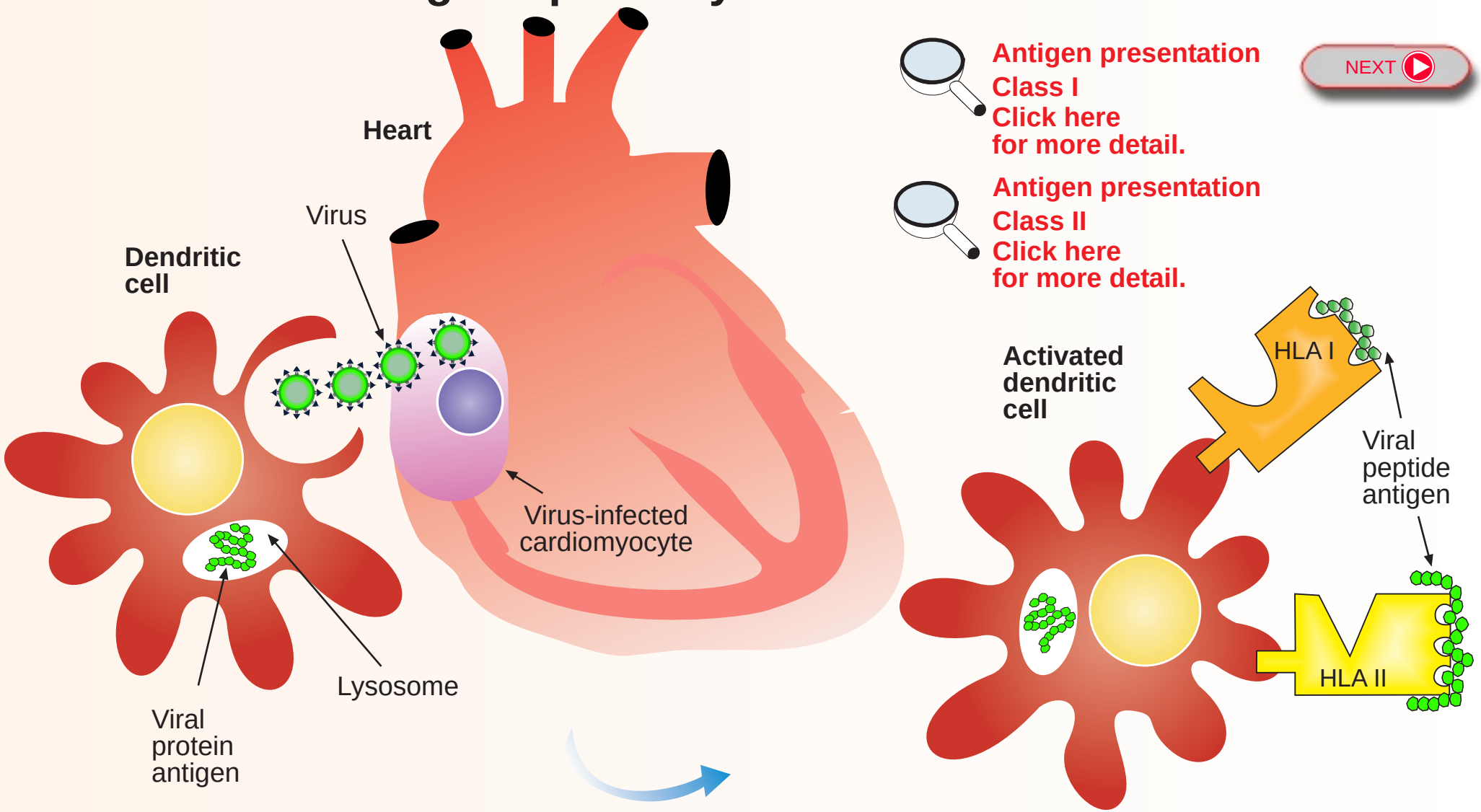
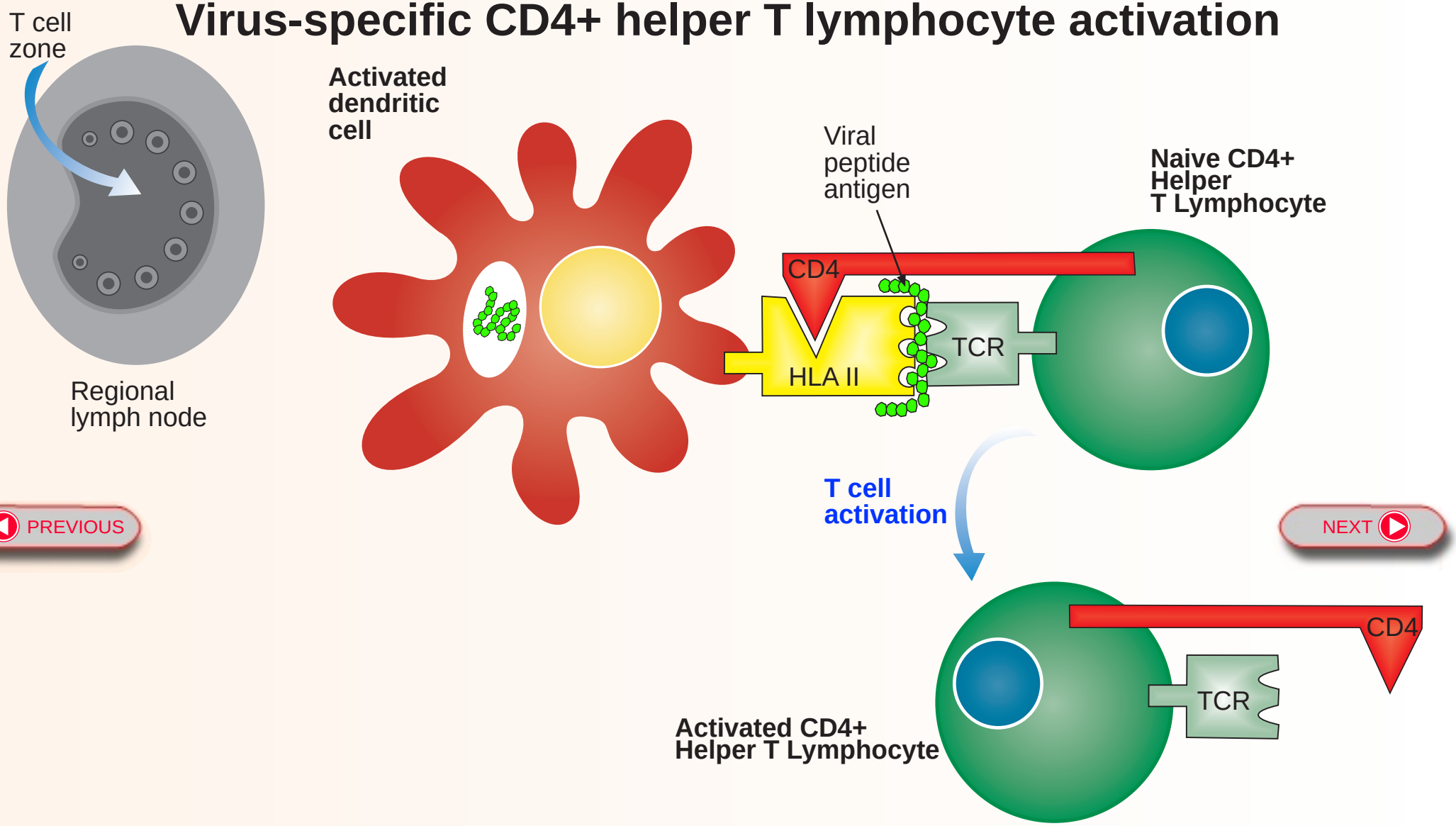
Antigen uptake by dendritic cells



