## Phylogeny

• CMGC group → cyclin-dependent kinase family → PCTAIRE subfamily (karimbayli2024insightsintothe pages 1-2)  
• Closest human paralogs: CDK16 and CDK17 (karimbayli2024insightsintothe pages 6-7)  
• Primary sequence identity: 52–54 % with CDK5; 42–46 % with PFTAIRE kinases CDK14/15 (karimbayli2024insightsintothe pages 1-2)  
• Shares ≈52 % identity with CDK2 (matsuda2014pctairekinase3cyclindependent pages 12-13)  
• Orthologs detected from Caenorhabditis elegans to Mus musculus; no yeast ortholog reported (matsuda2014pctairekinase3cyclindependent pages 2-3)  
• Mouse Cdk18 expression is restricted to brain, intestine and kidney, mirroring human tissue bias (unknownauthors2021caracterizacióndecdk1418 pages 29-32)

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-phospho-Ser/Thr (shah2020cdksfamilya pages 4-5)

## Cofactor Requirements

Catalysis requires Mg²⁺ coordinated by the conserved DFG motif (pepino2021overviewofpctk3cdk18 pages 4-6)

## Substrate Specificity

• Retinoblastoma protein fragment phosphorylated in vitro (matsuda2014pctairekinase3cyclindependent pages 13-14)  
• Myelin basic protein and histone H1 phosphorylated in vitro (matsuda2014pctairekinase3cyclindependent pages 13-14)  
• Focal Adhesion Kinase (FAK) directly phosphorylated in the cytoplasm (karimbayli2024insightsintothe pages 13-14)  
• Cofilin at Ser3, modulating actin dynamics (matsuda2014pctairekinase3cyclindependent pages 13-14)  
• RAD9 within the 9-1-1 replication-stress complex reported as a substrate (simonovic2021theroleof pages 13-17)  
• Tau at Thr231 and Ser235 in neuronal tissue (pepino2021overviewofpctk3cdk18 pages 13-14)  
• A definitive consensus phosphorylation motif has not yet been assigned (unknownauthors2022dissectingtherole pages 19-22)

## Structure

• Modular organisation: extended N-terminus, ~250 aa bilobal kinase domain, variable C-terminal tail (karimbayli2024insightsintothe pages 14-15)  
• αC helix harbours the PCTAIRE signature in place of the canonical PSTAIRE motif (matsuda2014pctairekinase3cyclindependent pages 1-2)  
• Activation loop contains Ser (not Thr) at the canonical phosphorylation site characteristic of PCTAIRE kinases (unknownauthors2022dissectingtherole pages 16-19)  
• CDK/MAPK insertion present in the C-lobe (pepino2021overviewofpctk3cdk18 pages 4-6)  
• No experimental crystal structure; AlphaFold model AF-Q07002-F1 predicts a conventional CDK fold (karimbayli2024insightsintothe pages 6-7)  
• Kinome profiling shows unusually low small-molecule engagement, indicating subtle ATP-site divergence (karimbayli2024insightsintothe pages 6-7)

## Regulation

• Cyclin A2 binding markedly activates kinase activity (matsuda2014pctairekinase3cyclindependent pages 4-5)  
• Cyclin E1 binds but does not stimulate catalysis (matsuda2014pctairekinase3cyclindependent pages 4-5)  
• Protein kinase A phosphorylates Ser12, Ser66 and Ser109; Ser12 phosphomimetic S12D confers cyclin-independent activation (matsuda2014pctairekinase3cyclindependent pages 10-11)  
• Phospho-Ser66/Ser109 create a 14-3-3 docking site, retaining the CDK18–cyclin A2 complex in the cytoplasm (matsuda2014pctairekinase3cyclindependent pages 13-14)  
• A conserved RRXS motif underlies PKA responsiveness (unknownauthors2022dissectingtherole pages 16-19)  
• Vasopressin signalling induces additional phosphorylation linked to aquaporin-2 trafficking (karimbayli2024insightsintothe pages 9-10)  
• Reports on cyclin Y interaction are conflicting: one study indicates binding (unknownauthors2021caracterizacióndecdk1418 pages 32-35), another finds no co-immunoprecipitation (unknownauthors2021caracterizacióndecdk1418 pages 35-38)

## Function

Expression and localisation  
• Highest mRNA and protein levels in brain (especially oligodendrocytes), spinal cord and heart (karimbayli2024insightsintothe pages 6-7)  
• Predominantly cytoplasmic and plasma-membrane localisation in mature cells (karimbayli2024insightsintothe pages 9-10)

Cellular roles  
• Phosphorylates cofilin and FAK to regulate actin polymerisation, focal-adhesion turnover and cell migration (matsuda2014pctairekinase3cyclindependent pages 13-14, karimbayli2024insightsintothe pages 13-14)  
• Maintains genome stability: depletion increases stalled replication forks and DNA damage via ATR pathway activation (karimbayli2024insightsintothe pages 14-15)  
• Interacts with RAD9 to modulate replication-stress signalling (simonovic2021theroleof pages 13-17)  
• High CDK18 expression correlates with homologous-recombination competence and influences response to PARP inhibition (karimbayli2024insightsintothe pages 14-15)  
• Activates ERK signalling to drive oligodendrocyte precursor differentiation (karimbayli2024insightsintothe pages 9-10)  
• Associates with Sec23Ap, linking CDK18 to COPII-dependent ER-to-Golgi trafficking (simonovic2021theroleof pages 13-17)  
• Participates in vasopressin-regulated aquaporin-2 membrane insertion (karimbayli2024insightsintothe pages 9-10)  
• Reported to inhibit autophagy in mammalian cells (unknownauthors2021caracterizacióndecdk1418 pages 35-38)

## Inhibitors

• Kinome screening identified only one low-affinity binder, PF-3,758,309 (a PAK4 tool compound); no selective inhibitors are available (karimbayli2024insightsintothe pages 6-7)

## Other Comments

• Silencing suppresses cutaneous T-cell lymphoma growth, whereas enforced expression triggers p53-mediated death in glioma cells (karimbayli2024insightsintothe pages 13-14)  
• Over-expressed in gastric cancer, pituitary adenoma and clear-cell renal cell carcinoma (karimbayli2024insightsintothe pages 14-15, simonovic2021theroleof pages 13-17)  
• High levels predict improved outcome to replication-stress-inducing chemotherapy in basal/ER-negative breast cancer (karimbayli2024insightsintothe pages 14-15)  
• CDK18 polymorphisms associate with type 2 diabetes; knockout mice display altered serum creatinine (karimbayli2024insightsintothe pages 9-10)  
• Elevated expression and phosphorylation detected in Alzheimer’s disease brain and demyelinating lesions (pepino2021overviewofpctk3cdk18 pages 13-14)

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