## Proposed EC/sub-subclass

2.7.11.22

## Accepted name

Cyclin-dependent kinase 6

## Synonyms

CDK6; member of the CDK4/6 sub-family; forms Cyclin D–CDK6 holoenzymes.

## Phylogeny

CDK6 is one of the serine/threonine protein kinases that expanded from a single ancestral CDK in lower eukaryotes to multiple specialised members in metazoans. It is confined to eumetazoans, groups with CDK4 in a distinct CDK4/6 clade of the CMGC kinase group, and has orthologues in all mammalian species (Asghar et al., 2015; Fassl et al., 2022; Malumbres & Barbacid, 2005; Malumbres, 2014).

## Reaction catalysed

ATP + L-seryl/threonyl-[protein] ⇄ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Huwe et al., 2003).

## Cofactor requirements

Mg²⁺ is essential for ATP binding and catalysis (Huwe et al., 2003).

## Substrate Specificity

When complexed with D-type cyclins, CDK6 preferentially phosphorylates Ser/Thr residues followed by Pro (S/T-P sites). Its best-characterised substrates include retinoblastoma protein (Rb) and nucleophosmin (NPM1). Cyclin partner choice further modulates substrate affinity and context (Asghar et al., 2015; Huwe et al., 2003; Fassl et al., 2022; Malumbres, 2014).

## Structure

CDK6 adopts the canonical bilobal kinase fold: an N-terminal β-sheet lobe containing the glycine-rich loop and a predominantly α-helical C-terminal lobe that houses the catalytic residues. Key features include a conserved ATP-binding pocket, an activation loop subject to regulatory phosphorylation and a C-helix whose orientation is cyclin-dependent. Cyclin D binding stabilises the active conformation. Compared with CDK4, CDK6 shows distinct surface features that influence inhibitor binding and interaction with regulators such as p16^INK4A (Ferrer et al., 2006; Wood & Endicott, 2018; Fassl et al., 2022).

## Regulation

• Activation requires association with D-type cyclins induced by mitogenic signals (Asghar et al., 2015; Fassl et al., 2022).  
• Phosphorylation of the activation loop by CDK-activating kinases (e.g., CDK7–cyclin H) augments activity (Malumbres, 2014; Lolli & Johnson, 2005).  
• INK4 family inhibitors (p16^INK4A and relatives) prevent cyclin binding and distort the ATP pocket (Sausville, 2002; Sielecki et al., 2000).  
• Cip/Kip proteins (p21^Cip1, p27^Kip1) can inhibit or scaffold cyclin D–CDK6 complexes depending on their phosphorylation state (Fassl et al., 2022; Peyressatre et al., 2015).

## Function

Principal driver of G1-phase progression: phosphorylation of Rb releases E2F transcription factors and triggers S-phase gene expression (Asghar et al., 2015; Suryadinata et al., 2010).  
Tissue-specific roles include proliferation of haematopoietic cells, erythroid progenitors, pancreatic β-cells, thymocytes, and neuronal progenitors (Sherr et al., 2016; Malumbres, 2011). CDK6 also modulates differentiation programmes and transcription factors such as RUNX1 and influences cytoskeletal dynamics in astrocytes (Malumbres, 2014). A cyclin D3–CDK6 complex has additional metabolic functions that promote cancer cell survival (Wang et al., 2017).

## Inhibitors

Clinically approved ATP-competitive inhibitors targeting CDK6 include palbociclib, ribociclib and abemaciclib; they block Rb phosphorylation and arrest cells in G1 (Sherr et al., 2016; Peyressatre et al., 2015). Numerous additional small-molecule inhibitors have been reported (Huwe et al., 2003; Knockaert et al., 2002; Tadesse et al., 2018).

## Other Comments

CDK6 is frequently overexpressed or hyperactivated in cancer, making it a prime therapeutic target. Unique structural elements relative to other CDKs provide avenues for highly selective inhibitor development (Wood & Endicott, 2018; Ferrer et al., 2006). Beyond proliferation, CDK6 participates in centrosome organisation and senescence control (Malumbres, 2014; Suryadinata et al., 2010).

