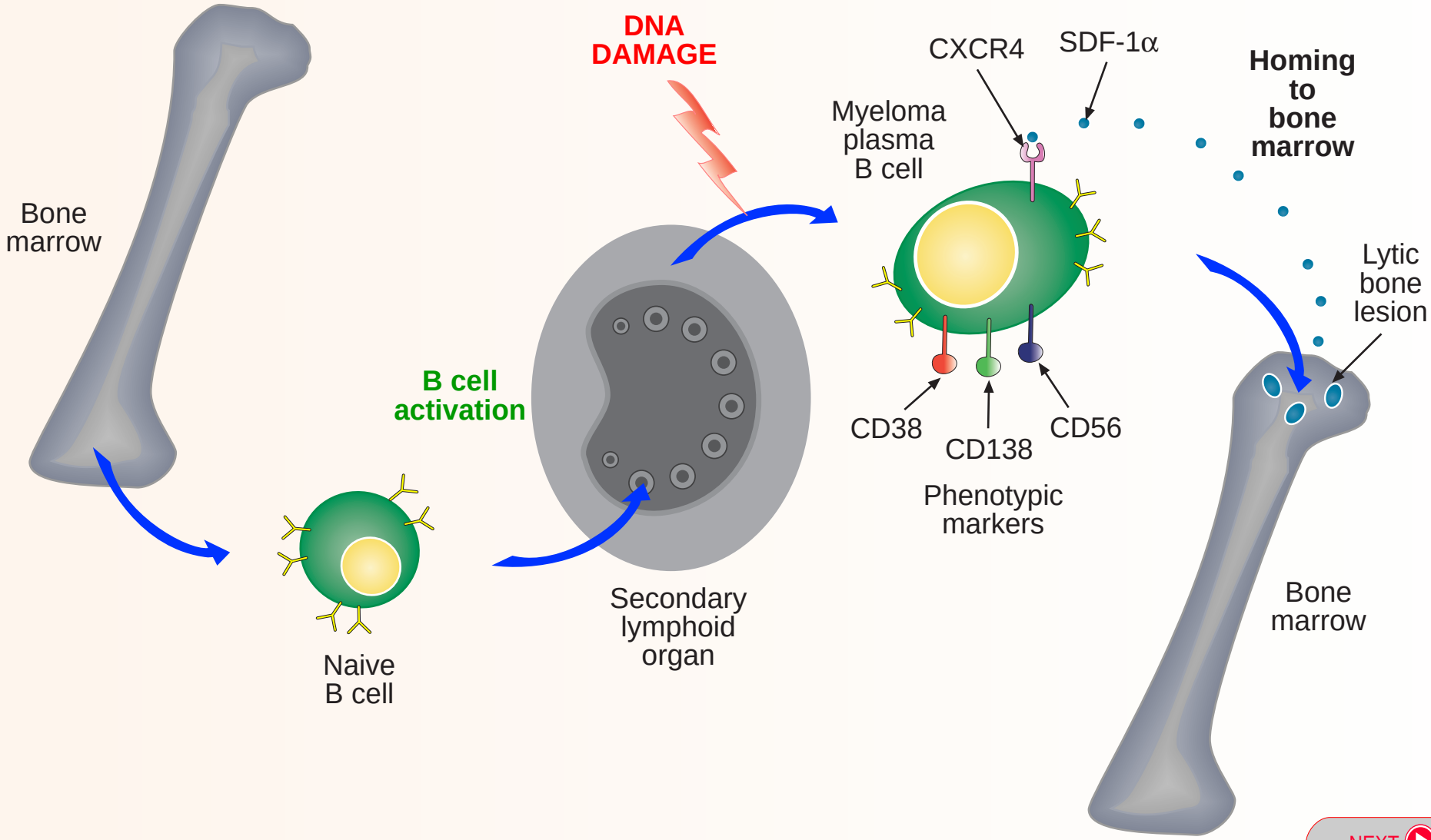
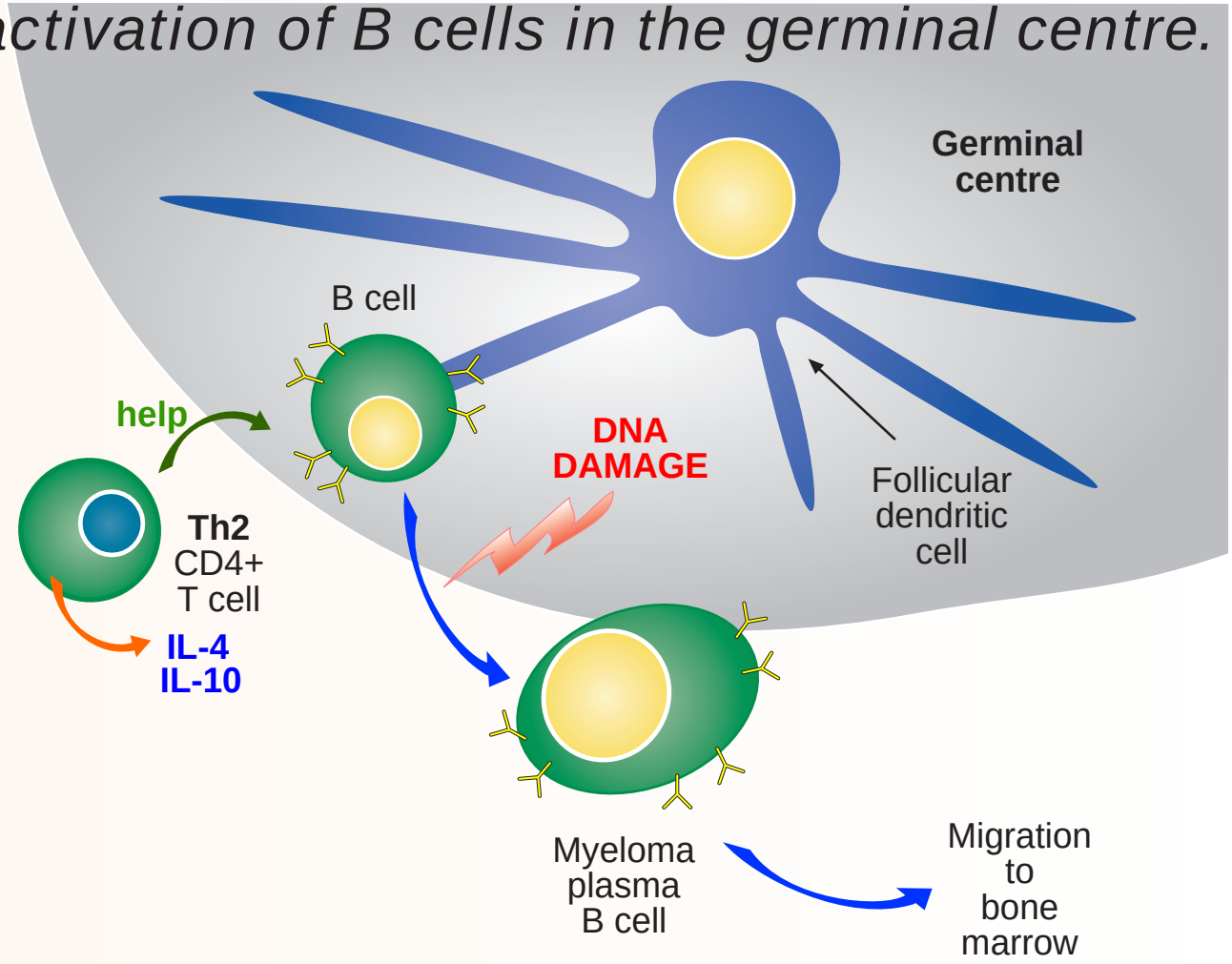
Generation of post-germinal centre myeloma plasma B cell.



