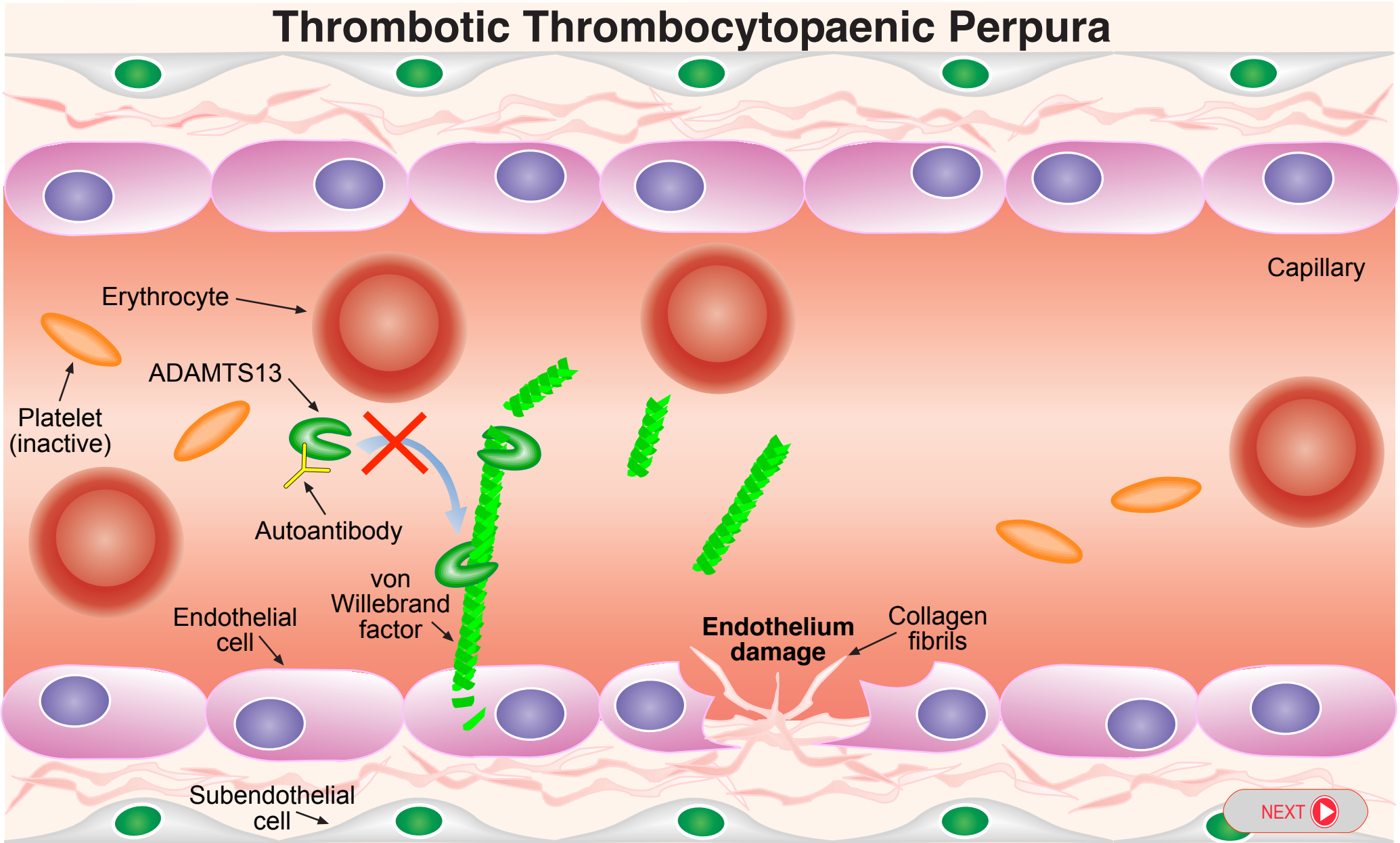