Autoimmune myocarditis is thought to be precipitated by an initial infection with a pathogen, such as a virus, that expresses surface B-cell epitopes highly similar to host epitopes found on the cell surface of cardiomyocytes (molecular mimicry). Viruses with tropism for myocardiocytes such as Adenovirus and Coxsackie B viruses are frequently associated with viral myocarditis. In a model for viral myocarditis, viral infection in the heart is first detected by the innate immune response involving phagocytes (macrophages and dendritic cells) that engulf virus and viral antigens released from infected cells. Viral peptide antigens are processed by dendritic cells and bound to HLA class I and II receptors for presentation to CD4+ and CD8+ T cells in regional lymph nodes.

Virus-specific CD4+ helper T lymphocyte activation



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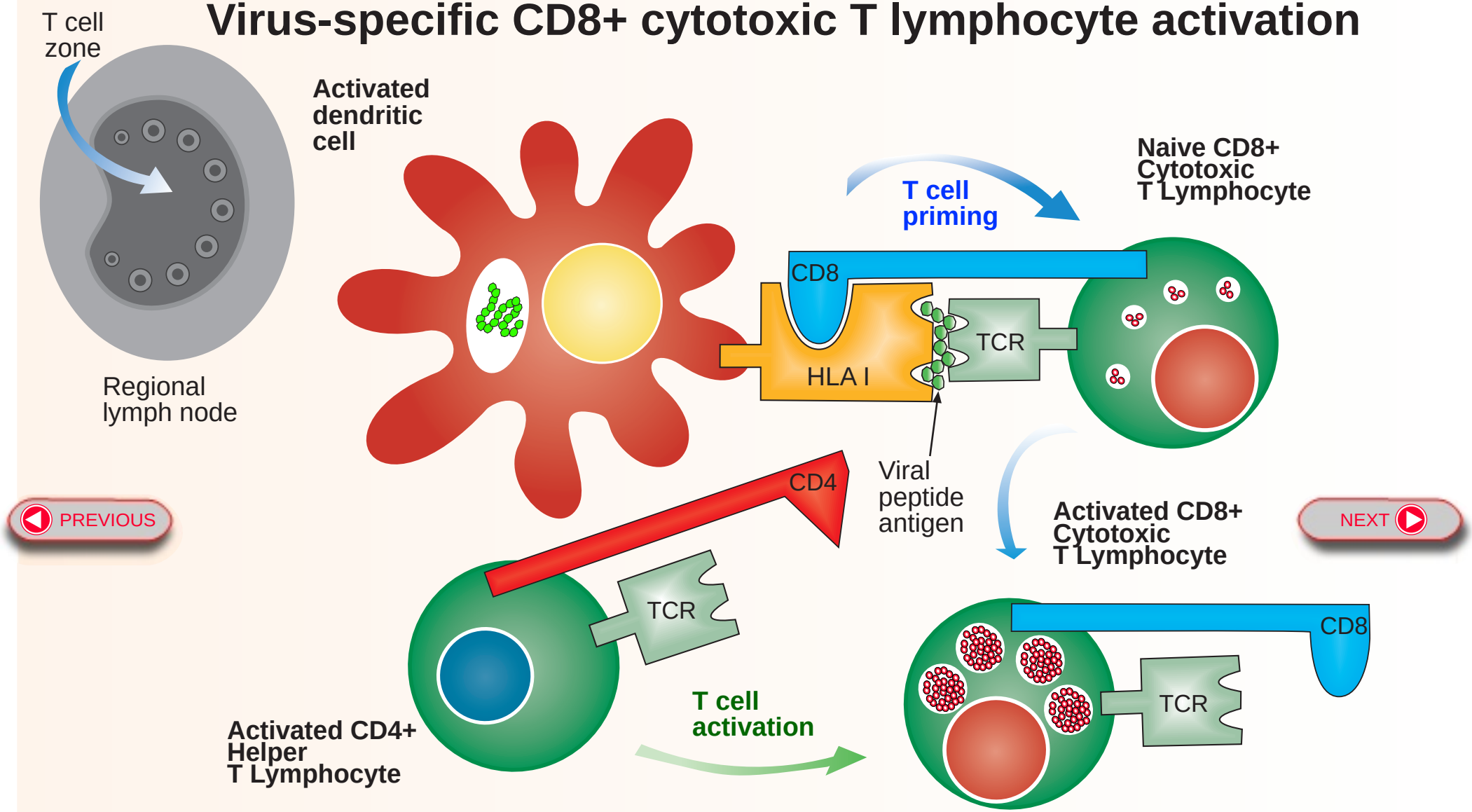
Dendritic cells present peptide antigens bound to surface HLA class II receptors to naive CD4+ helper T lymphocytes in the T cell zone of secondary lymphoid tissue (lymph nodes). CD4+ T cells that express T cell receptors that recognise antigen become activated and proliferate into effector and memory CD4+ T cell populations. Effector CD4+ T cells migrate to inflamed tissue where they further stimulate the immune response.