Multiple myeloma is a malignancy of plasma B cells caused by alterations to genetic material following B cell activation in the germinal centres of secondary lymphoid organs. Genetic defects include primary translocations of immunoglobulin heavy/light chain genes to other chromosomes near oncogenes/cell-cycle proteins and secondary changes including duplication/loss of chromosomes and/or mutations in cell growth/tumour suppressor genes. Myeloma plasma B cells also express CXCR4 receptors for SDF-1α, a chemokine that regulates homing to the bone marrow where bone disease develops.

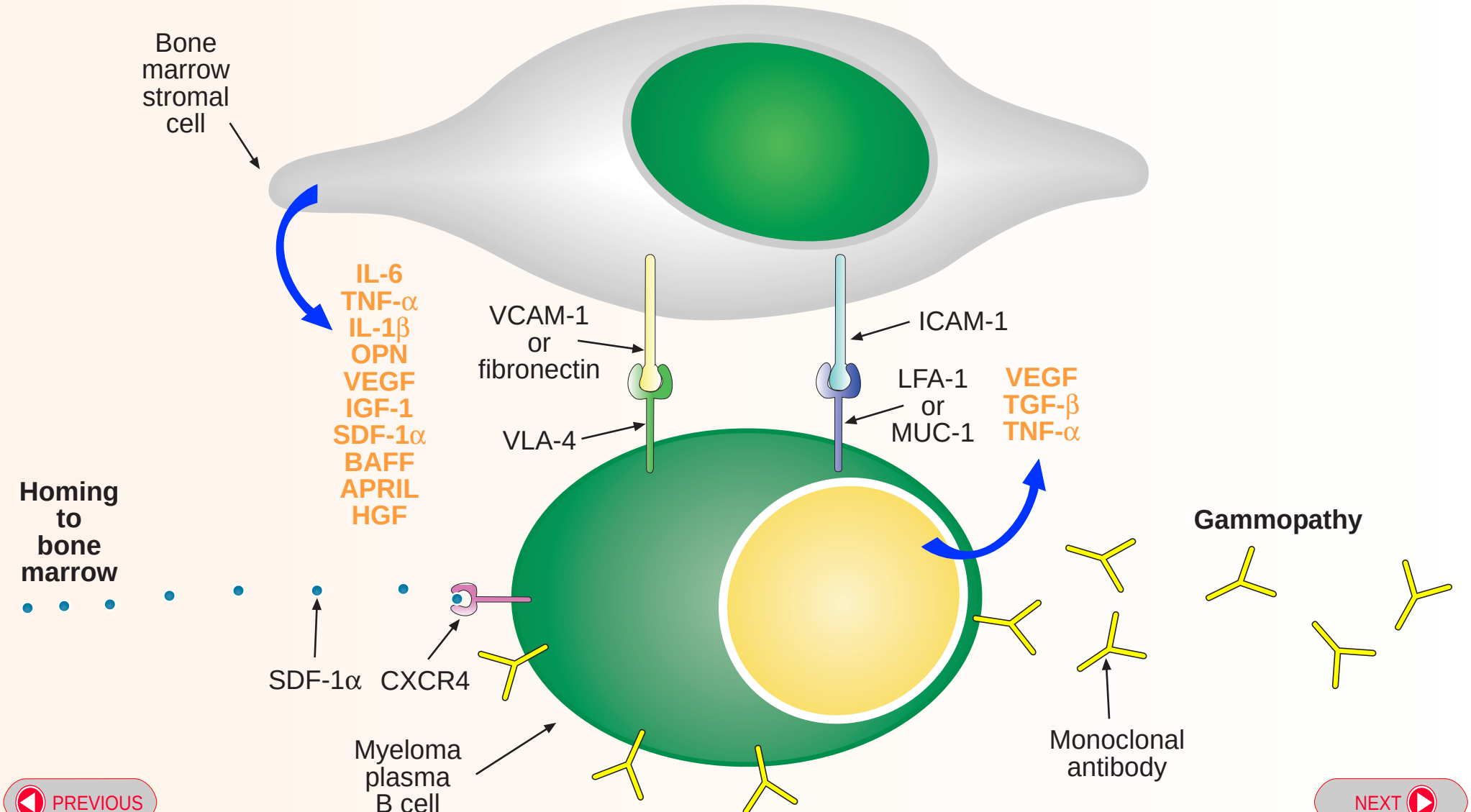
DNA damage following activation of B cells in the germinal centre.