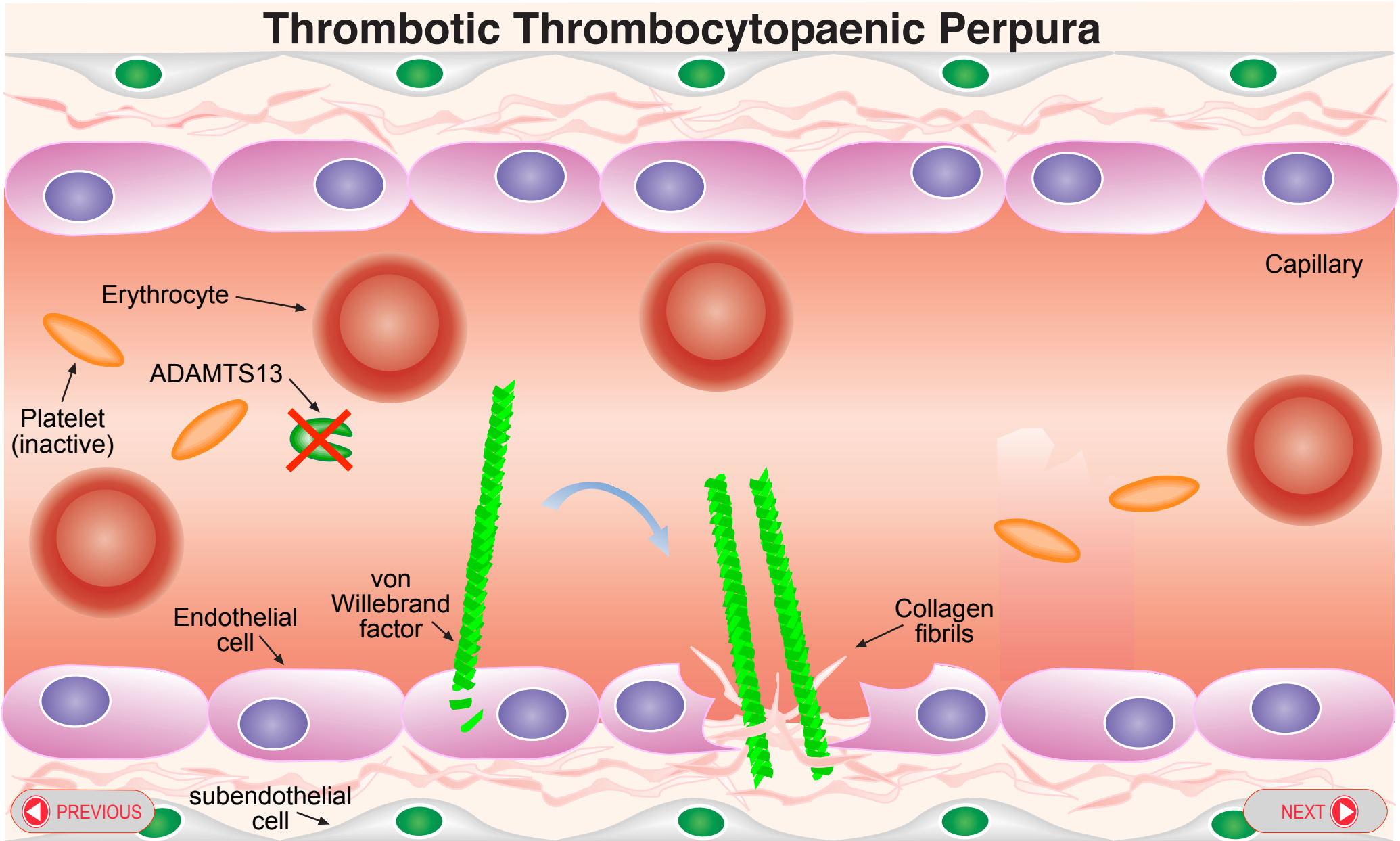
Thrombotic Thrombocytopaenic Perpura



