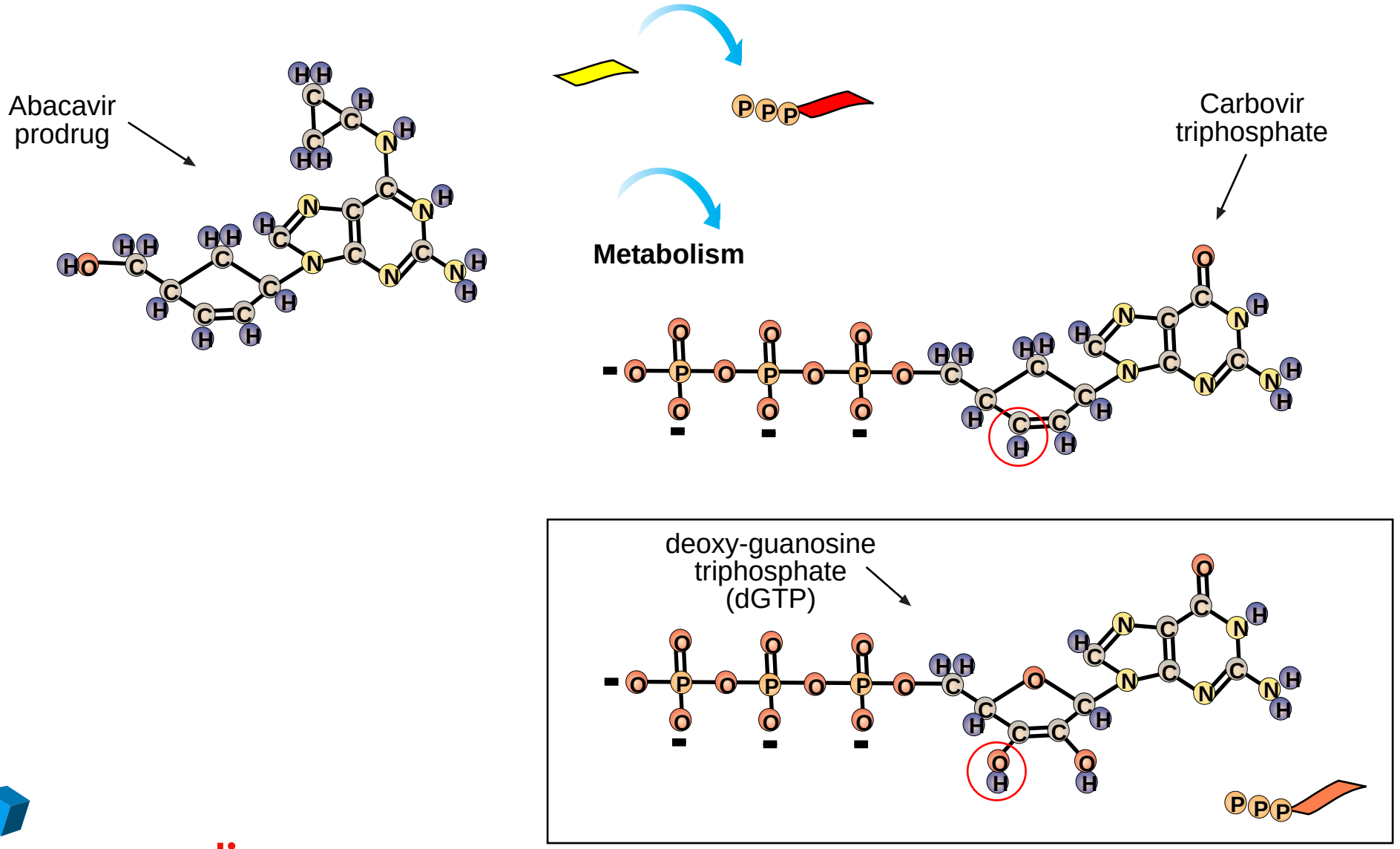
Abacavir chemical structure



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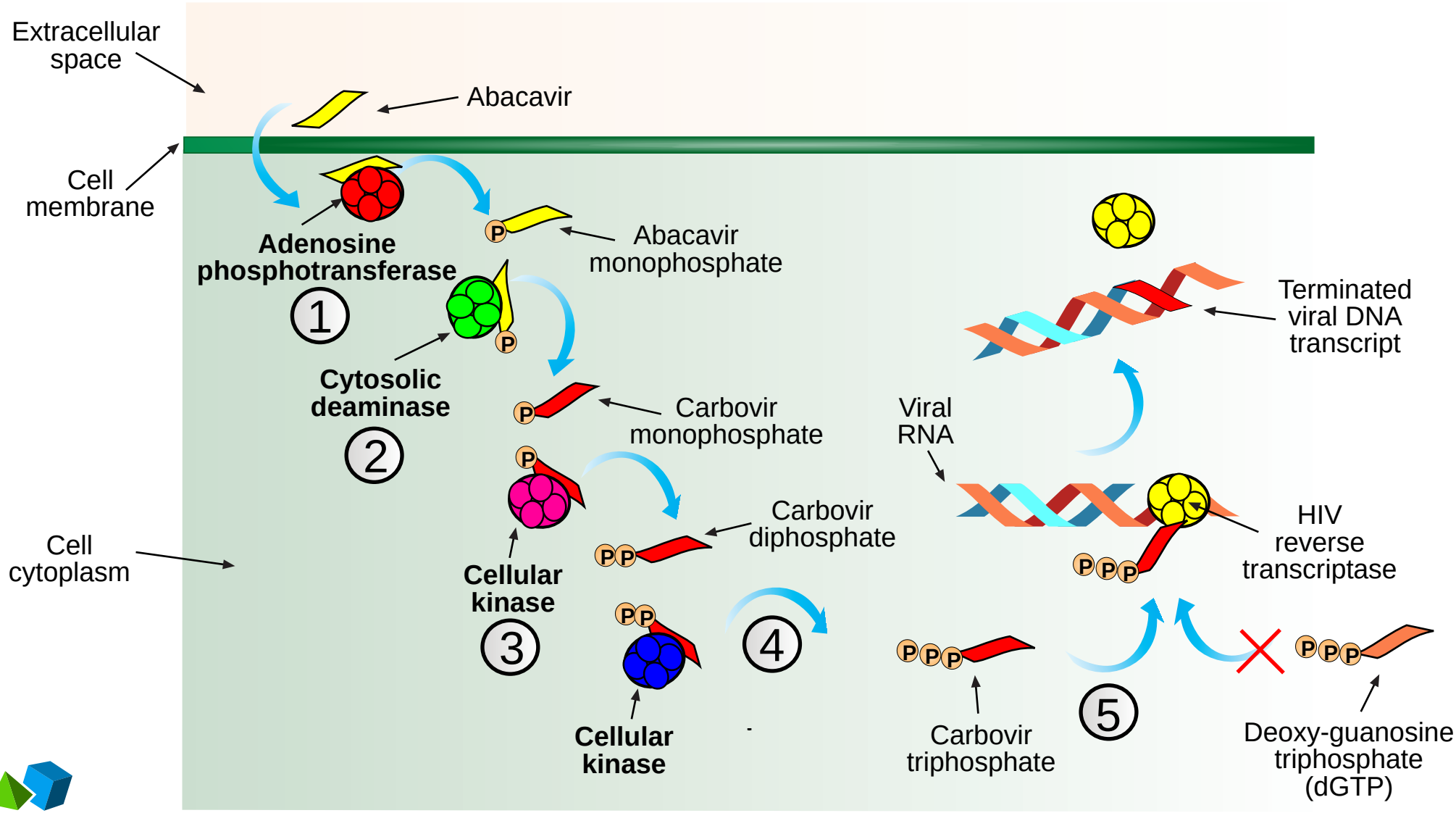
Abacavir (ABC) is a nucleoside reverse transcriptase inhibitor (NRTI). The prodrug is metabolised by cellular enzymes to generate carbovir triphosphate. Carbovir triphosphate competes with deoxy-guanosine triphosphate (dGTP) for incorporation into viral DNA by HIV reverse transcriptase. Carbovir triphosphate does not contain the necessary hydroxyl group on the ribose sugar for further extension and hence causes the DNA chain to terminate (red circle).