Virus-specific CD8+ cytotoxic T lymphocyte activation



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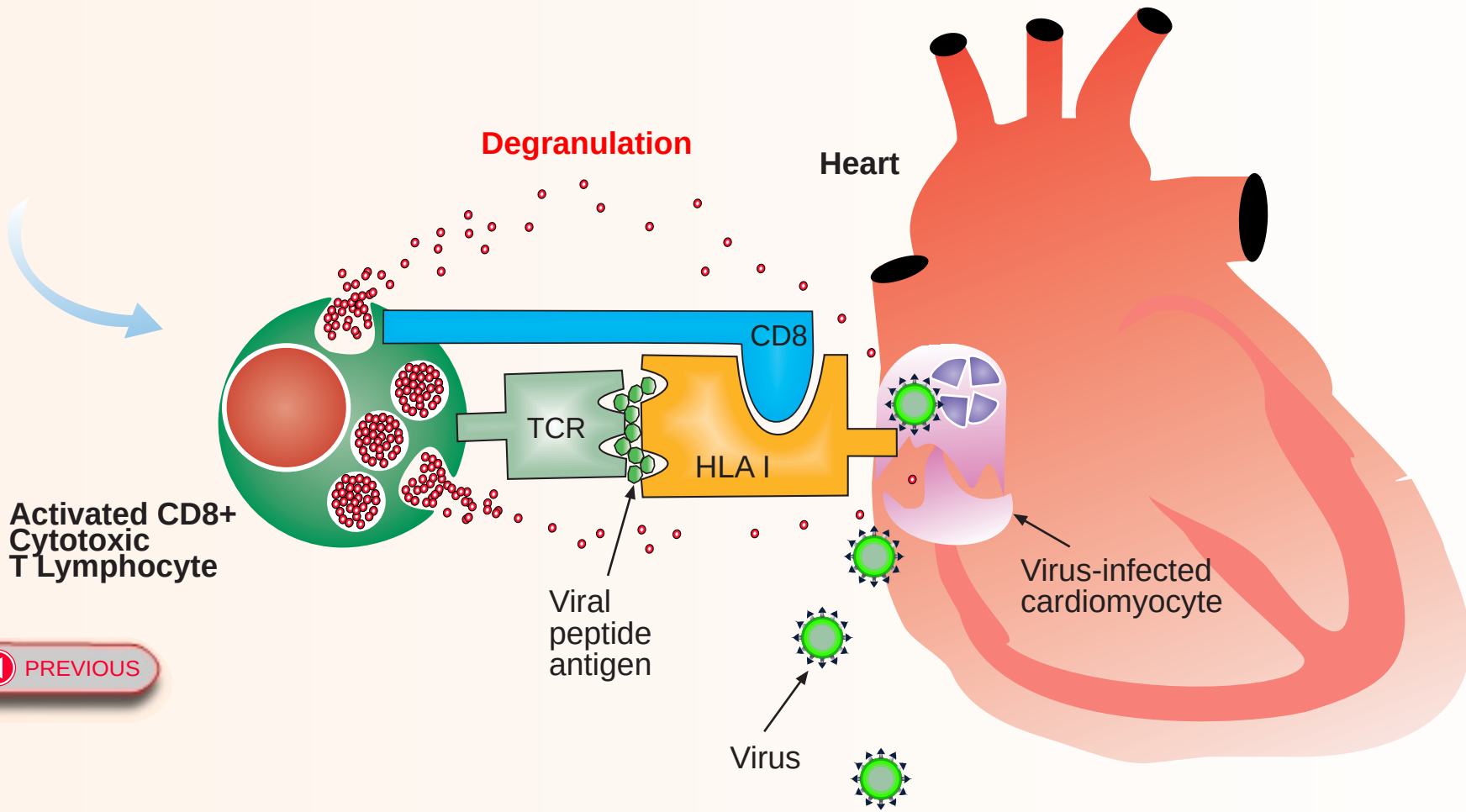
Dendritic cells also present peptide antigens bound to surface HLA class I receptors to naive CD8+ cytotoxic T lymphocytes in the T cell zone of secondary lymphoid tissue (lymph nodes). CD8+ T cells that express T cell receptors that recognise antigen become primed for cell-killing function, however, activation signals from CD4+ helper T lymphocytes are required. Once activated CD8+ T cells differentiate into effector and memory CD8+ cytotoxic T cell populations. Effector CD8+ T cells migrate to inflamed tissue where they are capable of killing host cells bearing viral peptide antigens bound to HLA class I receptors.