## References

Asghar, U., Witkiewicz, A. K., Turner, N. C., & Knudsen, E. S. (2015). The history and future of targeting cyclin-dependent kinases in cancer therapy. Nature Reviews Drug Discovery, 14, 130–146. https://doi.org/10.1038/nrd4504

Fassl, A., Geng, Y., & Sicinski, P. (2022). Cdk4 and Cdk6 kinases: From basic science to cancer therapy. Science. https://doi.org/10.1126/science.abc1495

Ferrer, J.-L., Dupuy, J., Borel, F., Jacquamet, L., Noel, J. P., & Dulic, V. (2006). Structural basis for the modulation of CDK-dependent/independent activity of cyclin D1. Cell Cycle, 5, 2760–2768. https://doi.org/10.4161/cc.5.23.3506

Huwe, A., Mazitschek, R., & Giannis, A. (2003). Small molecules as inhibitors of cyclin-dependent kinases. Angewandte Chemie, 42(19), 2122–2138. https://doi.org/10.1002/anie.200200540

Knockaert, M., Greengard, P., & Meijer, L. (2002). Pharmacological inhibitors of cyclin-dependent kinases. Trends in Pharmacological Sciences, 23, 417–425. https://doi.org/10.1016/S0165-6147(02)02071-0

Lolli, G., & Johnson, L. N. (2005). CAK—cyclin-dependent activating kinase: A key kinase in cell cycle control and a target for drugs? Cell Cycle, 4, 565–570. https://doi.org/10.4161/cc.4.4.1607

Malumbres, M. (2011). Physiological relevance of cell cycle kinases. Physiological Reviews, 91, 973–1007. https://doi.org/10.1152/physrev.00025.2010

Malumbres, M. (2014). Cyclin-dependent kinases. Genome Biology, 15, 122. https://doi.org/10.1186/gb4184

Malumbres, M., & Barbacid, M. (2005). Mammalian cyclin-dependent kinases. Trends in Biochemical Sciences, 30, 630–641. https://doi.org/10.1016/j.tibs.2005.09.005

Peyressatre, M., Prével, C., Pellerano, M., & Morris, M. (2015). Targeting cyclin-dependent kinases in human cancers: From small molecules to peptide inhibitors. Cancers, 7, 179–237. https://doi.org/10.3390/cancers7010179

Sausville, E. A. (2002). Complexities in the development of cyclin-dependent kinase inhibitor drugs. Trends in Molecular Medicine, 8, S32–S37. https://doi.org/10.1016/S1471-4914(02)02308-0

Sherr, C. J., Beach, D., & Shapiro, G. I. (2016). Targeting CDK4 and CDK6: From discovery to therapy. Cancer Discovery, 6, 353–367. https://doi.org/10.1158/2159-8290.CD-15-0894

Sielecki, T. M., Boylan, J. F., Benfield, P. A., & Trainor, G. L. (2000). Cyclin-dependent kinase inhibitors: Useful targets in cell cycle regulation. Journal of Medicinal Chemistry, 43, 1–18. https://doi.org/10.1021/jm990256j

Suryadinata, R., Sadowski, M., & Sarcevic, B. (2010). Control of cell cycle progression by phosphorylation of cyclin-dependent kinase substrates. Bioscience Reports, 30, 243–255. https://doi.org/10.1042/BSR20090171

Tadesse, S., Caldon, E. C., Tilley, W., & Wang, S. (2018). Cyclin-dependent kinase 2 inhibitors in cancer therapy: An update. Journal of Medicinal Chemistry, 62, 4233–4251. https://doi.org/10.1021/acs.jmedchem.8b01469

Wang, H., Nicolay, B. N., Chick, J. M., Gao, X., Geng, Y., Ren, H., … Sicinski, P. (2017). The metabolic function of cyclin D3–CDK6 kinase in cancer cell survival. Nature, 546, 426–430. https://doi.org/10.1038/nature22797

Wood, D. J., & Endicott, J. A. (2018). Structural insights into the functional diversity of the CDK–cyclin family. Open Biology. https://doi.org/10.1098/rsob.180112