## Phylogeny

CDK6 is a member of the cyclin-dependent kinase family (CMGC group) that arose from a single ancestral serine/threonine kinase in lower eukaryotes and expanded in metazoans (asghar2015thehistoryand pages 1-2; malumbres2014cyclindependentkinases pages 2-3). It belongs to the CDK4/6 subfamily, which is restricted to eumetazoans and is particularly relevant for regulating G1-phase entry in higher organisms (asghar2015thehistoryand pages 1-2; malumbres2014cyclindependentkinases pages 8-9). Orthologs are present across all mammalian species, and phylogenetic analyses of the human kinome cluster CDK6 with other cell-cycle kinases such as CDK4 and CDK1 (fassl2022cdk4andcdk6 pages 1-3; malumbres2005mammaliancyclindependentkinases pages 1-2).

## Reaction Catalyzed

ATP + [protein]-(L-serine/L-threonine) → ADP + [protein]-(L-serine/L-threonine)-phosphate + H⁺ (huwe2003smallmoleculesas pages 1-3).

## Cofactor Requirements

Mg²⁺ is required for ATP binding and catalysis (huwe2003smallmoleculesas pages 1-3).

## Substrate Specificity

• Substrate choice is largely dictated by association with D-type cyclins (asghar2015thehistoryand pages 9-10).  
• Prefers serine/threonine residues followed by proline; well-characterised substrates include retinoblastoma protein (Rb) and NPM1 (asghar2015thehistoryand pages 9-10; huwe2003smallmoleculesas pages 1-3).  
• Cyclin partner–induced conformational changes further refine specificity toward cell-cycle regulators (fassl2022cdk4andcdk6 pages 3-4; malumbres2014cyclindependentkinases pages 3-5).

## Structure

CDK6 adopts the canonical bilobal protein-kinase fold: an N-terminal β-sheet–rich lobe with a glycine-rich loop for ATP binding and a larger C-terminal α-helical lobe containing the catalytic residues (ferrer2006structuralbasisfor pages 3-4; wood2018structuralinsightsinto pages 1-2). Key features include a conserved ATP-binding pocket, a phosphorylatable activation loop, and a regulatory C-helix. Binding of D-type cyclins stabilises the active conformation and aligns catalytic residues (ferrer2006structuralbasisfor pages 3-4). Compared with CDK4, CDK6 shows differences in C-terminal lobe solvent exposure and distinct interfaces for inhibitor or p16^INK4A binding (fassl2022cdk4andcdk6 pages 1-3; ferrer2006structuralbasisfor pages 5-6).

## Regulation

• Activation requires D-type cyclin binding during G1 (asghar2015thehistoryand pages 1-2; fassl2022cdk4andcdk6 pages 1-3).  
• Further stimulated by activation-loop phosphorylation by CDK-activating kinases (malumbres2014cyclindependentkinases pages 5-6).  
• Inhibited by INK4 proteins (e.g., p16^INK4A) that block cyclin association and ATP binding (sausville2002complexitiesinthe pages 1-2; sielecki2000cyclindependentkinaseinhibitors pages 5-6).  
• Cip/Kip proteins (p21^Cip1, p27^Kip1) can bind cyclin D–CDK6 complexes, acting as inhibitors or assembly factors depending on phosphorylation state (fassl2022cdk4andcdk6 pages 3-4; peyressatre2015targetingcyclindependentkinases pages 27-30).

## Function

CDK6 drives the G1/S transition by phosphorylating Rb, releasing E2F transcription factors and promoting S-phase gene expression (asghar2015thehistoryand pages 9-10; suryadinata2010controlofcell pages 3-4). Beyond cell-cycle control, it supports proliferation of hematopoietic cells, erythroid progenitors, pancreatic β-cells, and neuronal progenitors (sherr2016targetingcdk4and pages 1-2). CDK6 modulates differentiation programs, affecting actin cytoskeleton organisation in astrocytes and interacting with transcription factors such as RUNX1 to restrain myeloid differentiation while sustaining progenitor proliferation (malumbres2014cyclindependentkinases pages 6-9).

## Inhibitors

Clinically approved ATP-competitive inhibitors include palbociclib, ribociclib, and abemaciclib, which block Rb phosphorylation and induce G1 arrest (sherr2016targetingcdk4and pages 1-2; tadesse2018cyclindependentkinase2 pages 18-23).

## Other Comments

CDK6 is frequently overexpressed or hyperactivated in cancer, making it a major oncology target (asghar2015thehistoryand pages 9-10; peyressatre2015targetingcyclindependentkinases pages 15-17). It also participates in thymocyte development, regulation of senescence, and centrosome organisation (suryadinata2010controlofcell pages 9-10). Unique structural elements offer opportunities for highly selective inhibitor design (wood2018structuralinsightsinto pages 6-7; ferrer2006structuralbasisfor pages 5-6).

## 9. References

(asghar2015thehistoryand pages 1-2); (asghar2015thehistoryand pages 9-10); (fassl2022cdk4andcdk6 pages 1-3); (fassl2022cdk4andcdk6 pages 3-4); (huwe2003smallmoleculesas pages 1-3); (malumbres2014cyclindependentkinases pages 2-3); (malumbres2014cyclindependentkinases pages 3-5); (peyressatre2015targetingcyclindependentkinases pages 27-30); (sausville2002complexitiesinthe pages 1-2); (sielecki2000cyclindependentkinaseinhibitors pages 5-6); (malumbres2014cyclindependentkinases pages 5-6); (asghar2015thehistoryand pages 9-10); (malumbres2011physiologicalrelevanceof pages 3-4); (suryadinata2010controlofcell pages 3-4); (suryadinata2010controlofcell pages 9-10); (ferrer2006structuralbasisfor pages 3-4); (ferrer2006structuralbasisfor pages 5-6); (wood2018structuralinsightsinto pages 1-2); (wood2018structuralinsightsinto pages 6-7); (sherr2016targetingcdk4and pages 1-2); (tadesse2018cyclindependentkinase2 pages 18-23).