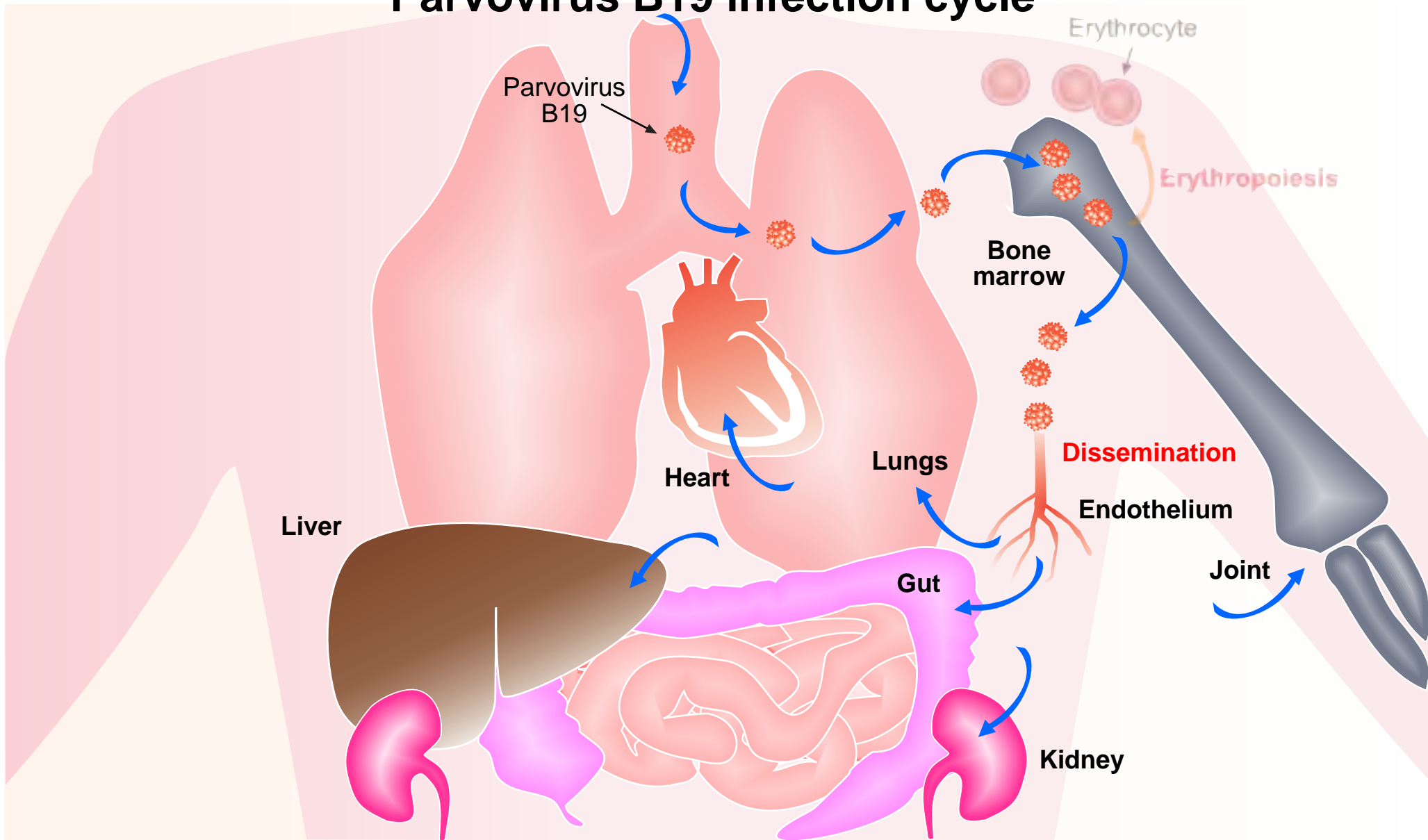
