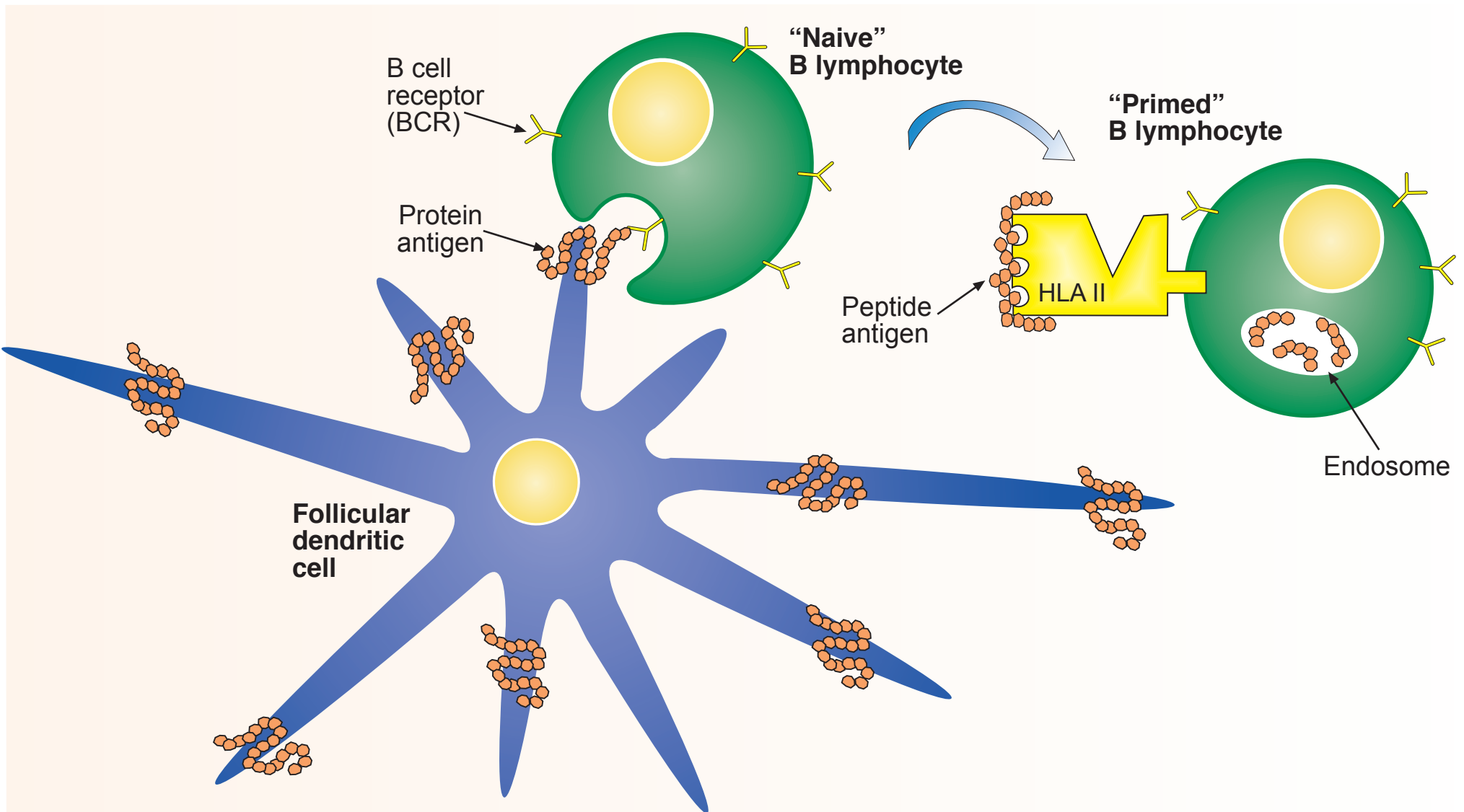


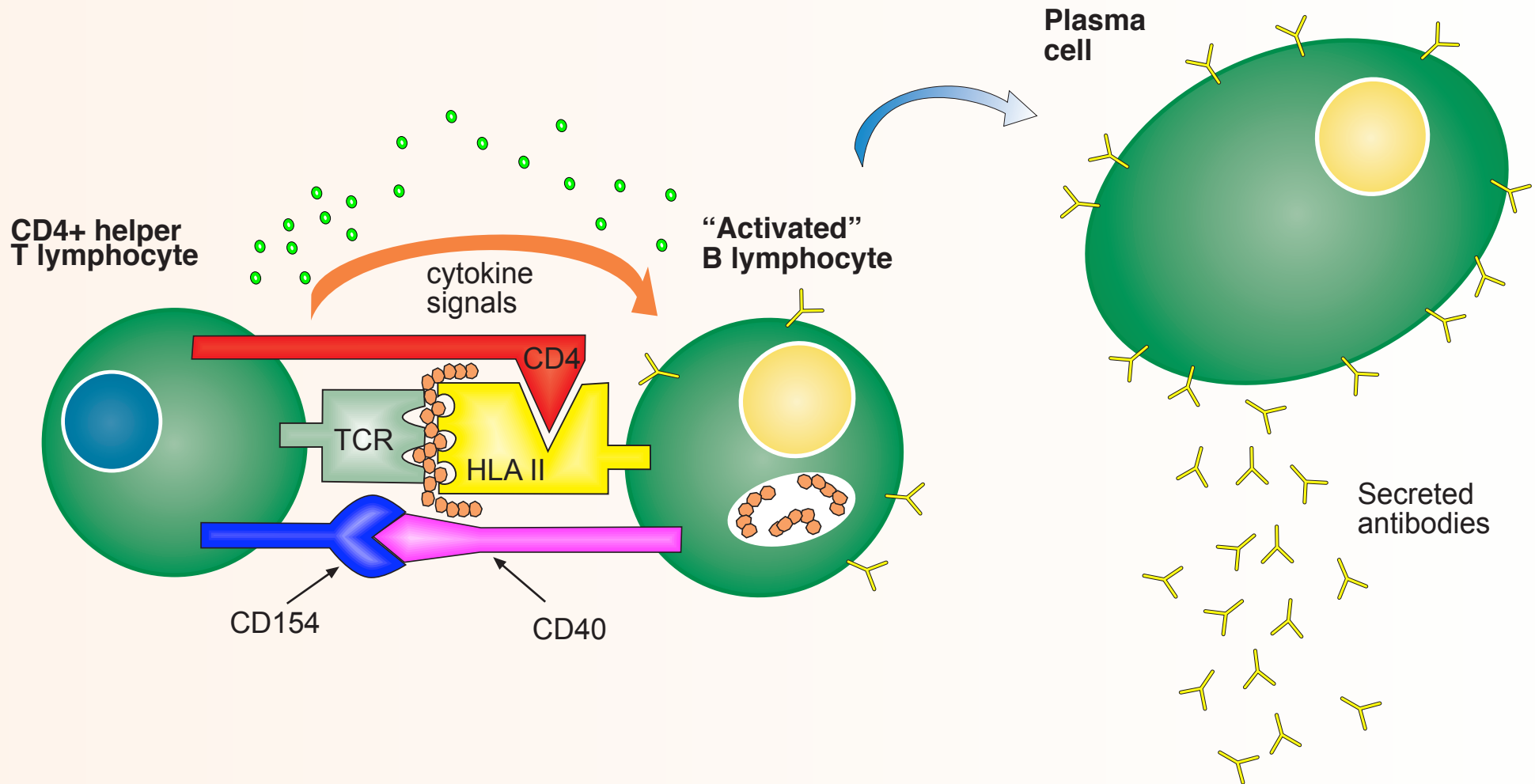
B lymphocyte priming



"Naive" B lymphocytes develop in the bone marrow from long-lived haematopoietic stem cells. They migrate from the bone marrow to the germinal centre (B cell zone) of secondary lymphoid organs where they contact antigen-bearing follicular dendritic cells. Recognition of protein antigens by the B cell receptor (BCR) initiates endocytosis of the antigen-BCR complex. The antigen is processed into short peptide antigens which associate with HLA class II receptors on the cell surface. The B lymphocyte is now "primed" for antibody production and migrates to the T cell zone for activation.



