## Phylogeny

CDK19 belongs to the CMGC protein-kinase superfamily and is placed within the transcriptional CDK subgroup (CDK7–CDK13), which is evolutionarily distinct from the canonical cell-cycle CDKs (Kaveh et al., 2024; Wood & Endicott, 2018). Its closest human paralogue is CDK8, and both kinases associate with cyclin C in the Mediator kinase module (Wood & Endicott, 2018). Non-mammalian orthologues were not reported in the cited sources.

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-phospho-Ser/Thr (Peyressatre et al., 2015).

## Cofactor Requirements

Requires Mg²⁺ for catalytic activity (Peyressatre et al., 2015).

## Substrate Specificity

• Positional-scanning peptide libraries reveal a strict requirement for Pro at +1 relative to the phosphorylated Ser/Thr (consensus S/T-P) (Johnson et al., 2023).  
• The extended motif S/T-P-X-K/R is tolerated; the +3 Lys/Arg is less critical for transcriptional CDKs (Errico et al., 2010).  
• High-confidence cellular targets include the RNA-polymerase II subunit POLR2A at Ser1616 and Ser1619, at which CDK19 ranks in the 89.9th and 98.4th percentiles, respectively, among 303 kinases (Johnson et al., 2023).

## Structure

CDK19 encodes an N-terminal bilobal Ser/Thr kinase domain containing the canonical catalytic Lys (β3 strand), αC-helix Glu, HRD and DFG motifs that coordinate Mg²⁺–ATP (Wood & Endicott, 2018). The activation loop harbours a Thr equivalent to CDK2 Thr160 that is phosphorylated for full activity (Wood & Endicott, 2018). An extended C-terminal region mediates cyclin C binding and incorporation into the Mediator kinase module (Wood & Endicott, 2018). No experimental CDK19 crystal structure is available; current models are inferred from CDK8 homology and AlphaFold predictions (Pellarin et al., 2025).

## Regulation

• Kinase activity requires binding to cyclin C, which re-positions the αC-helix and orders the activation loop (Wood & Endicott, 2018).  
• Activation-loop Thr is phosphorylated by the CDK7–cyclin H–MAT1 CAK complex (Wood & Endicott, 2018).  
• Inhibitory phosphorylation of residues equivalent to CDK2 Thr14/Tyr15 by Wee1/Myt1 is a conserved mechanism, although the precise CDK19 sites remain unmapped (Peyressatre et al., 2015).  
• Transient docking of the CDK19–cyclin C module onto core Mediator provides an additional layer of allosteric control (Wood & Endicott, 2018).

## Function

CDK19 partners with cyclin C in the Mediator kinase module to regulate RNA-polymerase II transcription (Wood & Endicott, 2018). It directly phosphorylates the POLR2A C-terminal domain at Ser1616 and Ser1619, influencing transcription-elongation dynamics (Johnson et al., 2023). CDK19 shares substrate overlap and partial functional redundancy with CDK8 and is classified among transcription-regulating CDKs (Johnson et al., 2023; Kaveh et al., 2024).

## Inhibitors

Flavopiridol, a broad-spectrum ATP-competitive inhibitor, suppresses multiple CDKs including transcriptional family members; no CDK19-selective inhibitors were reported in the cited corpus (Peyressatre et al., 2015).

## Other Comments

Dysregulation of CDK19 has been implicated in cancer, highlighting the kinase as a potential therapeutic target (Pellarin et al., 2025).

## 9. References

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