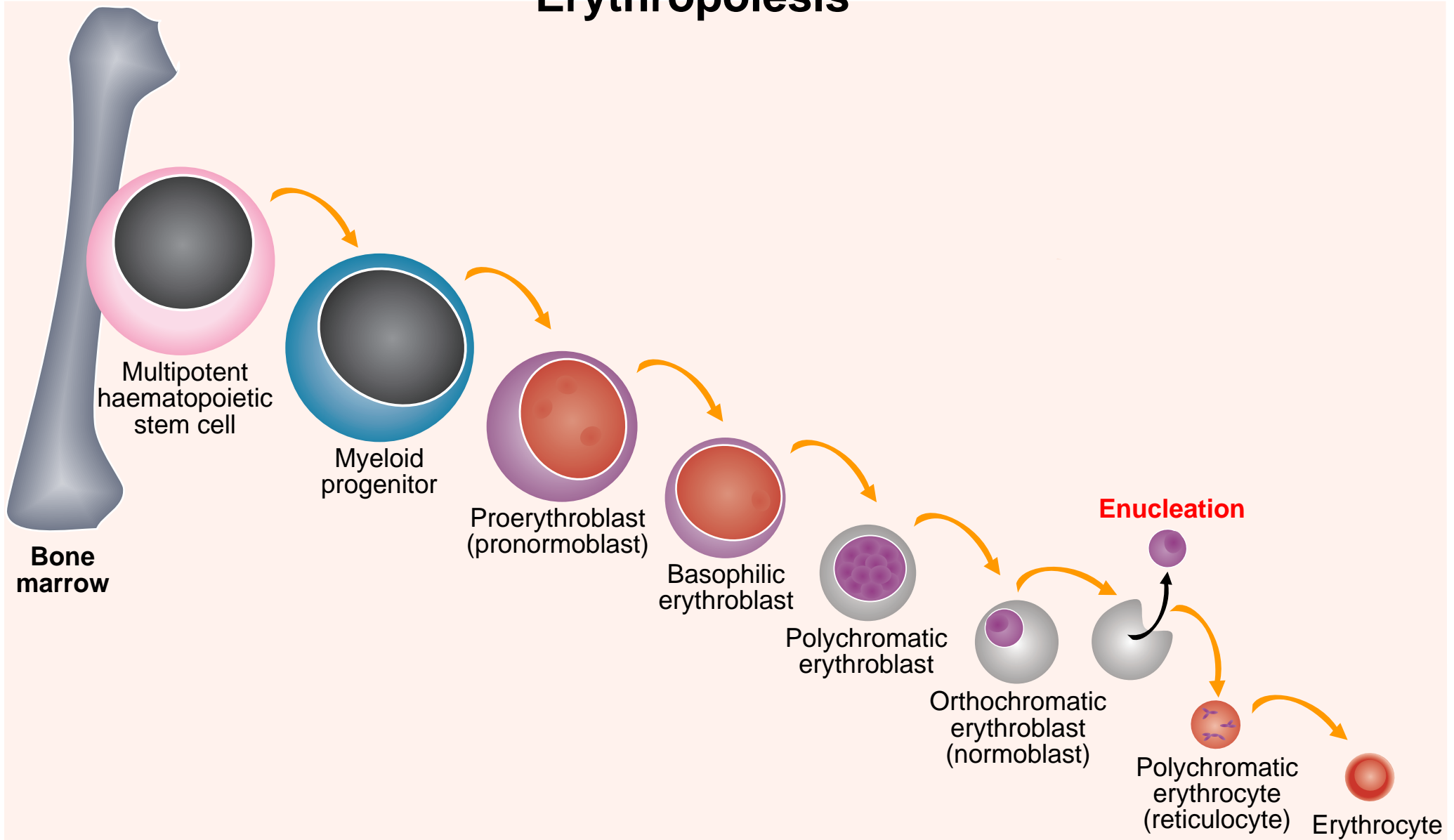


