Interleukin-2 (IL-2) plays a crucial role in regulating immune responses and maintaining peripheral self-tolerance by having both immuno-stimulatory and immuno-regulatory functions. It acts primarily as a T cell growth factor, essential for the proliferation and survival of T cells as well as the generation of effector and memory T cells. IL-2 is a four α-helical bundle cytokine that belongs to a family of structurally related cytokines that includes IL-4, IL-7, IL-9, IL-15, and IL-21. IL-2 is mainly produced by activated CD4+ T cells in response to antigen stimulation but can also be produced to a much lower extent by CD8+ T cells and innate immune cells such as activated dendritic cells (DCs) and natural killer (NK) cells. 

**IL-2: The Activator and Controller**

### Three is better than one: the IL-2 receptor
IL-2 binds to various forms of the IL-2 receptor (IL-2R), notably the monomeric, dimeric, and trimeric forms (Fig. 1). The monomeric IL-2R consists of the membrane-associated IL-2Rα (CD25) chain, which also exists in a soluble form; however, it is not capable of inducing signaling events. The dimeric IL-2R is comprised of the IL-2Rα (CD25) and IL-2Rβ (CD122) chains, with the latter also part of IL-15R. The trimeric IL-2R consists of IL-2Rα, IL-2Rβ, and IL-2Rγ, better known as the common γ-chain (γc) or CD132 and is shared by all members of the IL-2 cytokine family. In contrast to the monomeric IL-2R, both the dimeric and trimeric IL-2Rs lead to a downstream signaling cascade upon IL-2 binding. IL-2 binds with high affinity to the trimeric IL-2R but with low-moderate affinity to the dimeric IL-2R, varying the sensitivity of the cell to IL-2. Additionally, IL-2 can bind to IL2Rβ expressed on the surface of activated DCs for trans presentation to neighboring cells including antigen-specific naïve T cells and NK cells that express both IL2Rβ and IL2Rγ chains. This trans presentation of IL-2 has been shown to facilitate initial high affinity IL-2 signaling, required early in the immune response to prime naïve T-cells to produce IL-2. 

### IL-2 dependent signaling cascade
IL-2 is first captured by IL2Rα, bringing about a conformational change to IL-2, increasing its affinity for IL-2Rβ and IL-2Rγ. Association of IL-2 with the IL-2R induces the dimerization of the signaling motifs in the cytoplasmic tails of IL-2Rβ and IL-2Rγ leading to the phosphorylation of the Janus kinases, JAK1 and JAK3, which in turn exert kinase activity on key tyrosine residues in the tail of the IL-2Rβ subunit. Downstream signaling occurs via three major pathways, the JAK-STAT pathway, the phosphoinositide 3-kinase (PI3K)-AKT pathway, and the mitogen-activated protein kinase (MAPK) pathway. These pathways ultimately result in the transcription of target genes that contribute to IL-2-dependent biological actions, through the recruitment of the adaptor protein Shc and the transcription factor STAT5 (Fig. 1). Target genes of IL-2 signaling include cyclin D2, bcl-2, fasL, cd25 (encoding IL-2Rα), socs1-2, and the IL-2 silencing gene pdm1 which encodes for the transcription factor, BLIMP1. Specifically, the production of the negative regulator BLIMP1 is essential for maintaining the balance between effector T cells and Treg cells, which is crucial for immune homeostasis.

### The ‘innate’ arm of IL-2 production
Early in the immune response, the production of IL-2 by DCs requires the binding of specific microbial ligands such as lipopolysaccharide (LPS), peptidoglycan, zymosan, and CpG DNA to pattern recognition receptors (PRRs). Specifically, these agonists stimulate the translocation of NFAT (nuclear factor of activated T-cells) to the nucleus of DCs via the activation of the key calcium-dependent phosphatase, calcineurin. This ultimately leads to the NFAT-dependent expression of a number of genes including IL-2. It has been shown that calcineurin-mediated production of IL-2 by myeloid cells plays a fundamental role in the gut microbiota, maintaining intestinal homeostasis by influencing the balance between inflammatory and regulatory responses of CD4+ T cells.

### The ‘adaptive’ arm of IL-2 dependent activation
IL-2 plays a dual role in T cell activation by stimulating the proliferation and differentiation of ‘conventional’ T cells as well as maintaining and expanding the population of ‘suppressive’ Treg cells. The ‘conventional’ naïve CD4+ and CD8+ T cells express the dimeric IL-2R, and therefore require a