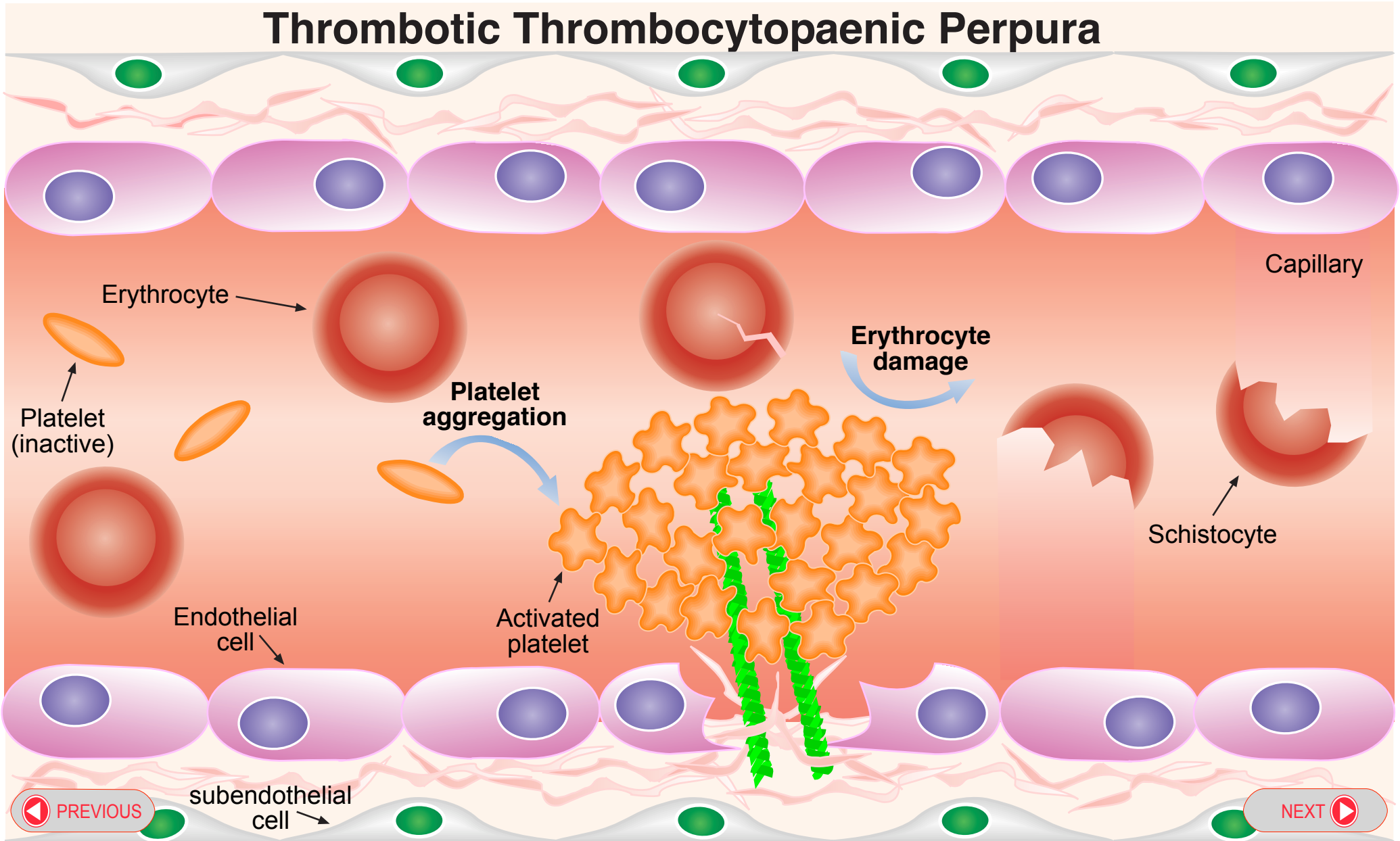
In TTP, the plasma-derived proteolytic enzyme ADAMTS13, that cleaves the large multimeric chains of von Willebrand factor into smaller fragments, is depleted due to the presence of an inhibitor, commonly an autoantibody. Autoantibodies can be produced through molecular mimicry following a humoral response to an infection or by disruption of regulation of immune responses to self-antigens, such as in autoimmune disease or HIV. TTP can also occur during pregnancy and may be related to the increased risk of developing autoantibodies when immune responses are polarised towards Th2 T lymphocyte activation which favours humoral immunity.