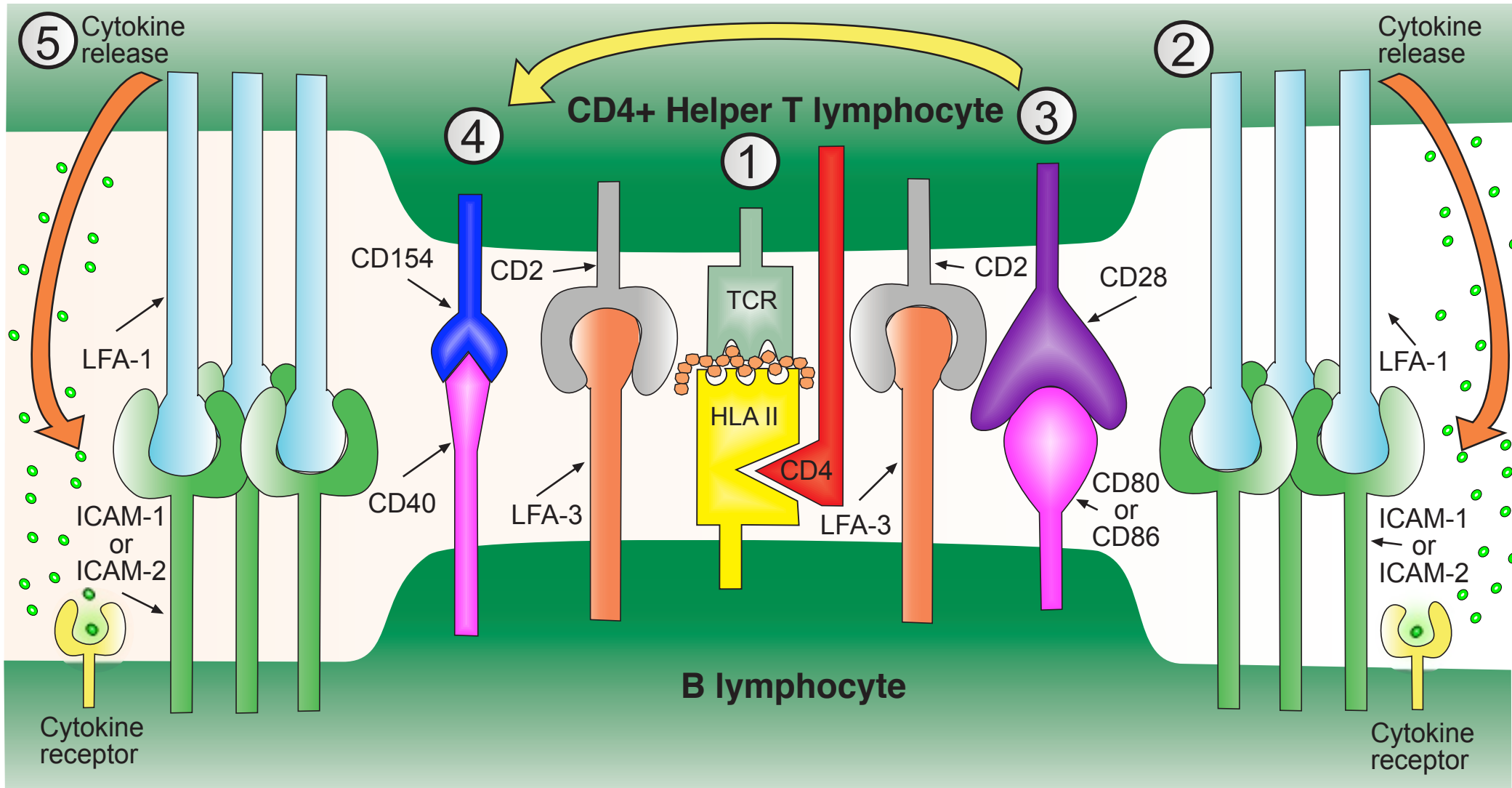
B lymphocyte activation



“Primed” B lymphocytes migrate from the germinal centres (B cell zone) to the T cell zone of the secondary lymphoid organ where they contact memory or effector CD4+ helper T lymphocytes. Recognition of peptide antigens bound to HLA class II receptors on the B lymphocyte by T cell receptors (TCR) on the CD4+ helper T lymphocyte initiates the formation of an immunological synapse. The CD4+ helper T lymphocyte is activated and expresses CD154 and releases cytokines. Stimulation of CD40 and cytokine signals promotes the B lymphocyte to differentiate into a plasma cell.