Abacavir drug action



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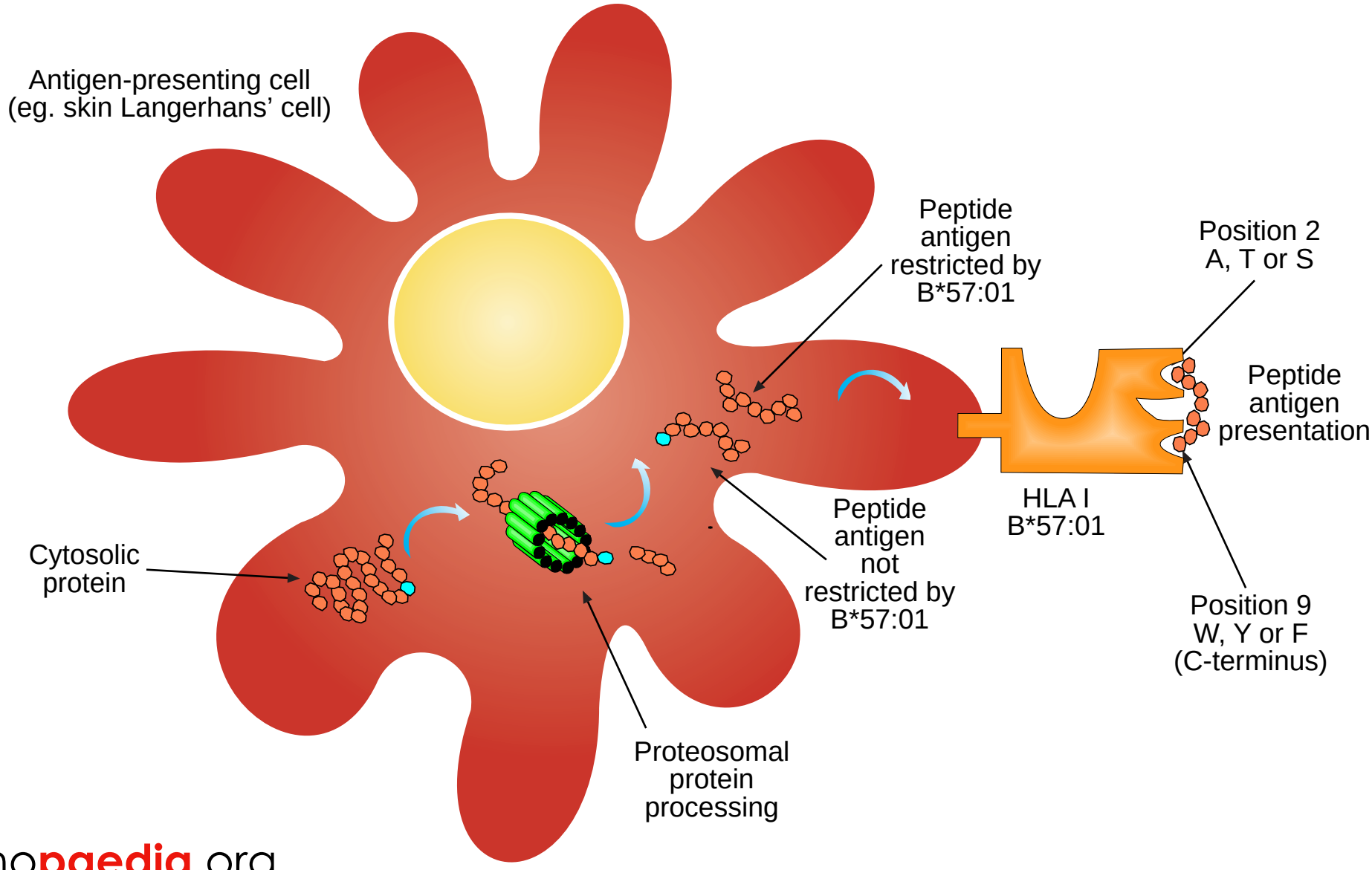
Inside cells, ABC is converted to the active drug, carbovir triphosphate, by cytosolic enzymes. Carbovir triphosphate competes with dGTP for incorporation into viral DNA by HIV reverse transcriptase. Once incorporated, the DNA chain is terminated thereby inhibiting HIV replication. (1) Adenosine phosphotransferase adds the first phosphate to abacavir to generate abacavir monophosphate; (2) A cytosolic deaminase removes an amine group to generate carbovir monophosphate; (3) Cellular kinases add a second phosphate to generate carbovir diphosphate; (4) Cellular kinases add a third phosphate to generate the active metabolite carbovir triphosphate; (5) Reverse transcription of viral RNA is inhibited by incorporation of carbovir triphosphate instead of dGTP resulting in chain termination.