CD8+ cytotoxic T lymphocyte-mediated killing of infected cells



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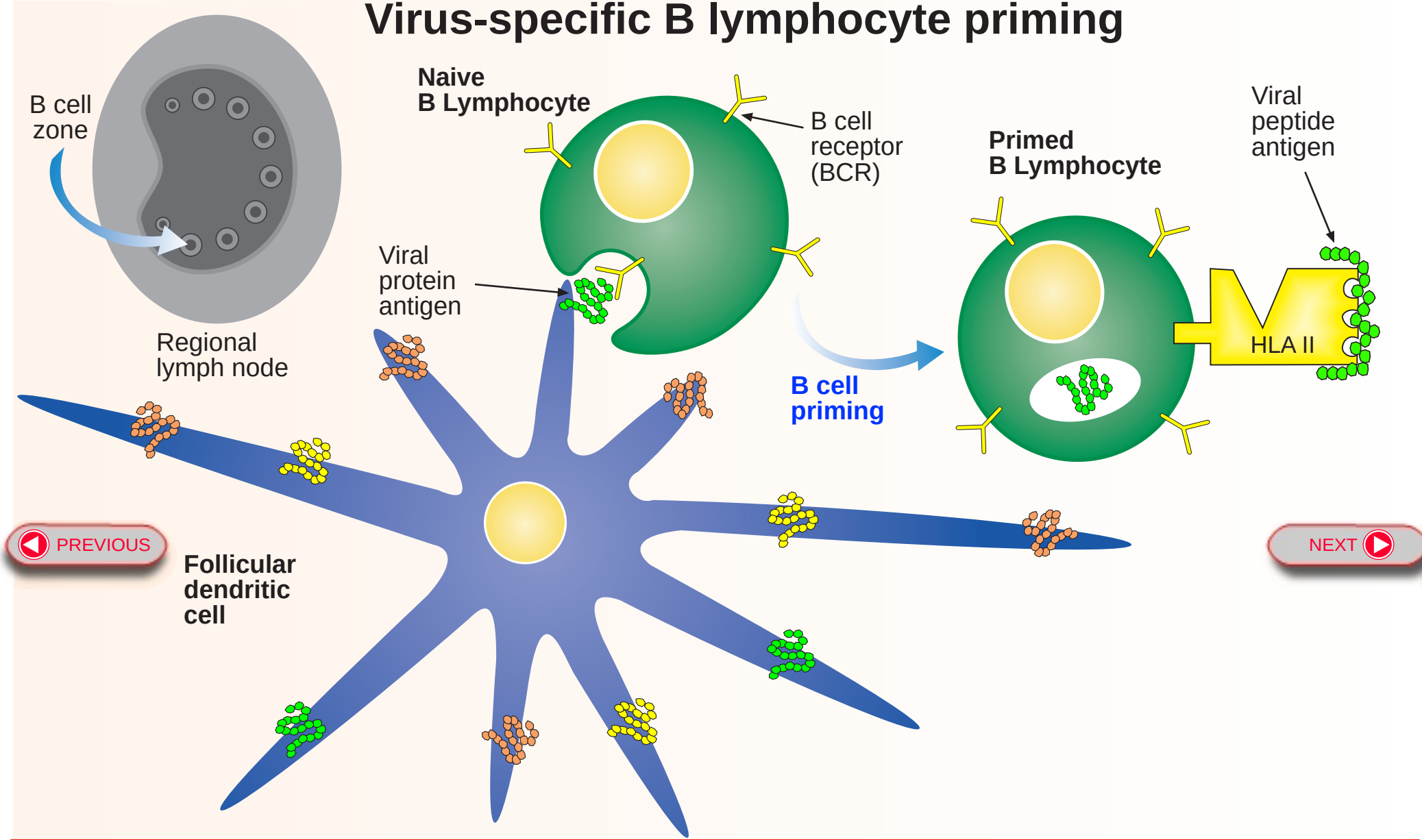
Cardiomyocytes infected with virus express surface HLA class I receptors with bound viral peptide antigens. Effector CD8+ cytotoxic T lymphocytes that express T cell receptors that recognise viral peptide antigens actively kill infected cells by degranulation of vesicles containing perforin and degradative molecules.