PREVIOUS NEXT

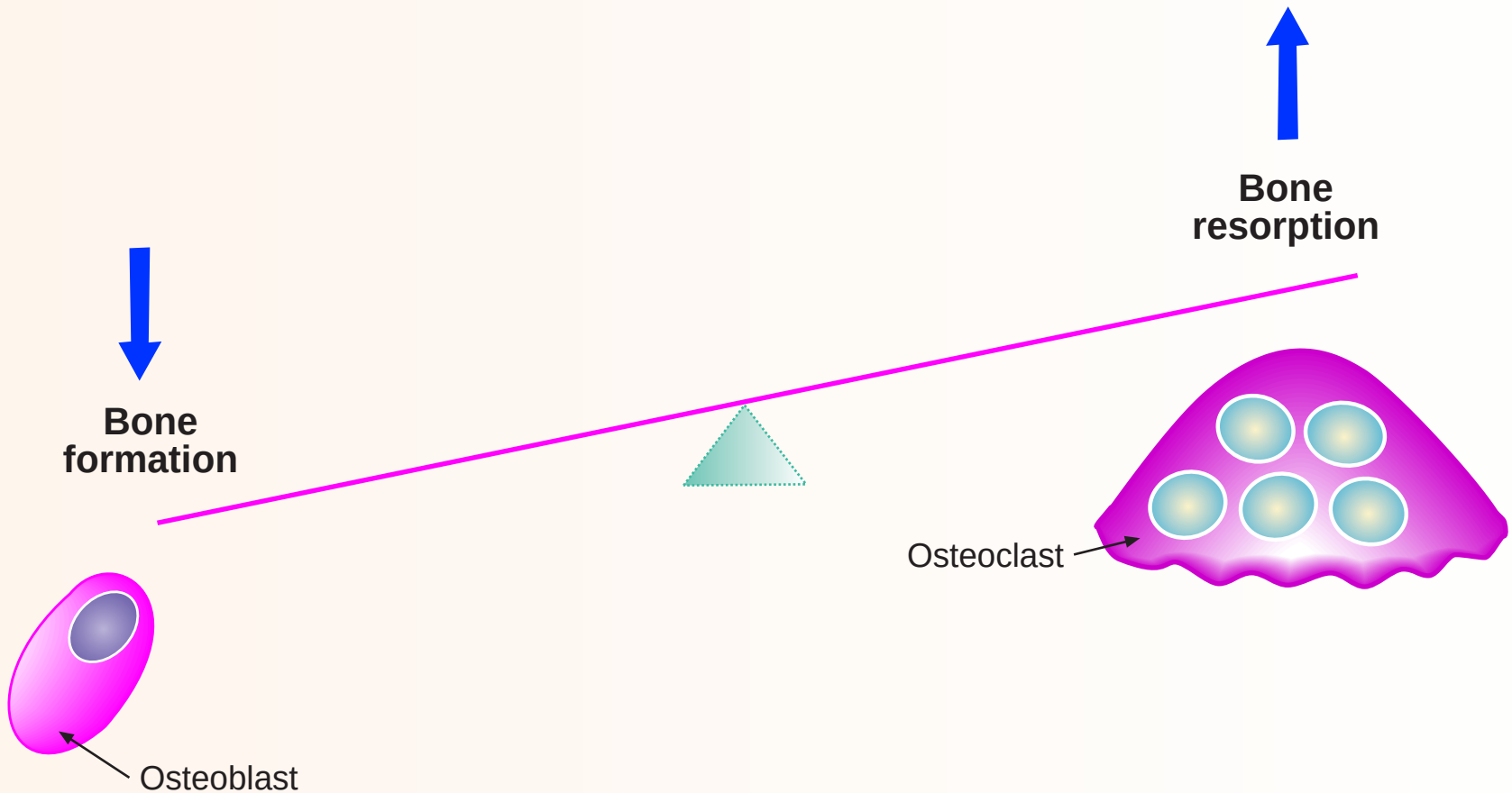
B cells are primed by B cell receptor recognition of antigens presented by follicular dendritic cells in the germinal centres of secondary lymphoid organs. CD4+ helper T cell interaction activates B cells to differentiate into plasma cells and also induces isotype switching and affinity maturation. During this process abnormal DNA recombination events translocate heavy and light immunoglobulin genes to other chromosomes and generate a malignant phenotype. Secondary genetic alterations involving duplication/deletion of chromosomes or mutations in other genes can follow. The myeloma plasma B cells continue to produce immunoglobulins resulting in a gammopathy and ultimately home to the bone marrow where bone disease develops.

