## Proposed EC/sub-subclass

EC 2.7.11.– (protein-serine/threonine kinase)

## Accepted name

Cyclin-dependent kinase 18

## Synonyms

PCTAIRE3; PCTK3

## Phylogeny

CDK18 is a member of the PCTAIRE sub-family of cyclin-dependent kinases that diverged from the canonical cell-cycle CDKs (e.g. CDK1, CDK2). Orthologues are conserved across higher eukaryotes and are enriched in post-mitotic tissues such as brain and testis (Cole, 2009; Karimbayli et al., 2024). A defining feature is the PCTAIRE helix motif (Ser substituted for the Pro of the classical PSTAIRE sequence), which groups these kinases with other atypical CDKs (Cole, 2009).

## Reaction catalysed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Barone et al., 2016)

## Cofactor requirements

Mg²⁺ is required for catalytic activity (Shah et al., 2020).

## Substrate Specificity

CDK18 phosphorylates serine or threonine residues within proline-directed motifs. A full consensus sequence is not yet defined, but documented substrates include RAD9, tau (Thr231, Ser235) and focal adhesion kinase, consistent with a preference for Pro at +1 of the phospho-acceptor (Cole, 2009; Pepino et al., 2021).

## Structure

The protein is ~500 aa and contains the canonical bilobed kinase core with conserved HRD (sub-domain VI) and DFG (sub-domain VII) motifs. An extended N-terminus harbours the PCTAIRE box that mediates cyclin binding and a putative PKA phosphorylation motif (Pepino et al., 2021). No crystal structure is available; homology models based on CDK16 predict a typical CDK fold with an activation loop requiring phosphorylation for full activity (Endicott & Noble, 2013; Karimbayli et al., 2024).

## Regulation

• Cyclin binding: activation by cyclin A2 (and possibly cyclin Y).  
• Phosphorylation: PKA-mediated phosphorylation at Ser12 can stimulate activity independently of cyclin; additional activation-loop phosphorylation is inferred (Barone et al., 2016; Karimbayli et al., 2024).  
• Protein interactions: association with 14-3-3 proteins and ubiquitin ligase STUB1 influences localization and stability (Pepino et al., 2021).

## Function

CDK18 supports ATR-mediated replication-stress signalling by stabilising RAD9 and RAD17 on chromatin, thereby protecting stalled replication forks and genome integrity (Barone et al., 2016). In the nervous system, it is highly expressed in neurons and oligodendrocytes where it phosphorylates tau and may regulate neurite outgrowth and synaptic activity (Cole, 2009; Pepino et al., 2021). CDK18 also modulates focal adhesion dynamics and cell migration through effects on FAK phosphorylation, with reported expression in brain, heart, testis and spinal cord and altered levels in cancer, metabolic and neurodegenerative conditions (Pepino et al., 2021; Karimbayli et al., 2024).

## Inhibitors

Highly selective inhibitors have not yet been described, although ongoing efforts aim to exploit structural features unique to CDK18 (Pepino et al., 2021).

## Other Comments

CDK18 shows copy-number gain in a subset of breast cancers and contributes to resistance against replication-stress-inducing chemotherapy in glioblastoma. Differential expression links it to pancreatic islet metabolism, depression, Alzheimer’s disease and demyelinating disorders, highlighting potential utility as both biomarker and therapeutic target (Pepino et al., 2021; Chaput et al., 2016; Karimbayli et al., 2024).

## References

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