Virus-specific B lymphocyte priming



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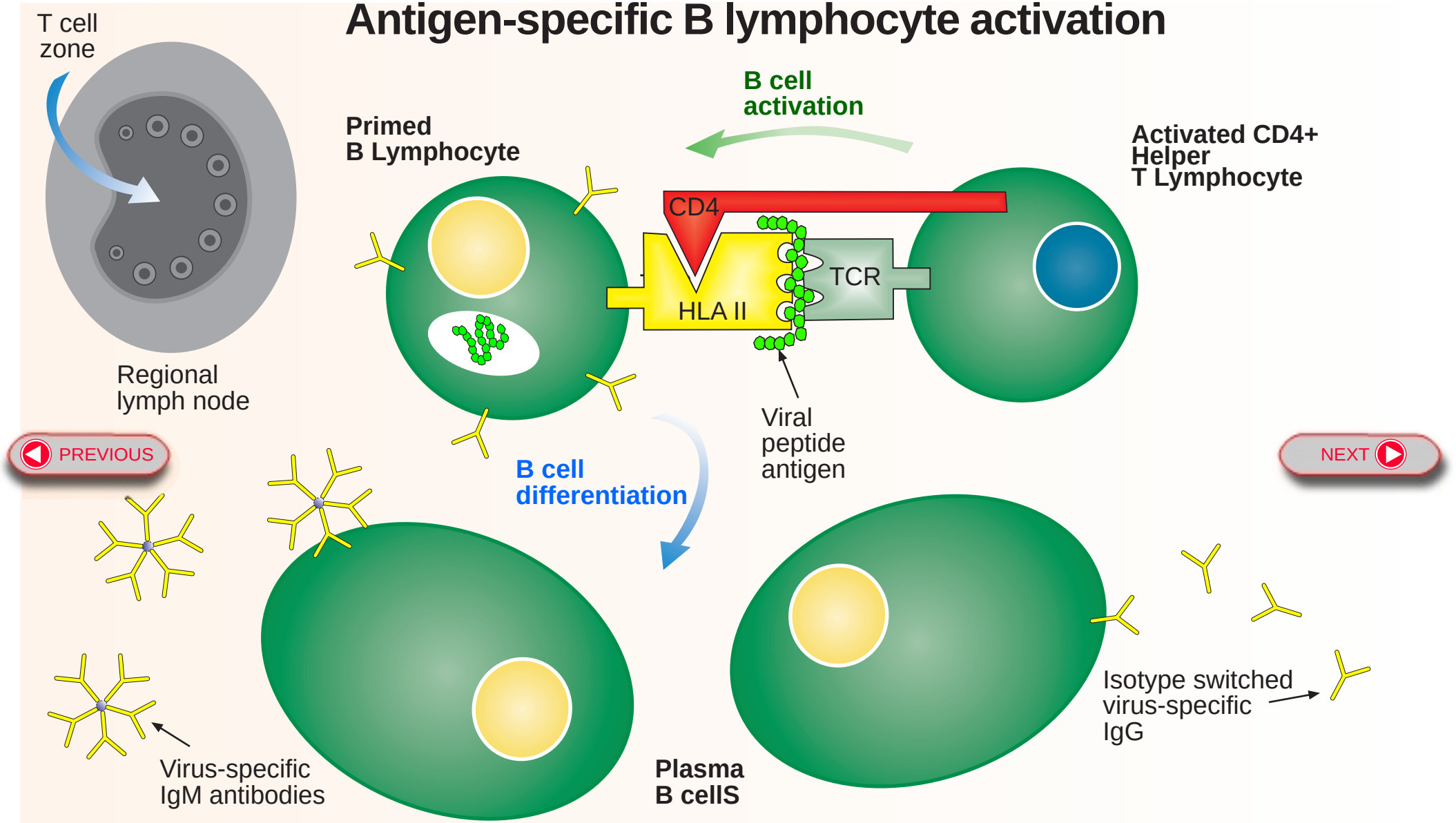
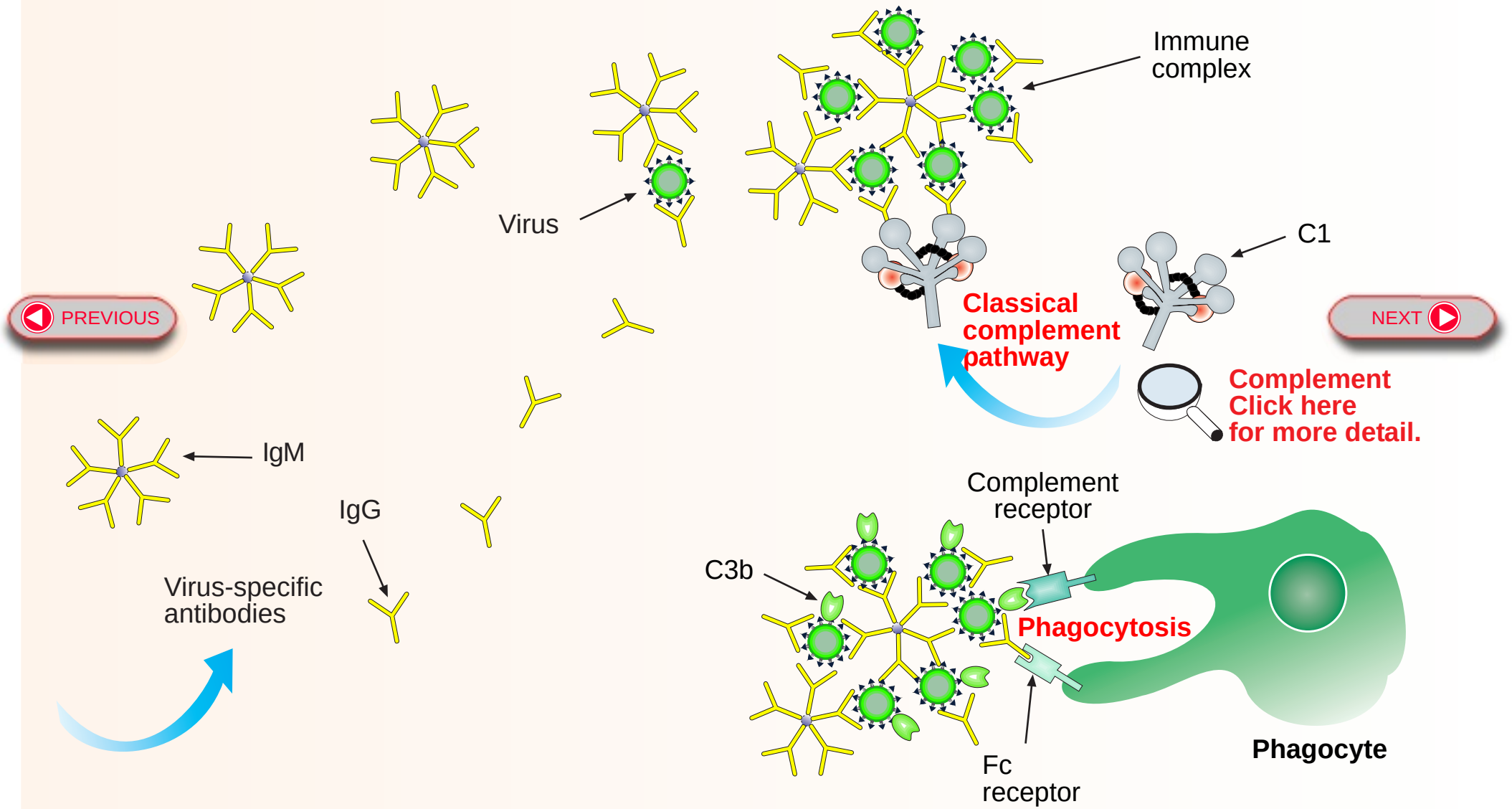
Virus-specific antibodies are synthesised by plasma B cells following priming and activation of virus-specific B lymphocytes. Naive B lymphocytes that express B cell receptors that recognise viral antigens displayed on the surface of follicular dendritic cells in the germinal centres (B cell zone) of secondary lymphoid tissue (lymph nodes) initiate endocytosis of the antigen-receptor complex. Peptide antigens are processed and bound to surface HLA class II receptors for presentation to CD4+ helper T cells in the T cell zone of secondary lymphoid tissue. The B cell is primed for antibody production, however, activation signals from CD4+ helper T lymphocytes are required. Primed B cells migrate to the T cell zone of the regional lymph node to acquire CD4+ T cell help.