*HLA-B*57:01 restricted peptide antigen presentation*



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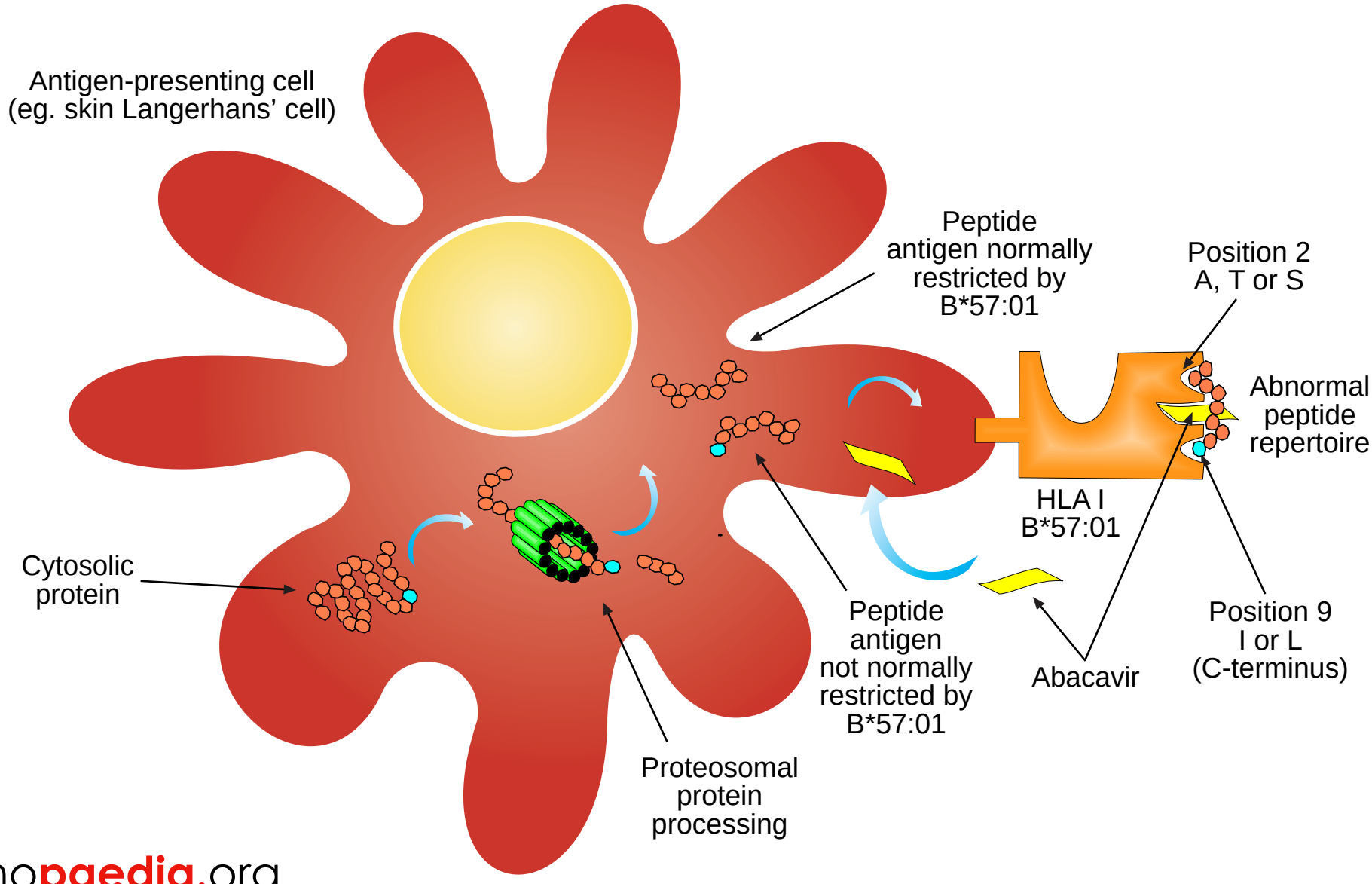
HLA-B*57:01 molecules bind peptides with particular amino acids at position 2 and 9 (the binding motif). Alanine, threonine or serine are preferred at position 2 while tryptophan, tyrosine or phenylalanine are preferred at position 9 (the C-terminus of the peptide). Peptide antigens with these residues are generated by proteosomal processing of cytosolic proteins and then bind to the HLA-B*57:01 molecule. In most cases these peptides will be derived from "self" proteins and will therefore not be recognised by CD8+ cytotoxic T cells due to negative selection in the thymus.

Immune hypersensitivity reaction to ABC: abnormal antigen presentation