Parvovirus B19 infection cycle



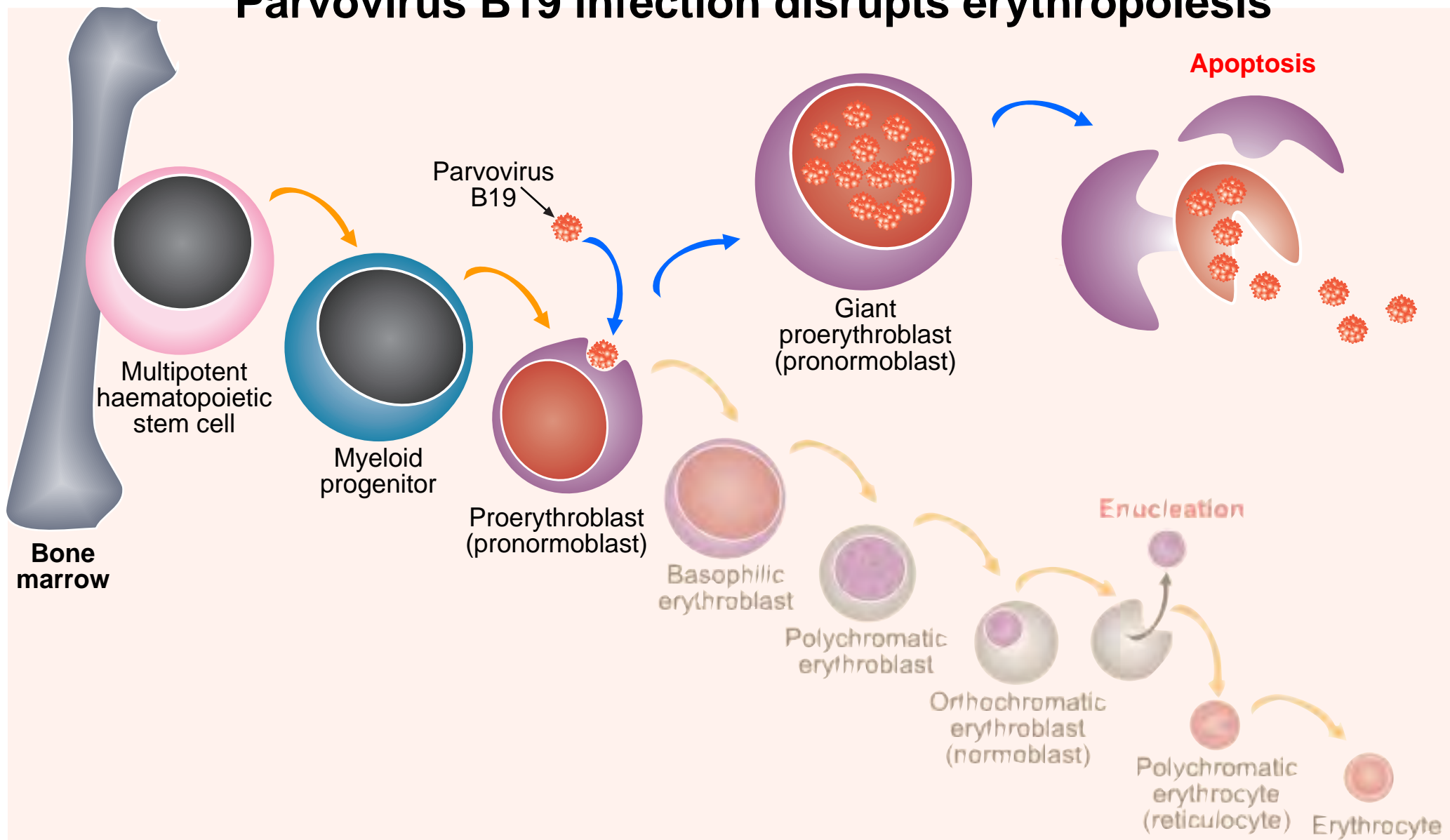
Parvovirus B19 is transmitted between humans by aerosol inhalation. The main target cells of parvovirus B19 are erythroid progenitor cells in bone marrow. It is not known whether the virus initially replicates in the respiratory tract before dissemination to the bone marrow or if the virus is able to cross the lung mucosa and then migrate to the bone marrow. To infect target cells, parvovirus B19 requires a primary receptor Gb4Cer (globoside) as well as co-receptors Ku80 autoantigen and $\alpha 5\beta 1$ integrin that mediate attachment and internalisation by endocytosis. The Gb4Cer receptor is found on the surface of erythrocytes, platelets and granulocytes and potentially plays a role in transference of bound virus to other tissues. The Gb4Cer receptor is also expressed in lung, heart, liver, kidney, synovium, endothelium and gut tissue where parvovirus B19 DNA can often be detected. This may be involved in autoimmune reactions and viral persistence.