Thrombotic Thrombocytopaenic Perpura



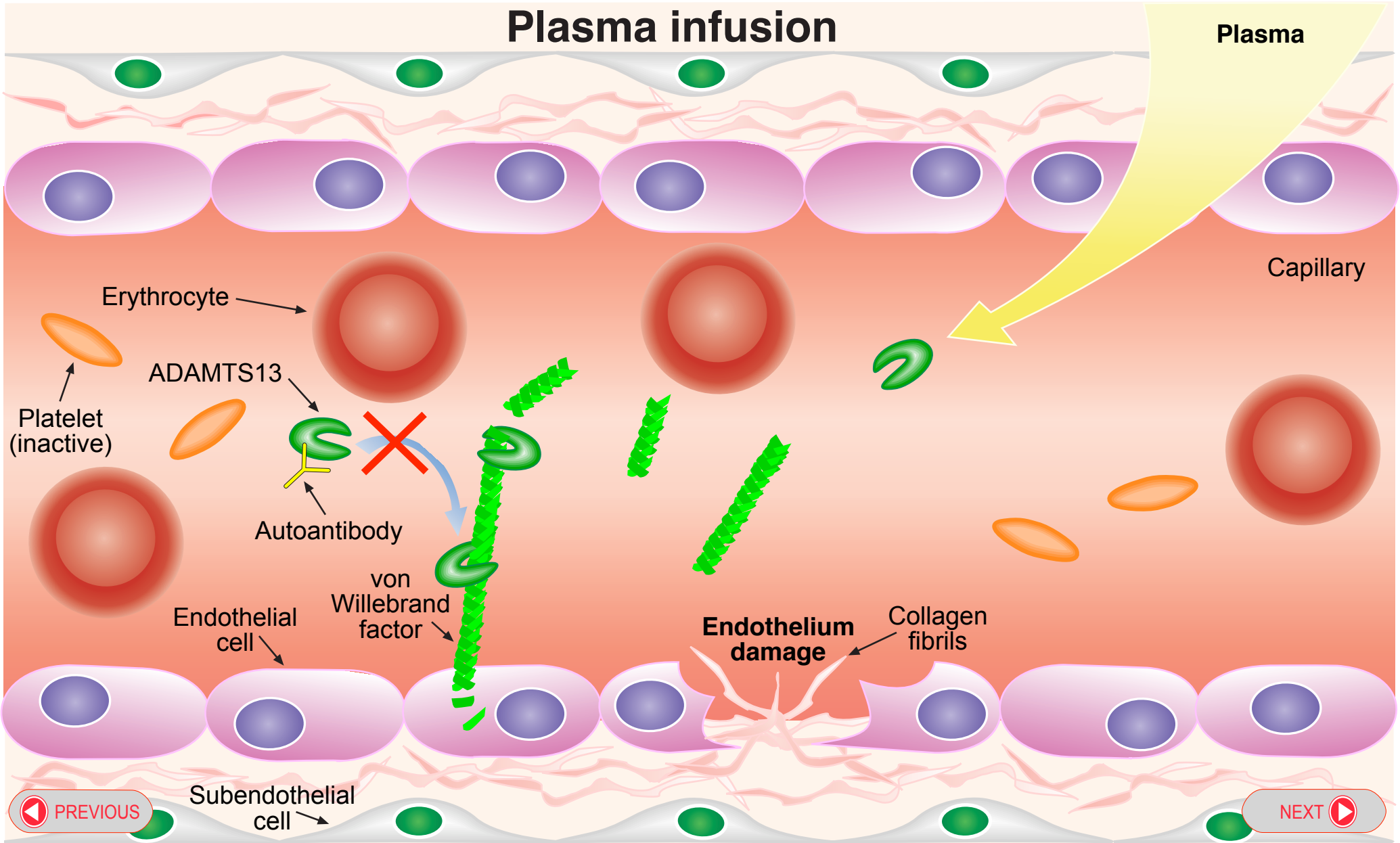
In the absence of ADAMTS13 proteolytic activity, there are higher levels of the large multimeric chains of von Willebrand factor in circulation that bind to exposed subendothelial collagen fibrils and initiate recruitment of large numbers of platelets to sites of endothelium damage.