Antigen-specific B lymphocyte activation



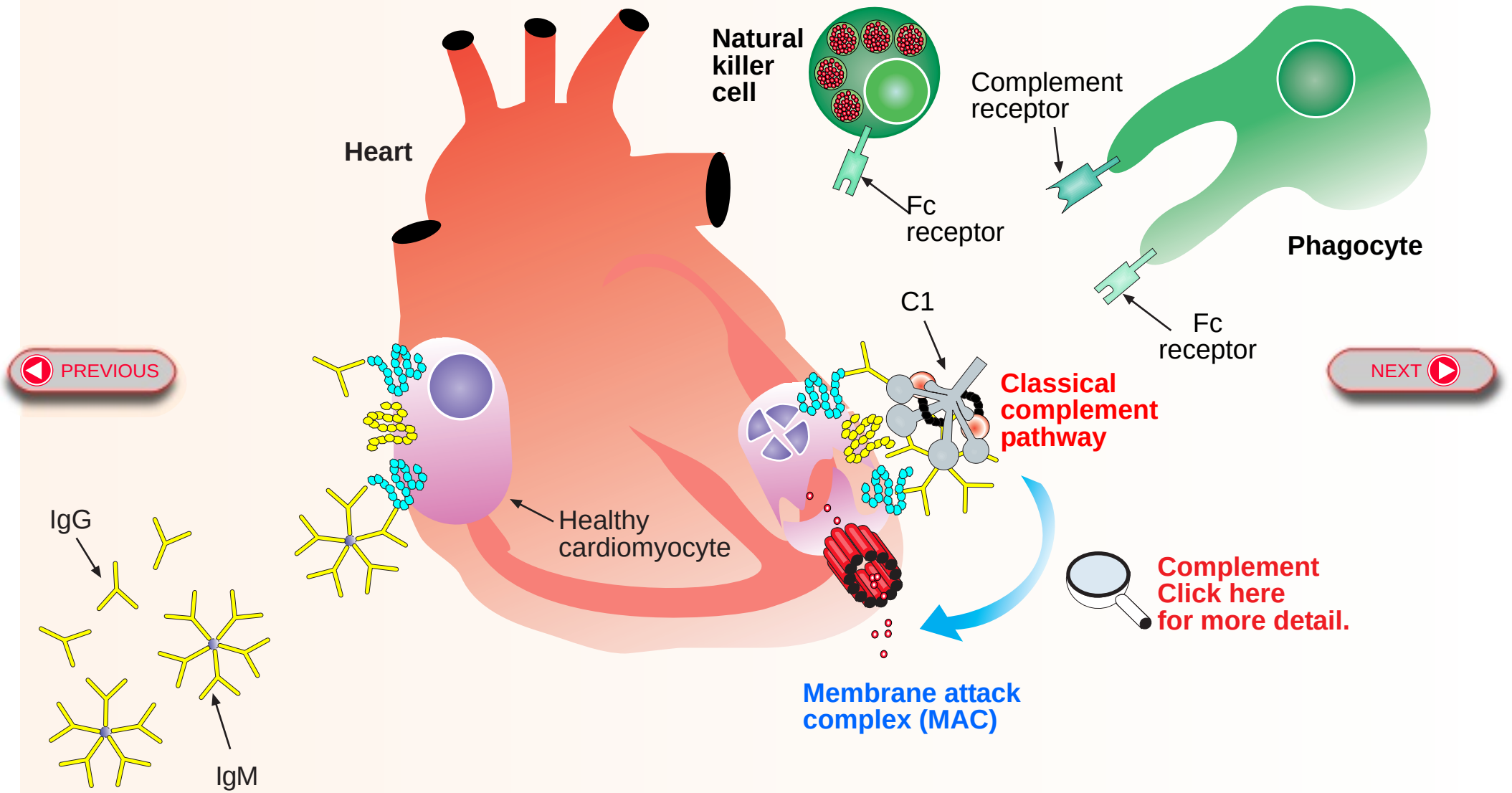
CD4+ helper T lymphocytes that recognise antigen bound to surface HLA class II receptors on B cells become activated and in turn provide activation signals to primed B cells to differentiate into effector plasma B cells that secrete antibodies and also memory B cells. Naive B cells initially synthesise IgM when they become activated, whereas re-stimulated memory B cells can undergo isotype-switching and affinity maturation which is dependent on the type of activation signals obtained from CD4+ helper T cells.