Erythropoiesis



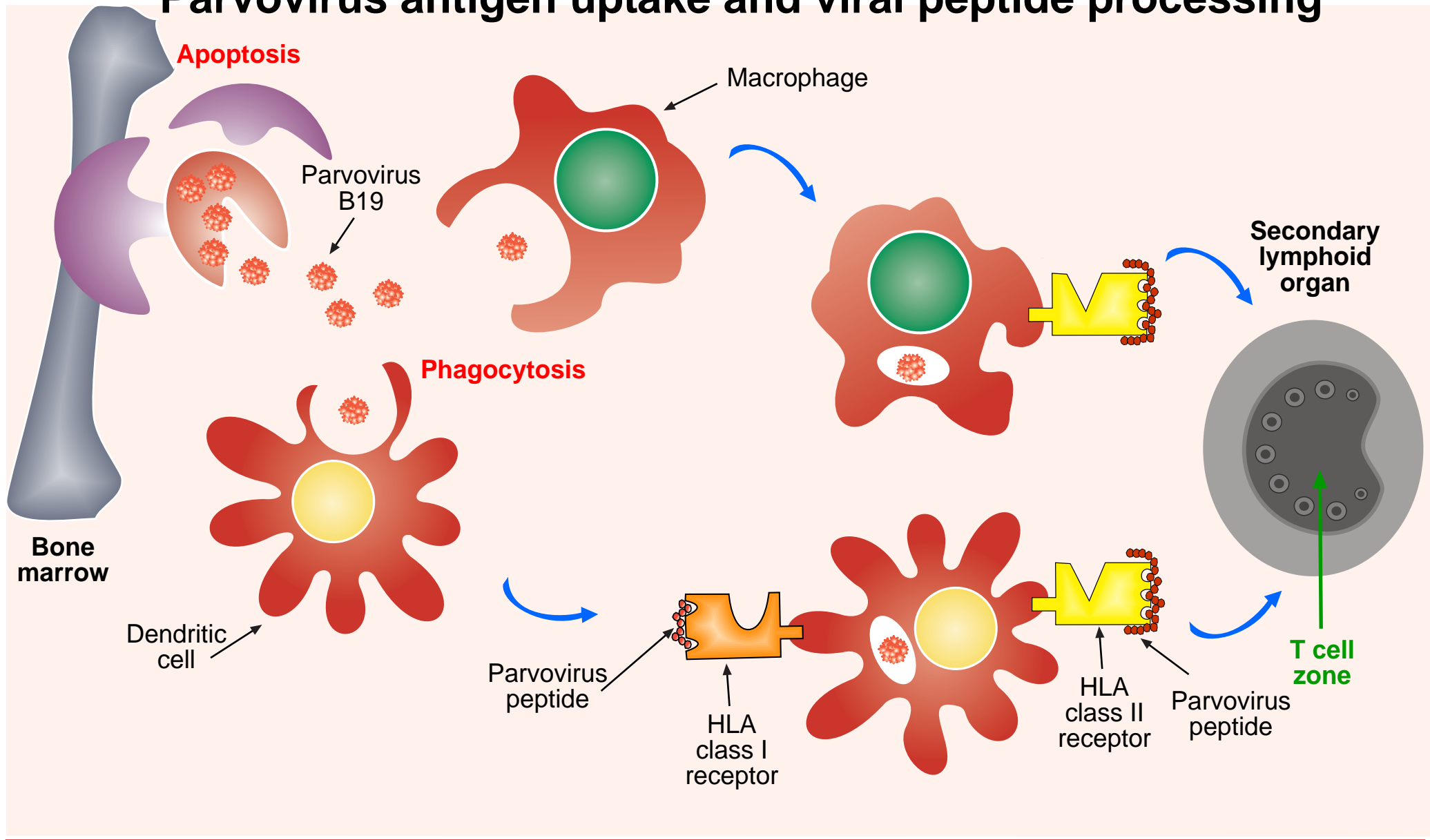
The development of erythrocytes in bone marrow is regulated by the hormone erythropoietin that stimulates the differentiation of progenitor cells into erythroid precursor cells. A number of intermediate cell stages can be identified beginning with the proerythroblast (pronormoblast). The cell nucleus is extruded at the orthochromatic erythroblast (normoblast) stage before formation of an enucleated polychromatic erythrocyte (reticulocyte). These cells are released into the circulation where they mature into functional erythrocytes.

