## Phylogeny

CDK14 is a member of the atypical CDK14-18 (PFTAIRE) subfamily within the CMGC protein-kinase group. It carries the signature PFTAIRE helix and shares a common ancestor with kinases such as CDK5 and CDK16 (Alonso, 2021; Malumbres et al., 2009; Mikolcevic et al., 2012). Orthologues are conserved across metazoans and the highest expression is reported in brain tissue and other post-mitotic cells; additional expression occurs in testis, heart, kidney, pancreas, and ovary (Alonso, 2021; Mikolcevic et al., 2012).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Alonso, 2021; Ferguson et al., 2019).

## Cofactor Requirements

Mg²⁺ is required for catalytic activity and proper ATP coordination (Alonso, 2021; Ferguson et al., 2019).

## Substrate Specificity

CDK14 phosphorylates Ser/Thr residues within proline-directed motifs. The CDK14–cyclin Y complex phosphorylates LRP6 at Ser1490 during G2/M (Alonso, 2021; Ferguson et al., 2019). In vitro, RB1 is also a substrate, though in-vivo significance remains unconfirmed (Alonso, 2021). Kinome-wide analyses predict a general S/T-P consensus preference, consistent with CMGC kinases (Johnson et al., 2023; Janáčková, 2023).

## Structure

The protein comprises a ~300-residue bilobal serine/threonine kinase domain with a β-sheet-rich N-lobe and an α-helical C-lobe. Conserved elements include the P-loop, DFG motif, catalytic loop, activation (T)-loop, C-helix and hydrophobic spines (Kamkar, 2015; Korolchuk, 2018). The unique PFTAIRE motif governs cyclin specificity. CDK14 forms an active complex with cyclin Y, whose N-myristoylation targets the complex to membranes (Alonso, 2021; Ferguson et al., 2019). AlphaFold models align with other CDKs, confirming the presence of the canonical catalytic architecture (Kamkar, 2015; Mikolcevic et al., 2012).

## Regulation

• Activation requires binding to cyclin Y, which dictates both kinase activity and plasma-membrane localisation (Alonso, 2021; Mikolcevic et al., 2012).  
• Phosphorylation of cyclin Y (Ser71/Ser73) negatively regulates complex stability (Alonso, 2021; Ferguson et al., 2019).  
• Autophosphorylation and additional, yet-unresolved, phosphorylation events on CDK14 likely fine-tune activity, as seen for other CDKs.  
• Potential interaction with 14-3-3 proteins has been noted but mechanistic details remain to be clarified (Alonso, 2021; Mikolcevic et al., 2012).

## Function

CDK14 is a serine/threonine kinase implicated in cell-cycle regulation and Wnt signalling. During G2/M, the CDK14–cyclin Y complex primes LRP6 phosphorylation, linking Wnt pathway activation to cell-cycle progression (Alonso, 2021; Ferguson et al., 2019). CDK14 expression in brain and other post-mitotic tissues suggests additional roles in neuronal differentiation and possibly meiosis (Alonso, 2021). It also acts as a negative regulator of insulin-responsive glucose transport (Alonso, 2021). Dysregulated CDK14 expression correlates with hepatocellular carcinoma, colorectal cancer and other tumours, influencing proliferation, migration and cytoskeletal dynamics (Alonso, 2021; Ferguson et al., 2019).

## Inhibitors

Covalent inhibitors such as FMF-04-159-2 irreversibly bind Cys218 in the ATP-binding pocket and display pan-TAIRE specificity, providing chemical probes for CDK14 function. No CDK14-selective drug is clinically approved (Ferguson et al., 2019).

## Other Comments

Genetic alterations and abnormal regulatory mechanisms affecting CDK14 have been reported in several cancers, but detailed mutation spectra remain to be defined (Alonso, 2021; Mikolcevic et al., 2012).

## 9. References

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