Adhesion of myeloma plasma B cells to bone marrow stromal cells.



The myeloma plasma B cells express CXCR4 receptors that bind SDF-1α , a chemokine that regulates homing to the bone marrow. Myeloma plasma B cells also express cellular adhesion molecules, such as VLA-4, LFA-1 and MUC-1, that interact with ligands expressed on bone marrow stromal cells. Stimulation of adhesion molecules on stromal cells generates intracellular signals that promote the secretion of soluble cellular factors that help to maintain the myeloma B cells in an anti-apoptotic and drug-resistant state. Soluble cellular factors that stimulate the bone marrow stromal cells are are also secreted by the myeloma B cells.

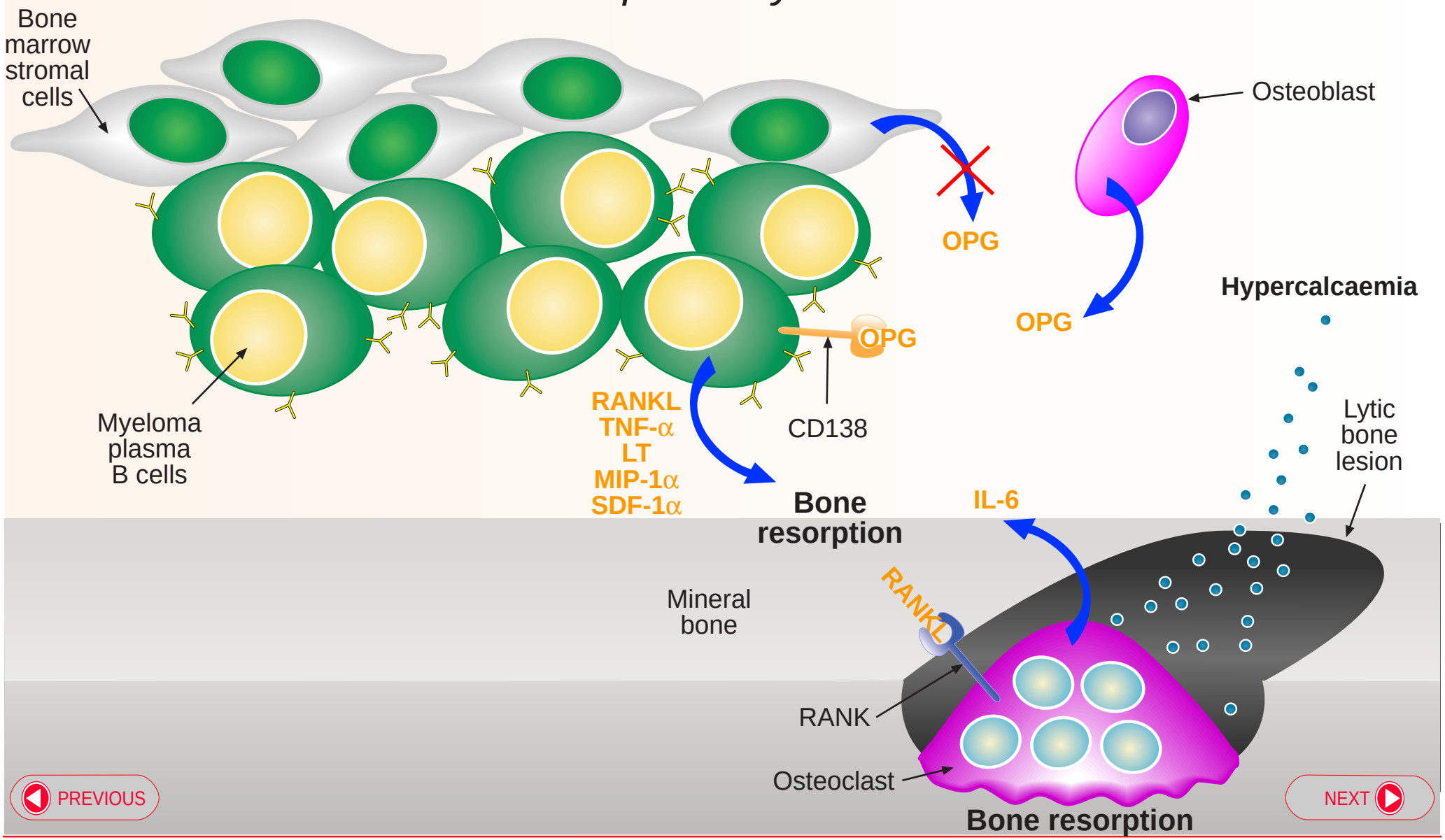
Bone destruction mediated by unbalanced bone formation/resorption.