Parvovirus B19 infection disrupts erythropoiesis



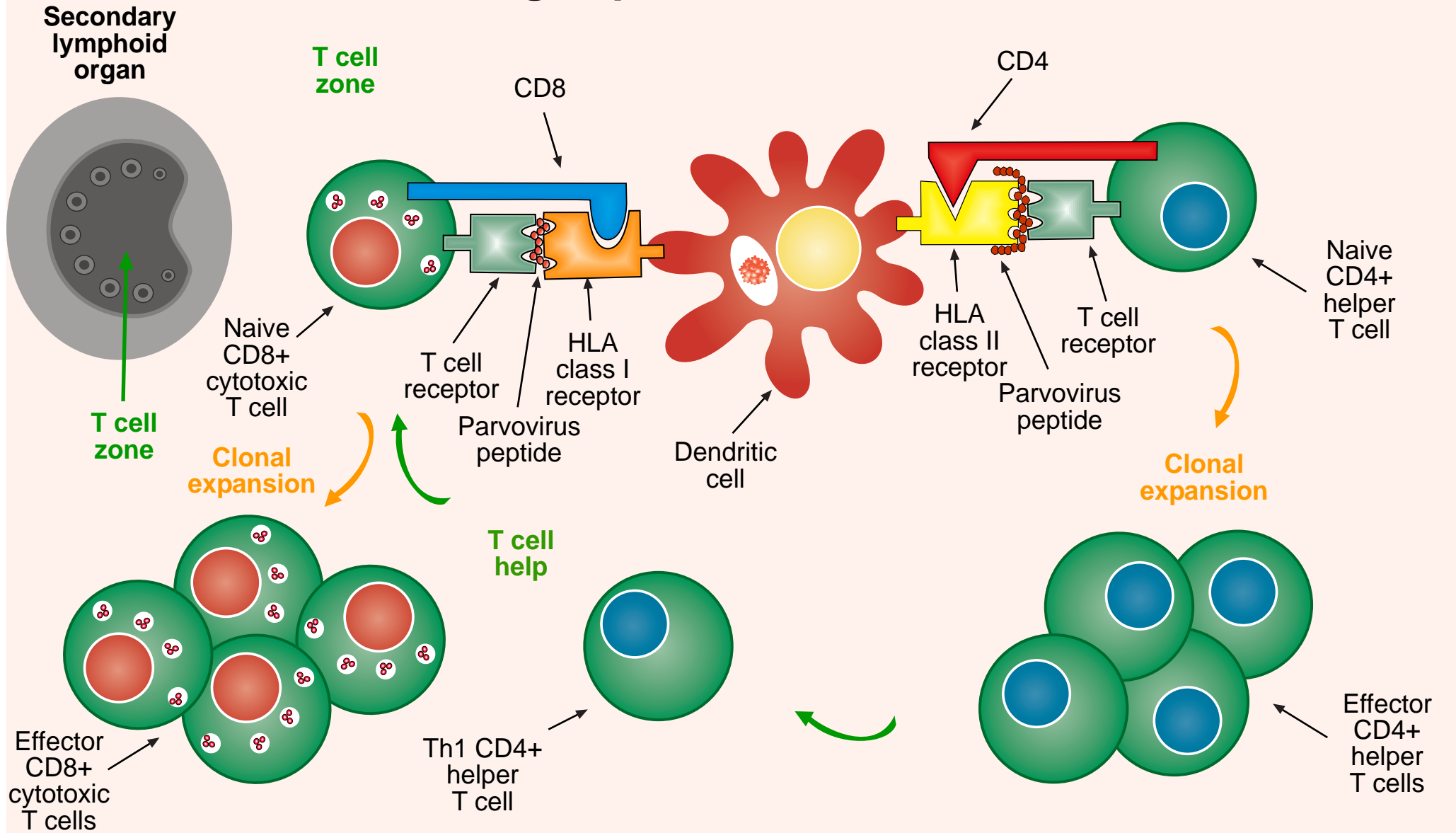
The main target cell of parvovirus B19 is the proerythroblast (pronormoblast) that expresses the primary receptor Gb4Cer (globoside) as well as co-receptors Ku80 autoantigen and $\alpha 5 \beta 1$ integrin required for attachment and virus internalisation by endocytosis. Due to viral cytopathic effects, the normal development of the proerythroblast is altered and fails to differentiate into mature erythroid precursor cells. Instead, infected proerythroblasts increase in size and produce new virus particles that assemble in the nucleus. Viral proteins such as NS1 and the 11kd protein are thought to mediate induction of apoptosis to facilitate release of virus particles. In severe cases of parvovirus B19 infection or in the immunocompromised, patients can develop anaemia due to reduced formation of erythrocytes. It is also possible that increased levels of apoptosis may expose intracellular antigens that could promote the development of autoimmune disease.