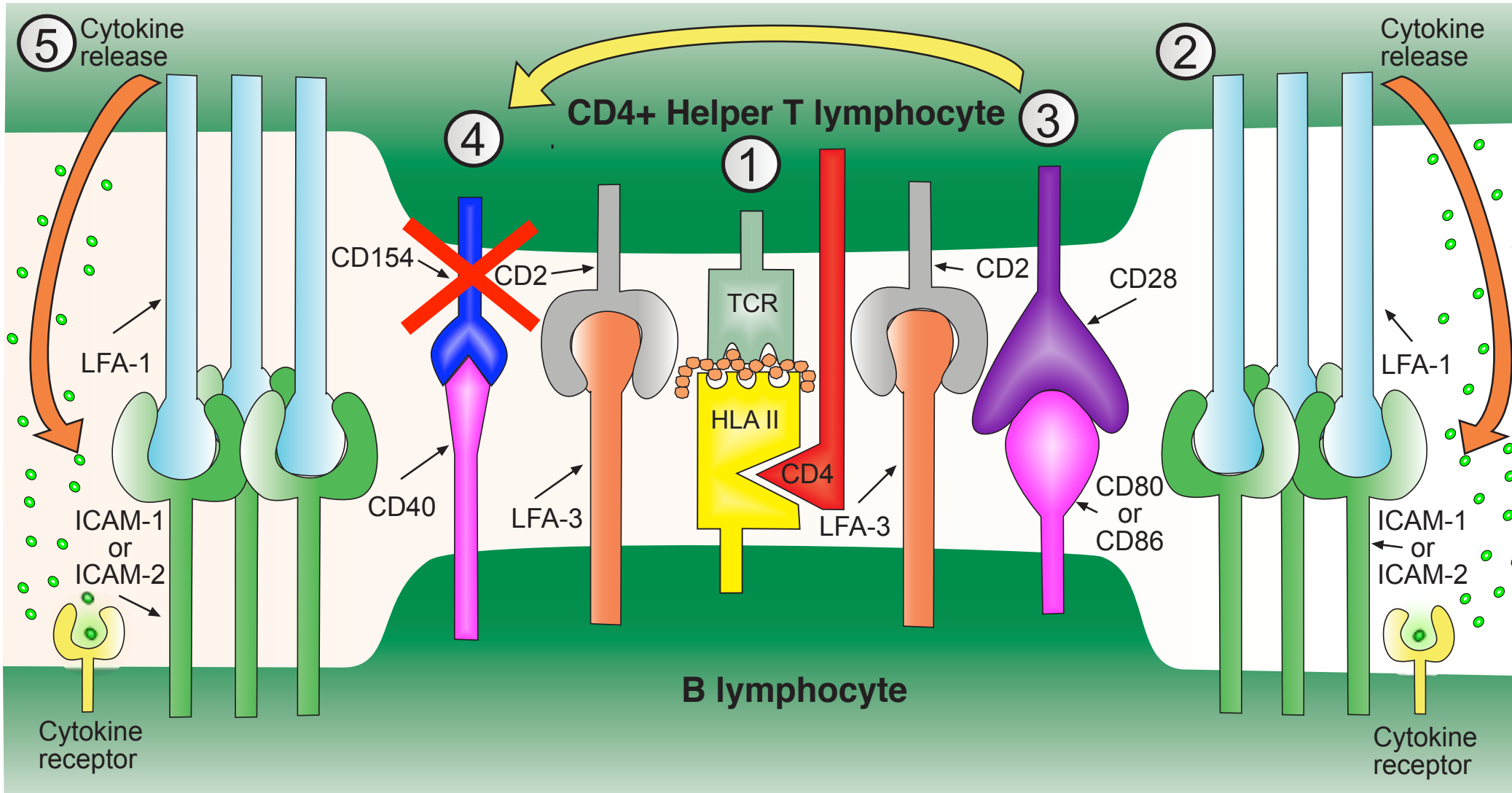
Immunological synapse



(1) The immunological synapse is initiated by recognition of peptide antigens bound to HLA class II receptors on the “primed” B lymphocyte by T cell receptors (TCR) on the CD4+ helper T lymphocyte. CD4 also binds to the HLA class II receptor. (2) The synapse is further organised and stabilised by binding of LFA-1 and ICAM-1 or ICAM-2 in the outer ring (or p-SMAC) and CD2 and LFA-3 in the inner ring (or c-SMAC). (3) Stimulation of CD28 by CD80 or CD86 activates the CD4+ helper T lymphocyte. (4) The activated CD4+ helper T lymphocyte produces cytokines and