culminates in the ***degradation of the inhibitors of NF-κB*** and the translocation of the active transcription factor into the nucleus.
5. **Phosphorylated LAT** also associates with the SH2 domain of **Grb2**, the now-familiar adapter molecule that brings in components of the Ras pathway to the signaling complex.
6. **Grb2** binds constitutively to **SOS**, the GEF that facilitates activation of the Ras pathway. In T cells, the **Ras pathway** is important both to the activation of the **transcription factor AP-1**, which functions to signal cytokine secretion, and to the passage of the signals that reorganize the actin cytoskeleton.



Molecular organization of a functional T cell receptor (TCR).

1. Signalling begins when the α and β subunits of the T cell receptor (TCR) detect antigen (red dot) held in the jaws of the major histocompatibility complex II (MHCII) embedded in the surface of the antigen-presenting cell.
2. The sequence begins with CD4 associating with MHCII, thereby bringing Lck into the complex to begin the phosphorylation cascade that also depends upon ζ-associated protein of 70 kDa (ZAP70).
3. The phosphates on the scaffolding protein then draw in the signal transducers, such as ph ospholipase Cγ1 (PLCγ1), PtdIns 3-kinase (PI 3-K) and the Ras complex, to activate the various signalling pathway.
4. The activation of Ca^{2+} signalling by inositol 1,4,5-trisphosphate (InsP3).