Parvovirus antigen uptake and viral peptide processing



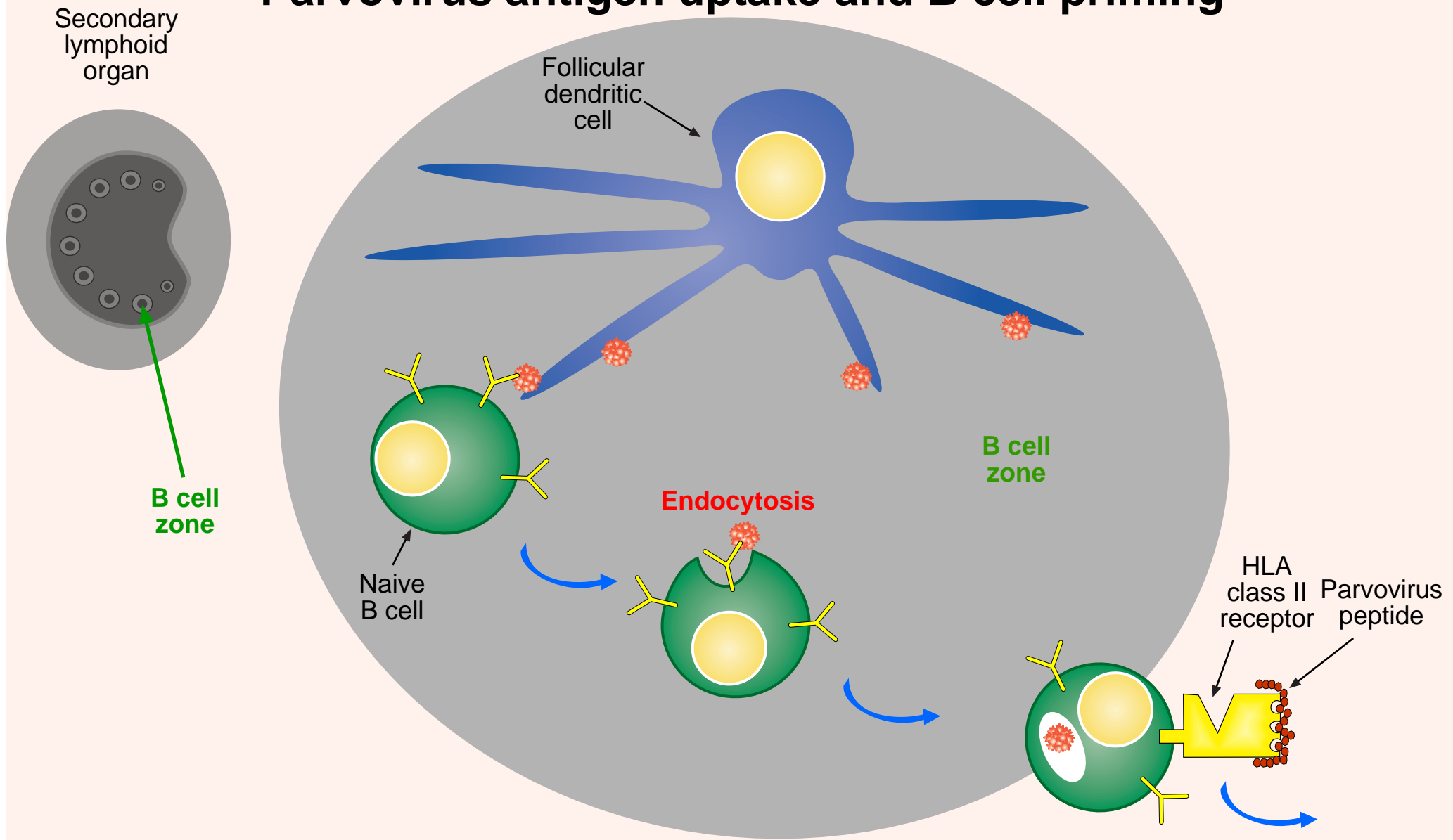
Adaptive immunity is necessary for control of parvovirus B19. Although both cell-mediated and humoral responses occur, it appears that neutralising antibodies play a dominant role in clearance of virus. This is observed during natural parvovirus B19 infection and also during treatment with IVIG. For humoral immune responses to occur, activation of CD4+ helper T cells and B cells is necessary. CD4+ helper T cells are activated in secondary lymphoid organs by antigen presenting cells, such as dendritic cells and macrophages, that phagocytose virus or viral antigens. Viral peptide antigens are then displayed on HLA class II receptors for interaction with the T cell receptor expressed on the surface of CD4+ helper T cells.

Parvovirus antigen presentation and T cell activation



Antiviral CD8+ cytotoxic T cell and CD4+ helper T cell responses can be detected following parvovirus B19 infection. It has been observed that these T cell responses can often remain sustained after resolution of primary infection and may relate to possible persistence of parvovirus B19 in other tissues. Naive CD8+ cytotoxic T cells require help from CD4+ helper T cells before proliferation and differentiation into effectors can occur. Similarly, for antibody production, CD4+ helper T cells are needed to activate B cells and allow them to proliferate and differentiate into plasma cells.