Antibody-mediated virus clearance



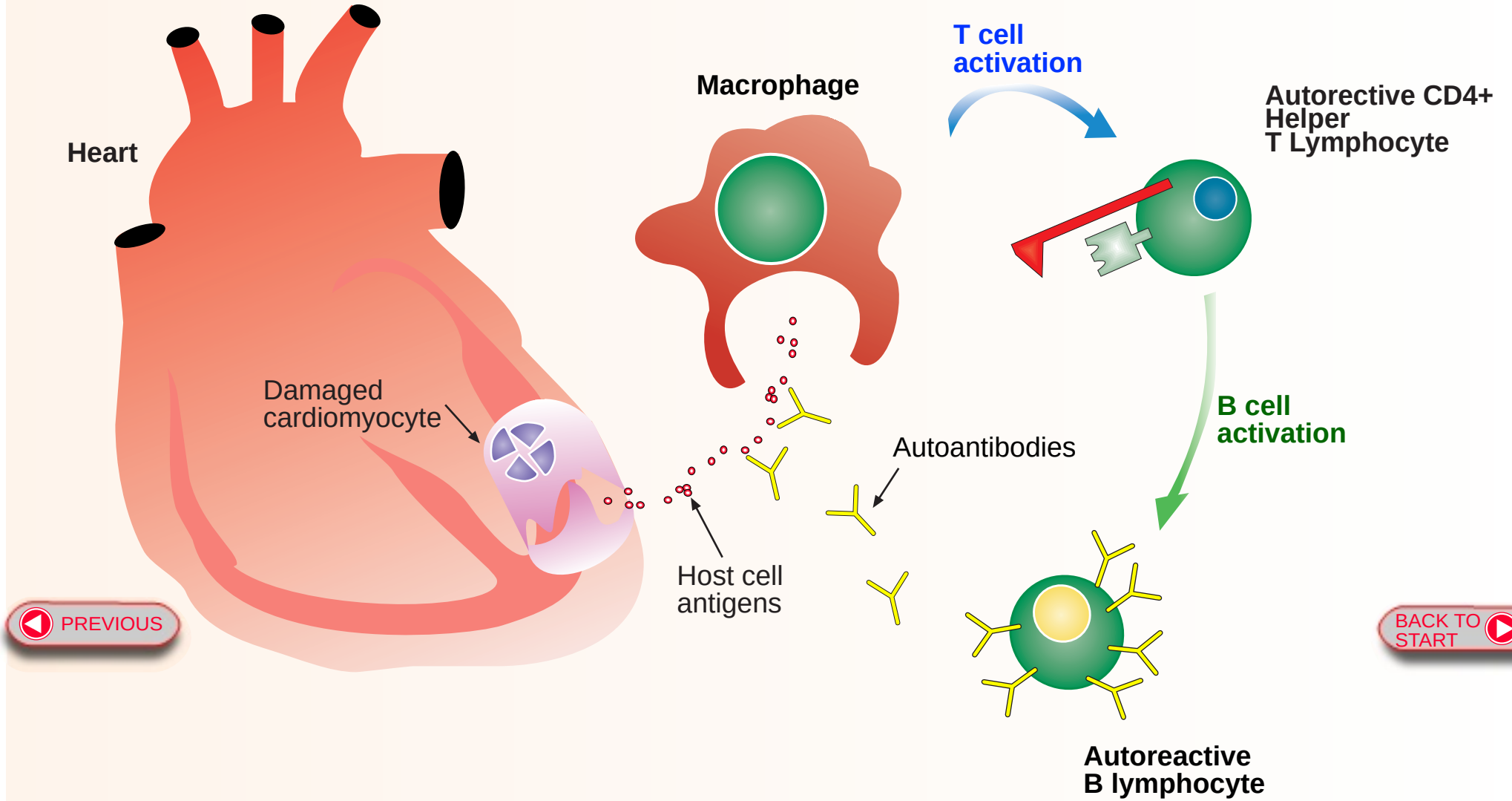
Virus-specific antibodies function to neutralise and opsonise free virus particles. Virus and viral antigens opsonised with antibodies also form immune complexes which can be detected and destroyed by phagocytes expressing Fc receptors. The classical complement cascade can further augment this response by opsonising virus and viral antigens with C3b complement proteins that are detectable by phagocytes expressing complement receptors. Immune complexes are also trapped by complement and Fc receptors on the surface of follicular dendritic cells in the germinal centres of secondary lymphoid tissue (lymph nodes) to further promote B cell responses.

Antibody recognition of self-antigen (autoimmunity)



Autoimmune disease as a consequence of viral myocarditis is thought to be mediated by virus-specific antibodies previously synthesised that cross-react with a surface protein expressed on cardiomyocytes (molecular mimicry). Antibodies of the IgM and IgG class can activate the classical complement cascade which leads to lysis of healthy cells. Natural killer cells and phagocytes bearing Fc receptors may also play a role in the destruction of antibody-bound host cells. C3b complement proteins bound to the cell surface can also enhance phagocytosis by phagocytes expressing complement receptors.

