## Proposed EC/sub-subclass

2.7.11.22

## Accepted name

Cyclin-dependent kinase 8

## Synonyms

CDK8; Srb10 (S. cerevisiae orthologue)

## Phylogeny

Member of the eukaryotic protein kinase (ePK) superfamily, CMGC group, and cyclin-dependent kinase (CDK) family (Manning et al., 2002; Malumbres, 2014). Classified as a transcriptional CDK, functionally distinct from cell-cycle CDKs (Malumbres, 2014; Menzl et al., 2019). Orthologues are present in Drosophila, Caenorhabditis, and Saccharomyces (Manning et al., 2002; Malumbres, 2014). Closely related to paralogues CDK19 and CDK11 (Manning et al., 2002; Philip et al., 2018).

## Reaction catalysed

ATP + protein-Ser/Thr → ADP + phospho-protein-Ser/Thr (Philip et al., 2018).

## Cofactor requirements

Mg²⁺ required for ATP coordination (Manning et al., 2002; Malumbres, 2014). Kinase activity strictly depends on binding Cyclin C (Xu & Ji, 2011).

## Substrate Specificity

Proline-directed Ser/Thr kinase preferring a Pro at +1; consensus [S/T]-P (Johnson et al., 2023). Small residues Gly/Ala enriched at positions –3 to –1 (Johnson et al., 2023). Verified substrates include RNA polymerase II CTD (Ser1616, Ser1619) within YSPTSPS repeats (Johnson et al., 2023; Schneider et al., 2011).

## Structure

Bilobal kinase fold: N-lobe (res. 1–96, β-rich) and C-lobe (res. 97–353, α-helical) (Philip et al., 2018; Schneider et al., 2011). Unique features: DMG motif in activation loop replacing canonical DFG; N-terminal αB helix for Cyclin C recognition; nine-residue insertion before αG; extended C-terminus; SMSACRE cyclin-binding motif (Xu & Ji, 2011; Philip et al., 2018; Xi et al., 2019). Key catalytic residues Lys52, Glu66, Asp173 (Philip et al., 2018). ≥25 crystal structures of the CDK8–Cyclin C complex deposited (e.g., PDB 5F9W, 5I2C) (Xi et al., 2019).

## Regulation

Activity is controlled allosterically, not by T-loop phosphorylation (Schneider et al., 2011; Ziada et al., 2024). Binding Cyclin C is essential; induces αC and DMG re-orientation (Philip et al., 2018; Xu & Ji, 2011). Further activation by Mediator subunit MED12 whose “activation helix” remodels the active site (Klatt et al., 2020; Knuesel et al., 2009). CycC Glu99 mimics a phosphoresidue to stabilize the DMG-in conformation (Ziada et al., 2024). A conserved Thr196 is not known to be phosphorylated (Xu & Ji, 2011).

## Function

Catalytic core of the Mediator kinase module (with Cyclin C, MED12, MED13) governing RNA polymerase II transcription initiation and elongation (Dannappel et al., 2019; Philip et al., 2018). Phosphorylates RNA Pol II CTD, Cyclin H, histone H3, and transcription factors STAT1/3/5, p53, E2F1, SMADs, SREBP-1C, NOTCH ICD (Dannappel et al., 2019; Philip et al., 2018; Xi et al., 2019; Yin et al., 2024). Modulates Wnt/β-catenin, TGF-β, NOTCH, NF-κB, interferon, glycolytic and hypoxic gene programs (Dannappel et al., 2019; Philip et al., 2018). Essential for embryonic development but largely dispensable in adult mouse tissues (Philip et al., 2018).

## Inhibitors

Experimental dual CDK8/19 ATP-competitive inhibitors: Senexin-A, Senexin-B, cortistatin A, SEL120-34A (Dannappel et al., 2019; Philip et al., 2018; Xi et al., 2019). Additional tools: 3MB-PP1 (analog-sensitive CDK8) and multi-kinase inhibitor sorafenib (Dannappel et al., 2019; Xi et al., 2019).

## Other Comments

CDK8 dysregulation is linked to colorectal, breast, prostate, gastric, pancreatic cancers, melanoma, and AML; frequent gene amplification in colorectal cancer correlates with poor prognosis (Philip et al., 2018; Xi et al., 2019; Yin et al., 2024). Exhibits context-dependent oncogenic or tumor-suppressive roles (Philip et al., 2018; Yin et al., 2024). Kinase-dead mutation D173A abolishes activity; cancer-associated mutation at Asp189 identified (Xu & Ji, 2011). Alterations influence tumor growth, metabolism, chemoresistance, and inflammation (Dannappel et al., 2019).

## References

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