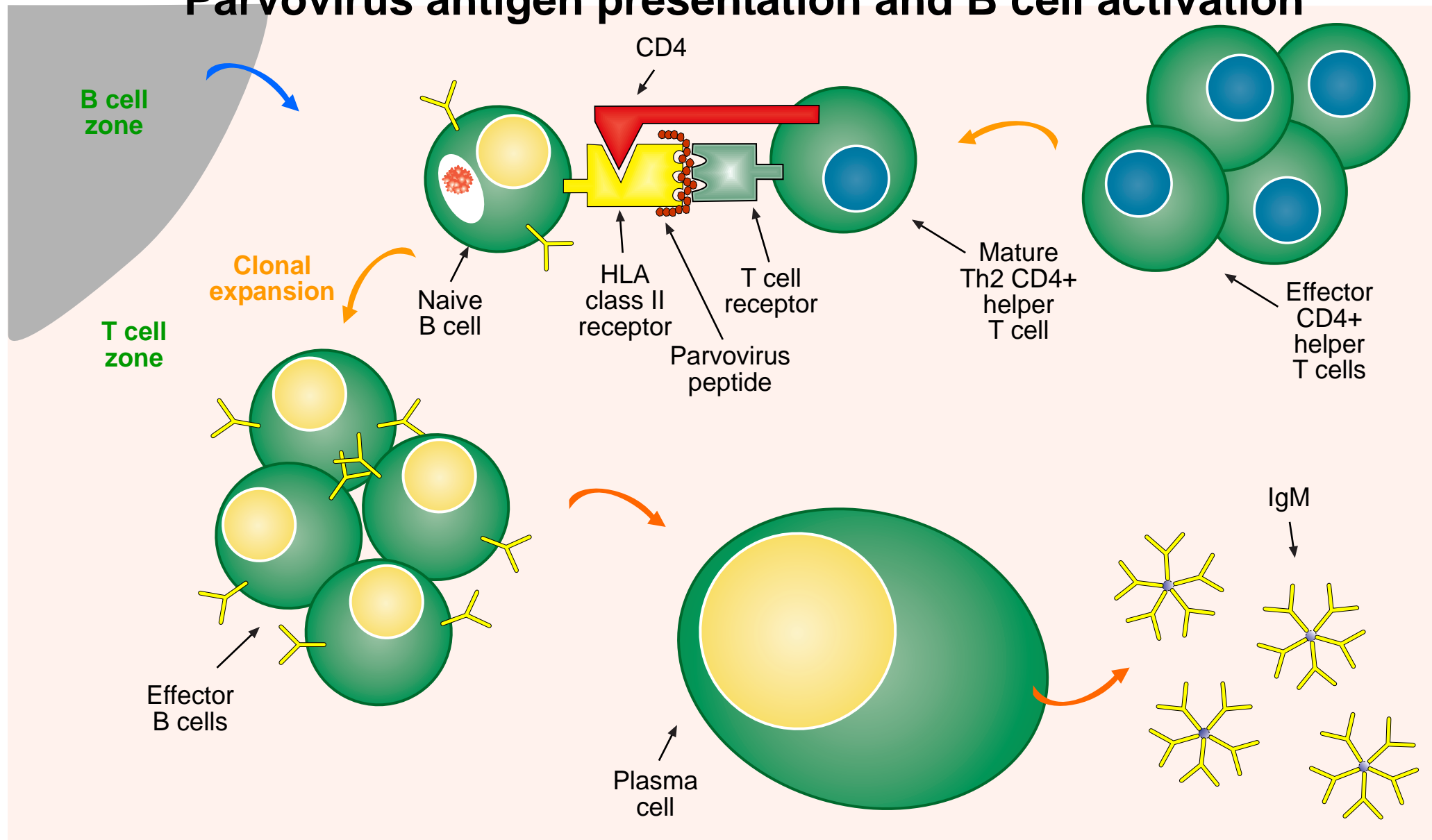
Parvovirus antigen uptake and B cell priming



Naive B cells are primed in the germinal centres of secondary lymphoid organs where they interact with follicular dendritic cells. Follicular dendritic cells display captured virus and viral antigens on the cell surface. B cells express cell surface immunoglobulins (B cell receptors) which may recognise and bind to these antigens. Binding of the B cell receptor triggers endocytosis of the receptor-antigen complex. The antigen is processed and immunogenic peptides are displayed on HLA class II receptors on the cell surface. The B cell then migrates out of the germinal centre into the T cell zone for activation by CD4+ helper T cells.