Secondary autoantibody production against self-antigens



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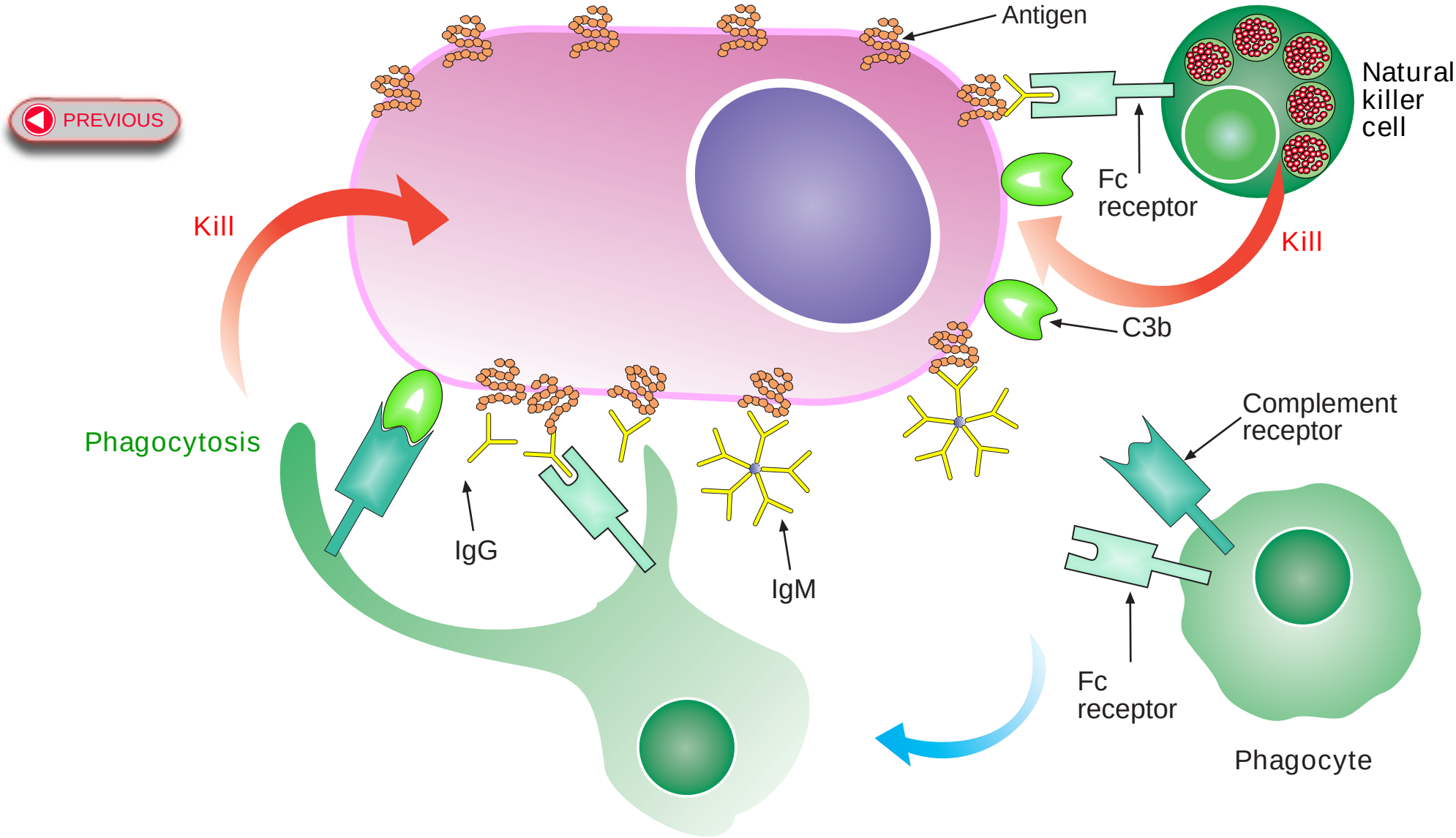
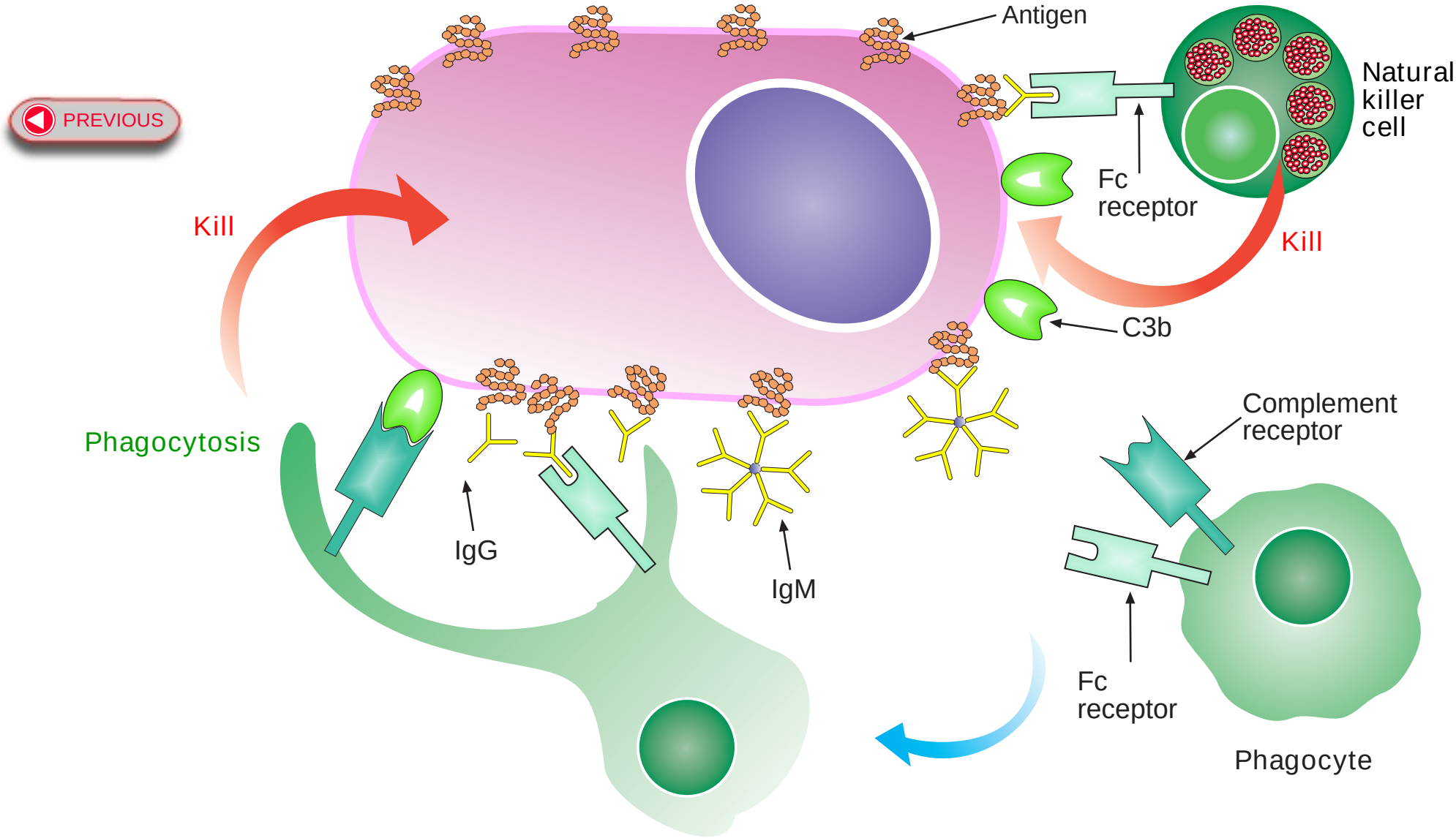
BACK TO START

Destruction of healthy cardiomyocytes results in the release of large quantities of intracellular antigens that are engulfed by macrophages. Macrophages present self-peptides to CD4+ T helper cells and a breakdown in tolerance of auto-antigens leads to the generation of autoreactive CD4+ helper T cells that can provide activation signals to autoreactive B cells. In this way secondary antibodies directed against intracellular host antigens derived from the heart can develop. These antibodies include anti-nucleic acid, anti-myosin and anti-actin specificities detectable in severe autoimmune myocarditis.



Enhanced phagocytosis of the target cell is mediated by surface-bound C3b complement protein that functions as an opsonin and is detected by complement receptors expressed by phagocytes. Opsonisation of the target cell by IgG is also detectable by phagocytes and Natural killer cells expressing Fc receptors. Phagocytes primarily include macrophages, neutrophils and dendritic cells and to a lesser extent basophils and eosinophils. Follicular dendritic cells in germinal centres also express complement and Fc receptors which enhances capture of immune complexes for presentation to B lymphocytes.



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