Thrombotic Thrombocytopaenic Perpura



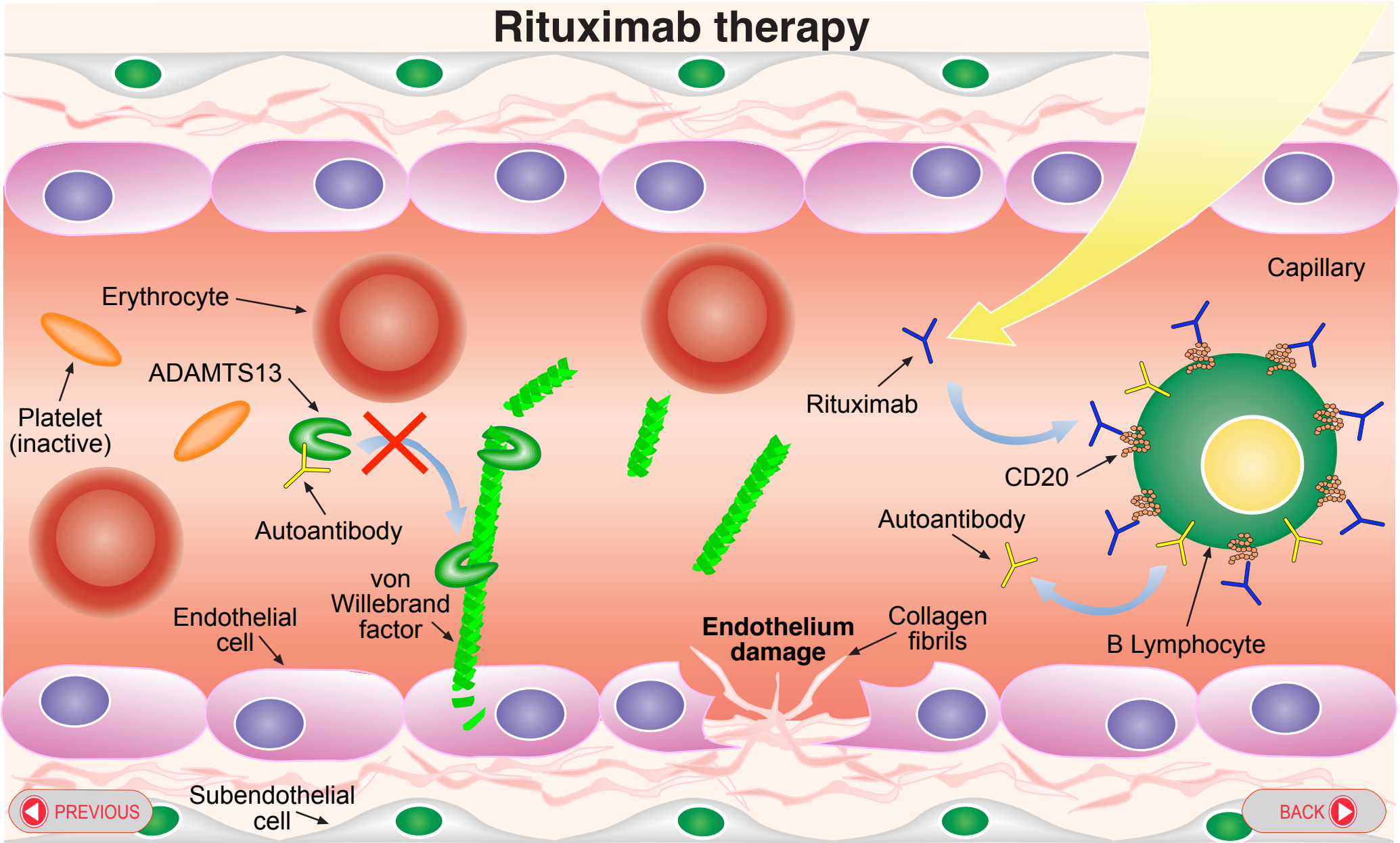
Platelets express cell surface GPIb receptors that recognise von Willebrand factor bound to collagen fibrils exposed at the site of endothelium damage. In TTP, the large multimeric chains of von Willebrand factor recruit and activate excessive numbers of platelets, which in turn leads to platelet depletion (thrombocytopaenia). The large aggregation of platelets also impedes the passage of erythrocytes through small blood vessels and can cause the cells to shear, resulting in anaemia and organ ischaemia. Fragments of erythrocytes are visible in blood smears and are known as schistocytes.

Plasma infusion



TTP can be treated by plasma infusion or exchange therapy which provides the missing enzyme ADAMTS13 and restores proteolytic cleavage of the large multimeric chains of von Willebrand factor into smaller fragments. Plasma exchange therapy additionally contributes to the removal of the ADAMTS13 inhibitor, such as autoantibodies.

Rituximab therapy



In some cases plasma infusion or exchange therapy fails to provide a long-term benefit. When autoantibodies are responsible for inhibition of ADAMTS13, this is likely a result of the persistance of autoantibody producing B lymphocytes that continue to secrete autoantibodies. Rituximab is an anti-CD20 binding monoclonal antibody that selectively binds to B lymphocytes and mediates their destruction. In HIV-infected people, Rituximab has been used succesfully without evidence of clinical worsening or increased opportunistic infection.