PREVIOUS NEXT

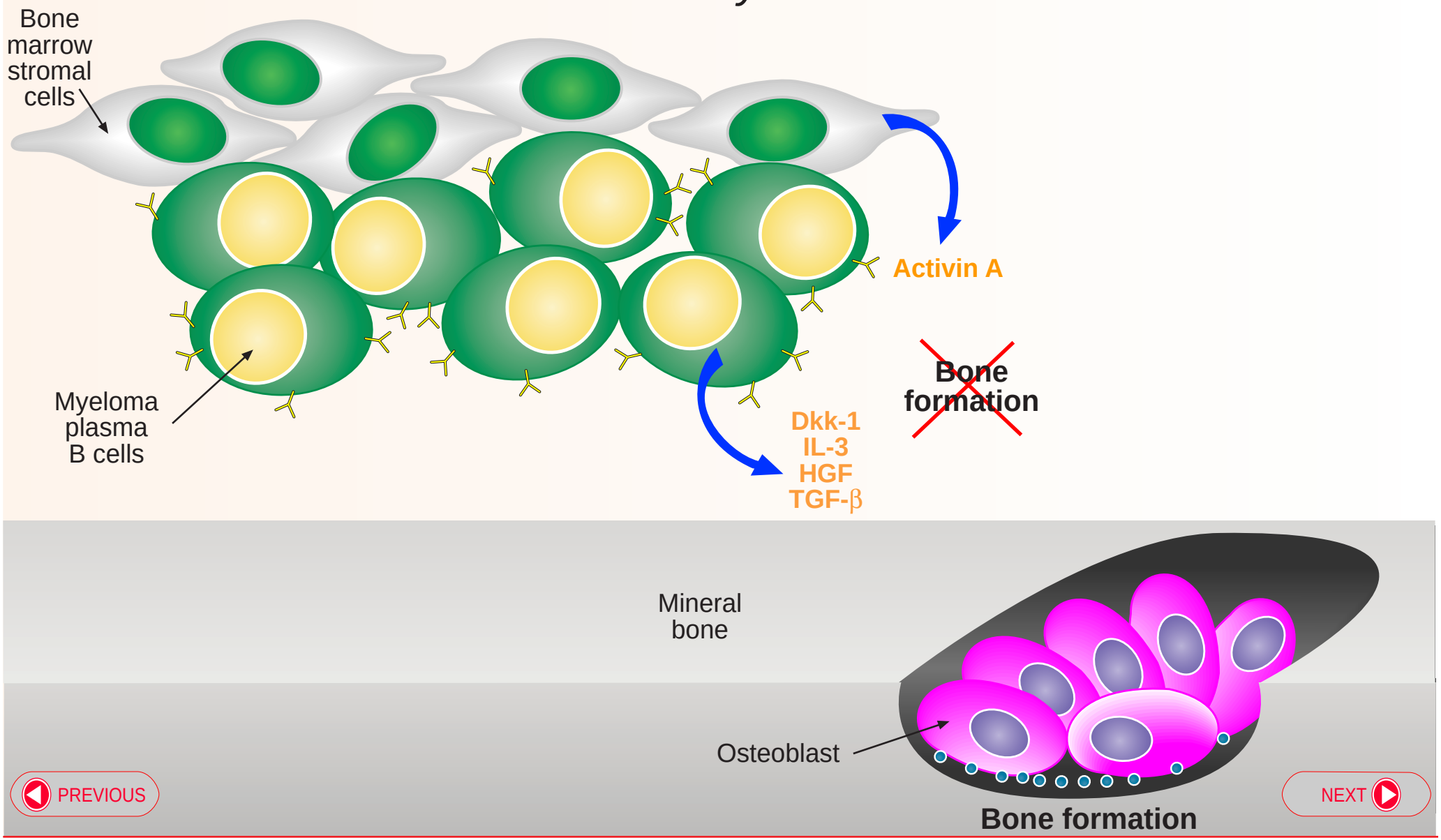
In multiple myeloma, bone disease is characterised by the presence of lytic bone lesions and raised blood calcium levels as a result of an imbalance between bone formation (mediated by osteoblasts) and bone resorption (mediated by osteoclasts). Myeloma plasma B cells home to bone marrow and via interaction with bone marrow stromal cells introduce changes in the bone marrow microenvironment. Various soluble factors secreted by cells in the bone marrow collectively reduce bone formation and promote bone resorption.

Increased bone resorption by osteoclast activation.