expresses CD154 which stimulates CD40 on the B lymphocyte. CD40 stimulation promotes the B lymphocyte to differentiate into a plasma cell. (5) CD40 stimulation and cytokine signals promotes isotype switching and somatic hypermutation to produce higher affinity antibodies of the IgA, IgG or IgE classes as well as the generation of memory B lymphocytes required for long-term immunity.



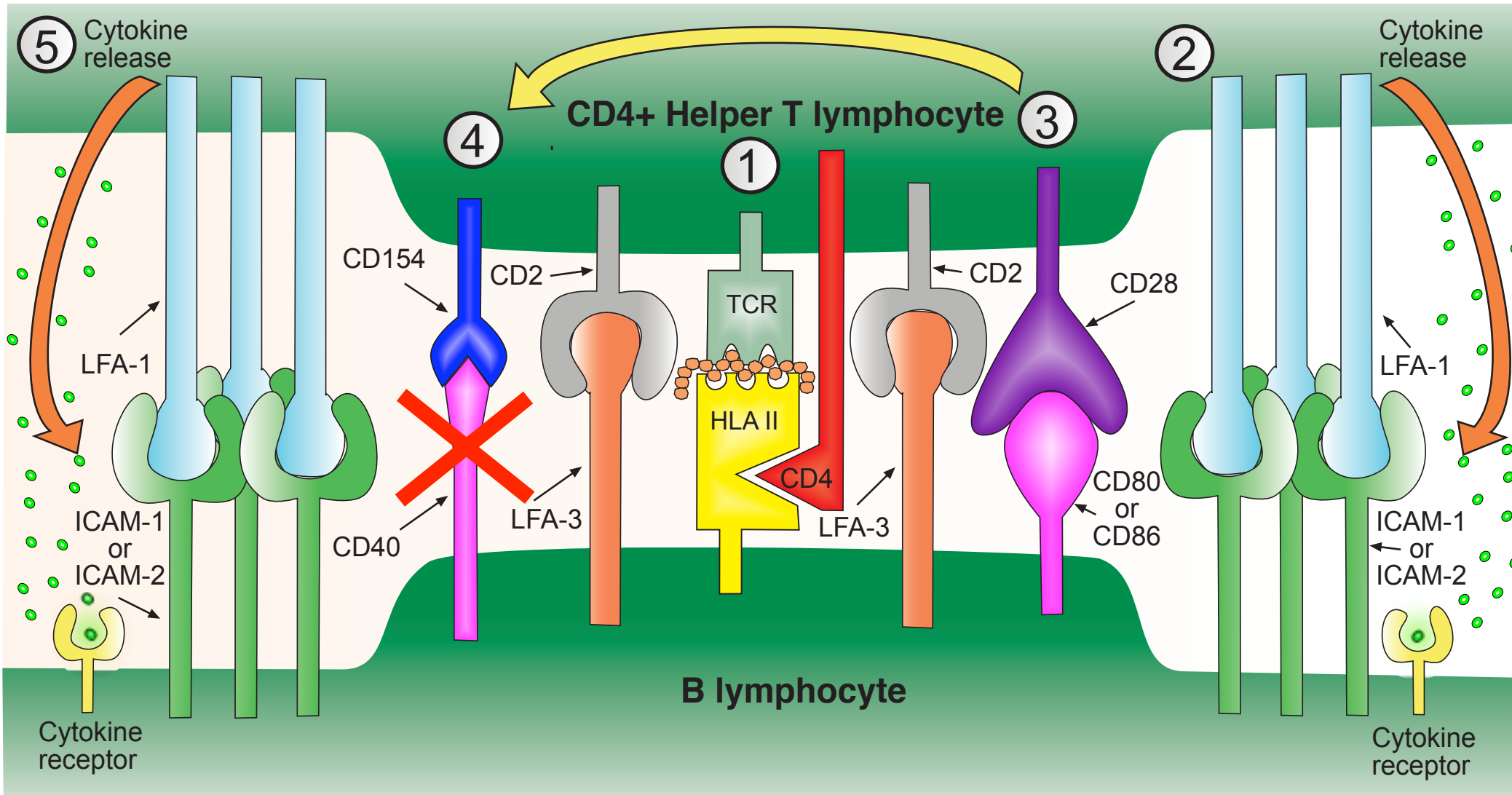
(1) Hyper-IgM syndrome



The most common form of hyper-IgM syndrome is the failure of CD4+ helper T lymphocytes to express cell surface CD154 receptors. This is also known as X-linked hyper-IgM syndrome since the gene for CD154 is carried by the X-chromosome. Failure of CD40 stimulation by CD154 prevents the B lymphocyte from receiving the required activation signal to differentiate into a plasma cell capable of secreting IgM or switching to a different antibody isotype such as IgG, IgA or IgE. In hyper-IgM syndrome it is thought that IgM is still capable of being produced by T cell independent mechanisms governed by toll like receptors (TLR) or antibody cross-linking. This mechanism does not, however, produce isotype switched antibodies and does not generate memory B lymphocytes required for long-term immunity.