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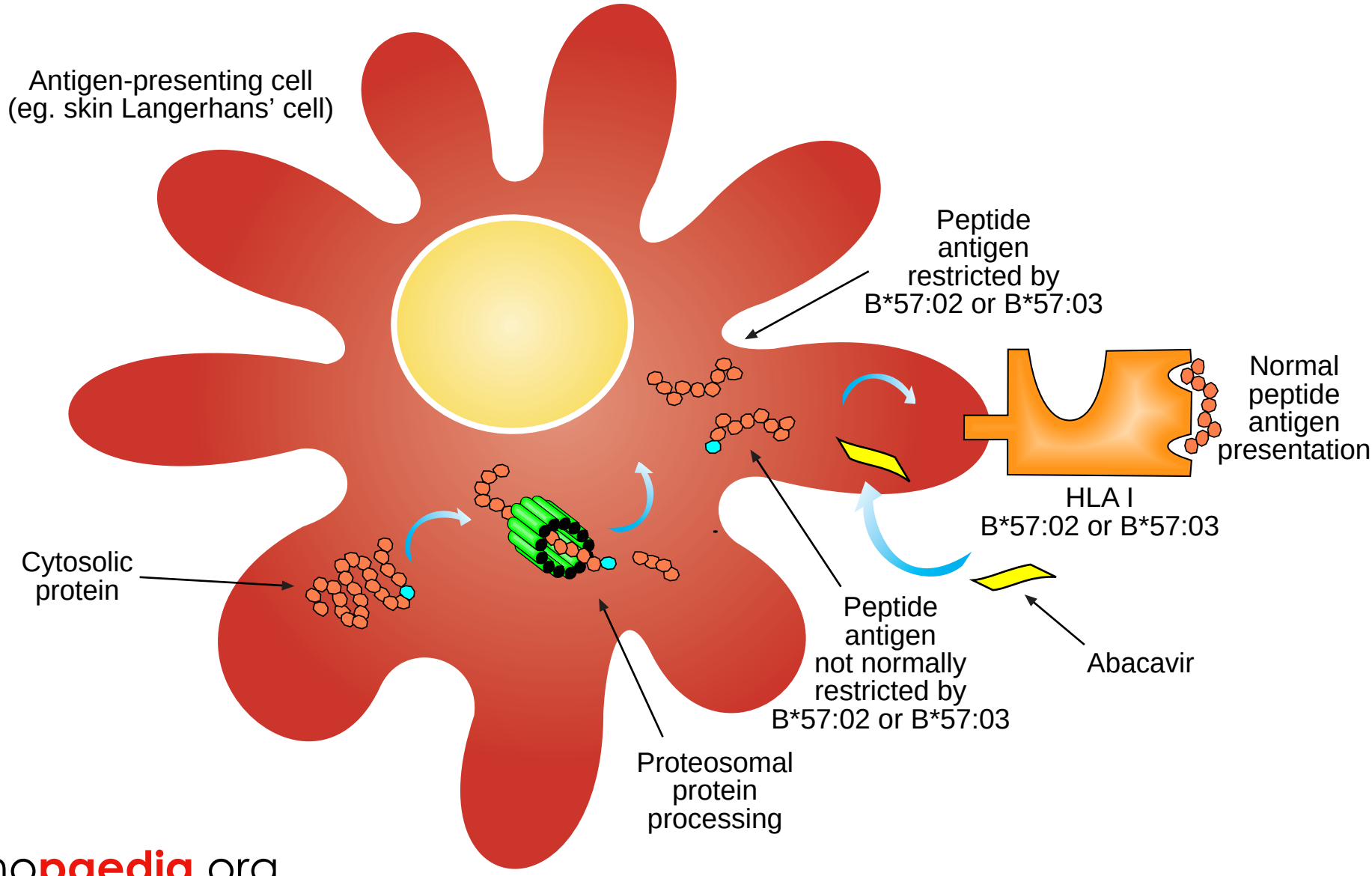
It has been shown that the unmetabolised ABC is able to bind to a site in the peptide binding cleft of the HLA-B*57:01 molecule and interacts with amino acid residues 114 and 116. This does not prevent peptide antigens from binding, however, the peptide specificity changes due to altered preference of amino acids at position 9. Instead of tryptophan, tyrosine or phenylalanine, peptides with other amino acids, particularly leucine or isoleucine, are selected at position 9. The amino acid preference at position 2 remains unchanged. Hence the binding of ABC to the HLA-B*57:01 molecule alters the peptide repertoire that is presented to CD8+ cytotoxic T cells. Recognition of "self" peptides by CD8+ cytotoxic T cells precipitates an autoimmune reaction resulting in attack of healthy cells and overproduction of pro-inflammatory cytokines, such as IFN-γ and TNF-α.