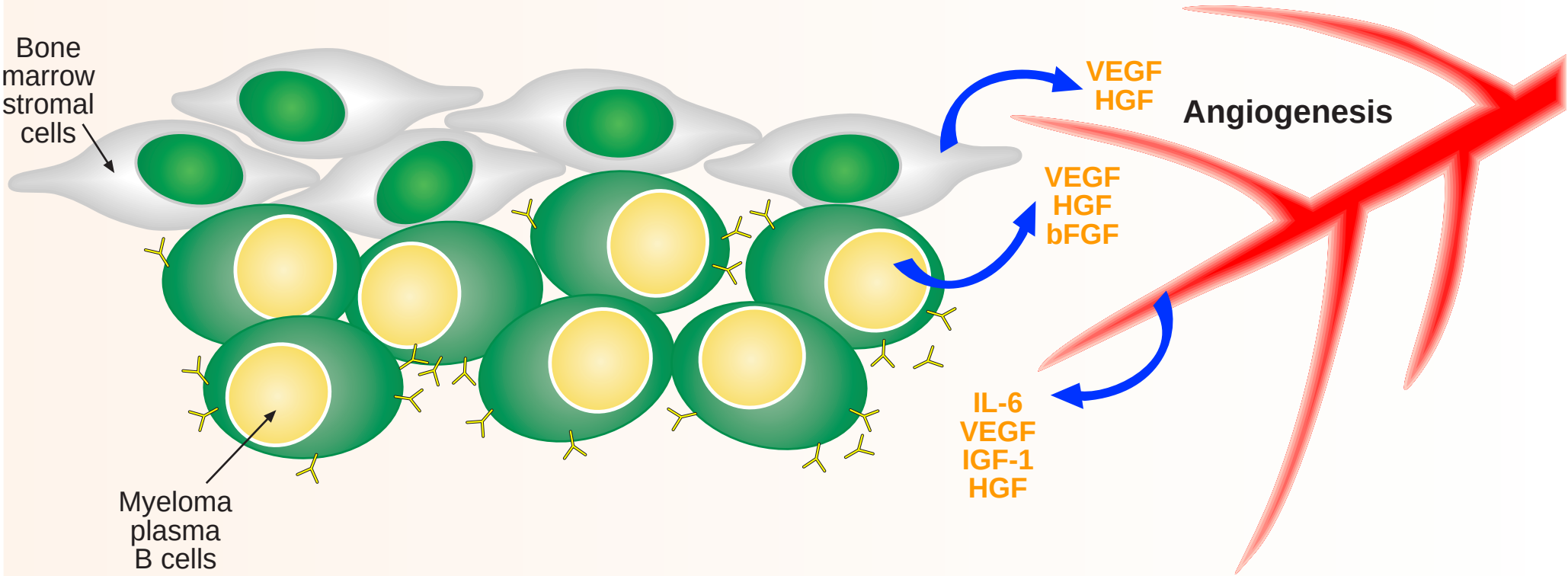
Bone destruction is mediated by the bone resorption activity of multinucleated osteoclasts. RANKL is a required activation signal for osteoclasts. RANKL is secreted along with other growth factors by myeloma plasma B cells. In addition, an inhibitor of osteoclast activation, osteoprotegerin (OPG), which is secreted by osteoblasts and bone marrow stem cells, is degraded by CD138 receptors expressed on myeloma plasma B cells. Bone marrow stromal cells also have reduced production of OPG. OPG acts as a decoy molecule that competes with RANKL for binding to RANK receptors expressed by osteoclasts. Activated osteoclasts secrete IL-6 that promotes the survival of myeloma plasma B cells.

Reduced bone formation by osteoblast inhibition.



Bone destruction is exacerbated by the inhibition of osteoblast activity needed for bone formation. Myeloma plasma B cells secrete soluble factors that inhibit osteoblast activity. In addition, bone marrow stromal cells secrete activin A which also inhibits osteoblast function.

Induced angiogenesis in bone marrow.