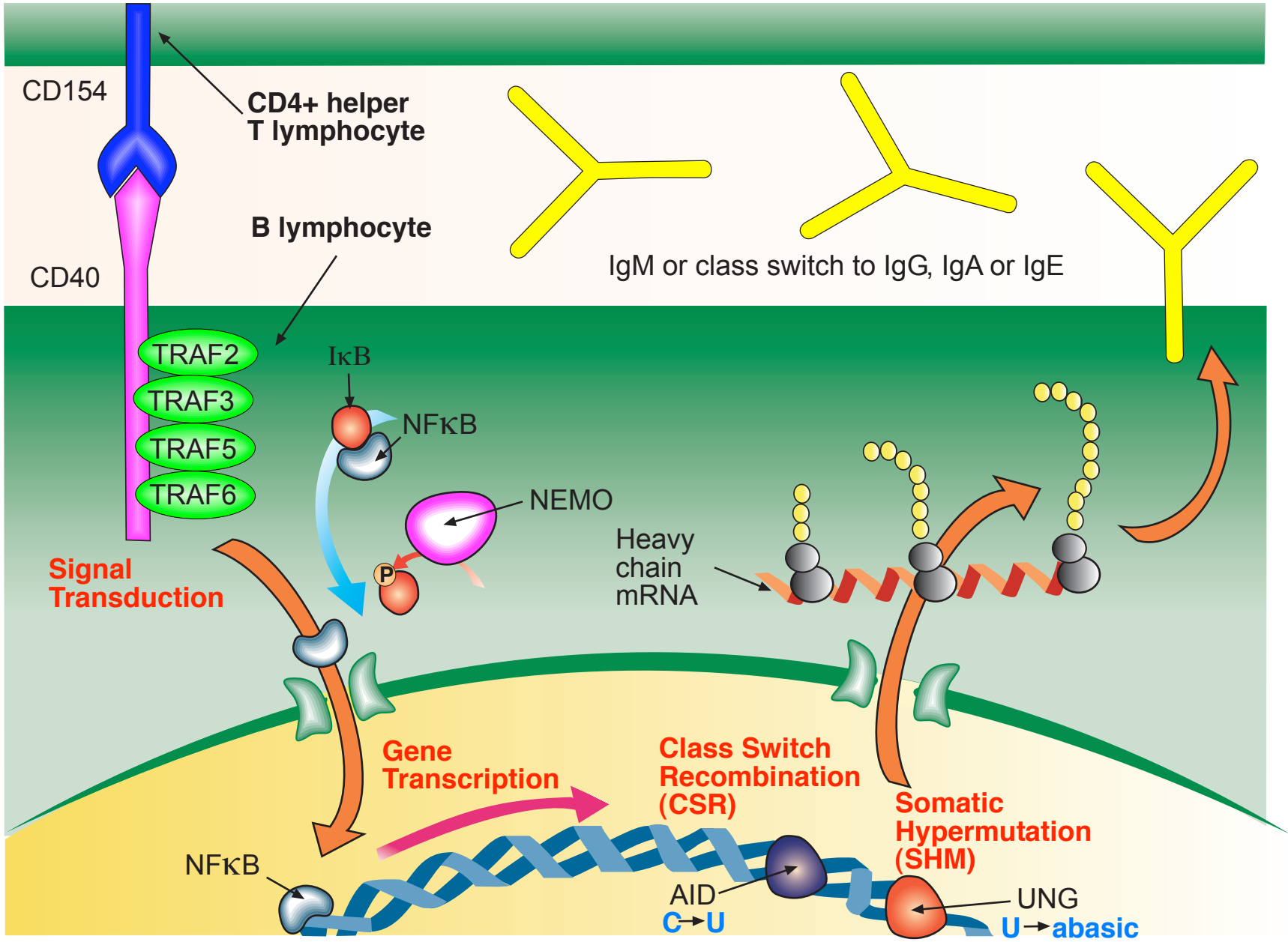
(2) Hyper-IgM syndrome



A second variant of hyper-IgM syndrome which is not X-linked is the failure of B lymphocytes to express cell surface CD40 receptors. Failure of CD40 stimulation by CD154 prevents the B lymphocyte from receiving the required activation signal to differentiate into a plasma cell capable of secreting IgM or switching to a different antibody isotype such as IgG, IgA or IgE. Thymus-independent mechanisms may still contribute to IgM production, however no memory B lymphocytes and isotype switched antibodies can be generated in this way.



(3) Hyper-IgM syndrome



The less common forms of hyper-IgM syndrome involve abnormalities in the signal transduction pathway of CD40 stimulation or the DNA processes involved in class switching and somatic hypermutation. Genetic mutations in NEMO, an enzyme needed to remove the inhibition factor from NFκB can prevent the initiation of gene transcription following CD40 stimulation. Genetic mutations in AID which deaminates cytidine residues to uracil in DNA or genetic mutations in UNG that removes uracil from DNA have also been found to cause a block in antibody production and isotype switching.