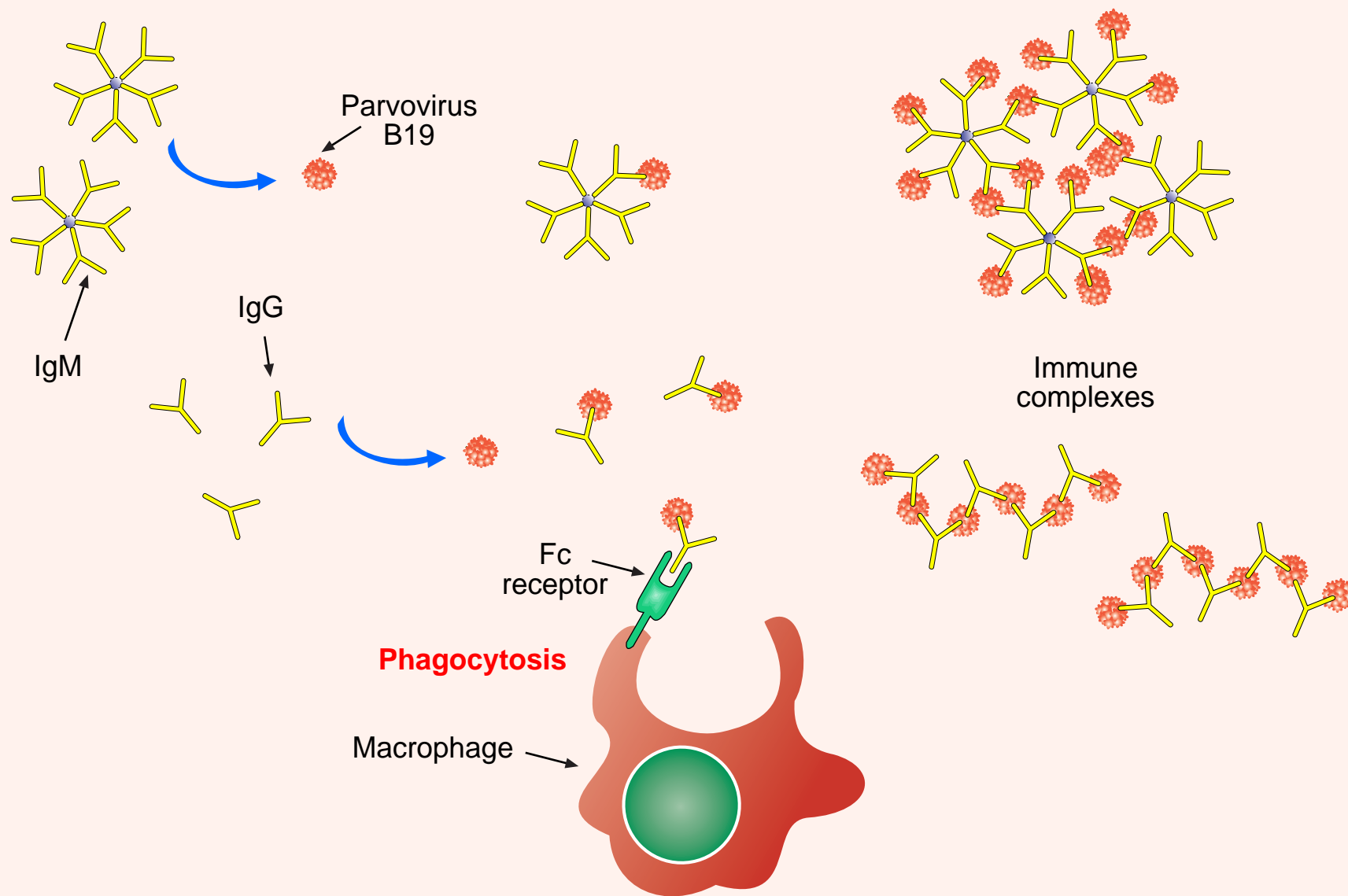


Parvovirus antigen presentation and B cell activation



B cells primed in the germinal centre require activation signals from CD4+ helper T cells before they can proliferate and differentiate into plasma cells. This interaction takes place in the T cell zone of the secondary lymphoid organs where activated Th2 CD4+ helper T cells are present. Once activated, naive B cells differentiate into plasma cells that produce antibodies of the IgM class.

Parvovirus B19 opsonisation and immune complex formation



Parvovirus B19 is effectively cleared by neutralising antibodies as observed in natural infection as well as during treatment with IVIG. Enhanced phagocytosis is mediated by Fc receptors expressed by phagocytes that engulf opsonised virus. Immune complexes can be generated in the presence of large quantities of virus. Immune complexes are thought to be the cause of skin rashes seen during parvovirus B19 infection and may also be responsible for a false-negative parvovirus antibody testing. It is also postulated that antibody-mediated autoimmune reactions may occur due to a similarity between parvovirus B19 epitopes and human proteins (molecular mimicry) such as arthritis which is often associated with parvovirus B19 infection.