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To improve oxygen and nutrient supply to the myeloma plasma B cells, the formation of new blood vessel is promoted by soluble factors secreted by both bone marrow stromal cells and myeloma plasma B cells. In addition, blood vessel endothelial cells also secrete growth factors that promote the survival of the myeloma plasma B cells.

List of abbreviations for soluble factors

IL-6	Interleukin-6
IL-1β	Interleukin 1-beta
OPN	Osteopontin
OPG	Osteoprotegerin
VEGF	Vascular endothelial growth factor
IGF-1	Insulin-like growth factor-1
IL-8	Interleukin-8
SDF-1α	Stromal cell derived factor 1-alpha
BAFF	B cell activating factor
APRIL	A proliferation-inducing ligand
HGF	Hepatocyte growth factor
TNF-α	Tumour necrosis factor-alpha
Dkk-1	Dickkopf homologue-1
IL-3	Interleukin-3
TGF-β	Transforming growth factor-beta
RANKL	Receptor activator of nuclear factor kappa B ligand
LT	Lymphotoxin
MIP-1α	mNacrophage inflammatory protein 1-alpha
bFGF	Basic fibroblast growth factor
VLA-4	Very kate activation antigen-4
VCAM-1	Vascular cell adhesion molecule-1
MUC-1	Mucin-1
LFA-1	Lymphocyte function-associated antigen-1
ICAM-1	Intercellular adhesion molecule-1