*No hypersensitivity reaction in B*57:02 or B*57:03 carriers treated with ABC*



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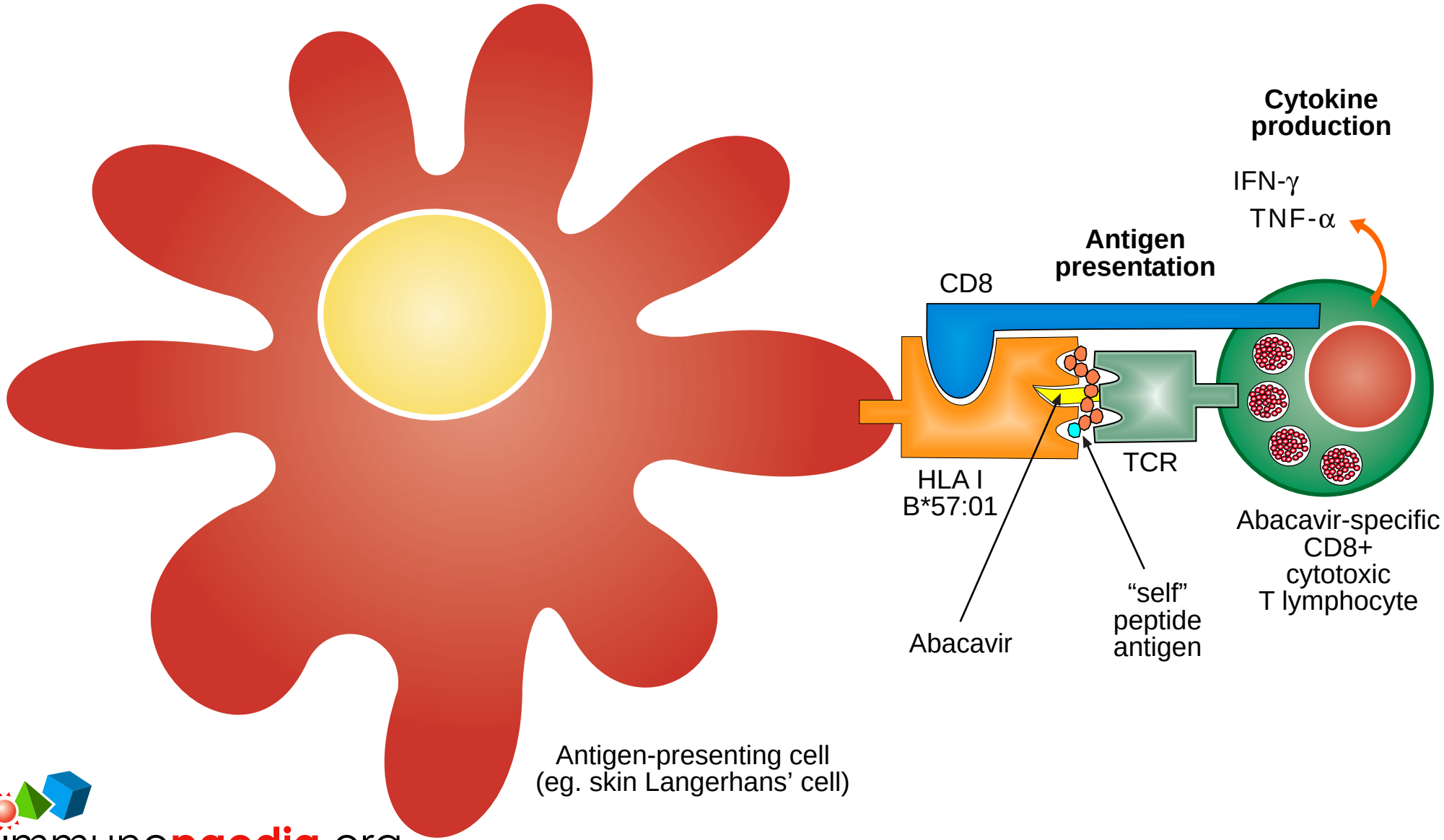
ABC binds preferentially to HLA-B*57:01 molecules and not to other members of the B*57 family, such as HLA-B*57:02 and HLA-B*57:03. This is due to a requirement of aspartate at position 114 and serine at position 116 which is present in the HLA-B*57:01 protein structure. These two amino acids map to the peptide binding cleft and interact directly with ABC. HLA-B*57:02 and HLA-B*57:03 molecules have asparagine at position 114 and tyrosine at position 116 which do not interact with the abacavir molecule.

Immune hypersensitivity reaction to ABC: CD8+ cytotoxic T cell activation



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ABC-specific CD8+ cytotoxic T cells secrete pro-inflammatory cytokines IFN-γ and TNF-α, which in excess, contribute to the symptoms and severity of the immune hypersensitivity reaction. IFN-γ enhances antigen-presentation by upregulating HLA molecules that facilitates antigen presentation to ABC-specific CD8+ cytotoxic T cells. Excessive production of TNF-α promotes fever and vascular permeability and can ultimately lead to sepsis and organ failure. Activation of ABC-specific CD8+ cytotoxic T cells appears to be polyclonal and may be CD4+ helper T cell independent, since these responses can be detected *ex vivo* in leukocytes from ABC-naive HLA-B*57:01 carriers and hypersensitivity reactions can also occur in HIV-infected individuals with low CD4 counts.