## 1. Phylogeny

Cyclin‐dependent kinase 14 (CDK14), also known as PFTK1 or PCTAIRE‐1, belongs to an atypical subfamily of cyclin‐dependent kinases that also comprises CDK15–CDK18. Phylogenetically, CDK14 shares significant sequence conservation in its catalytic domain with other members of this group, particularly those within the PFTAIRE/PCTAIRE family, and shows a closer relationship with CDK5, as evidenced by its position within the CDK5 subfamily clade (alonso2021caracterizacióndecdk1418 pages 114-118, mikolcevic2012orphankinasesturn pages 1-2). These kinases are evolutionarily conserved across metazoans, with CDK14 orthologs identified in vertebrates and many invertebrates. Moreover, evolutionary studies suggest that while classical cell cycle CDKs (such as CDK1, CDK2, CDK4, and CDK6) emerged early in eukaryotic evolution, CDK14 along with its atypical counterparts appear later, concomitant with the evolution of more specialized cellular processes including neuronal differentiation and complex developmental programs (alonso2021caracterizacióndecdk1418a pages 32-35, karimbayli2024insightsintothe pages 1-2).

## 2. Reaction Catalyzed

CDK14 is a serine/threonine protein kinase that catalyzes the phosphorylation reaction in which a phosphate group from adenosine triphosphate (ATP) is transferred to serine or threonine residues on substrate proteins. The reaction can be described as:  
  ATP + [protein]–(L-serine/threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺.  
A well‐characterized substrate of CDK14 is the low‐density lipoprotein receptor‐related protein 6 (LRP6), where CDK14 phosphorylates Serine-1490. This phosphorylation event occurs during the G2/M phase of the cell cycle and serves to “prime” LRP6 and thereby activate the Wnt/β-catenin signaling pathway (alonso2021caracterizacióndecdk1418 pages 114-118, alonso2021caracterizacióndecdk1418 pages 38-41). In vitro studies have also demonstrated that CDK14 can phosphorylate the retinoblastoma protein (RB1); however, the in vivo relevance of this activity remains to be conclusively determined (alonso2021caracterizacióndecdk1418 pages 35-38).

## 3. Cofactor Requirements

The kinase activity of CDK14, like that of most CDKs, is strictly dependent on certain cofactors. A critical cofactor is magnesium (Mg²⁺), which is essential for ATP binding and the subsequent transfer of the phosphate group (general CDK mechanism, inferred from accepted kinase chemistry). In addition, the full activation of CDK14 requires its association with regulatory cyclin partners. Cyclin Y has been identified as the primary cyclin that binds CDK14, facilitating not only its activation but also determining its subcellular localization, particularly recruiting the complex to the plasma membrane through cyclin Y’s N-myristoylation signal (alonso2021caracterizacióndecdk1418 pages 114-118, mikolcevic2012orphankinasesturn pages 1-2).

## 4. Substrate Specificity

CDK14 displays substrate specificity typical of serine/threonine kinases; however, its substrate preference is modulated by its cyclin regulatory partner. In its active state, CDK14 phosphorylates serine or threonine residues within target proteins that are critical for mediating cell cycle regulatory events and signaling pathways. A key physiological substrate is LRP6, phosphorylated at Ser-1490, which is a pivotal event in the activation of the canonical Wnt signaling pathway during the G2/M phase (alonso2021caracterizacióndecdk1418 pages 114-118). In vitro studies have also indicated that CDK14 is capable of targeting RB1, though the physiological relevance of this phosphorylation requires further validation (alonso2021caracterizacióndecdk1418 pages 35-38). While a precise consensus motif is less defined compared to other CDKs, CDK14’s substrate recognition appears to be influenced by the presence of specific residues in proximity to the phosphorylation site, in conjunction with the membrane localization conferred by cyclin Y binding (alonso2021caracterizacióndecdk1418a pages 29-32).

## 5. Structure

Structurally, CDK14 consists of a conserved serine/threonine kinase catalytic domain of approximately 300 amino acids that contains the hallmark motifs of the CMGC kinase family, such as the DFG motif critical for ATP binding and the HRD motif required for catalysis (malumbres2014cyclindependentkinases pages 6-7, mikolcevic2012orphankinasesturn pages 3-4). In addition to the central kinase domain, CDK14 harbors variable N-terminal and C-terminal extensions. These extensions play key roles in mediating interactions with cyclin partners—most notably cyclin Y—as well as other regulatory proteins. The cyclin Y binding is critical not only for the activation of CDK14 but also for its correct subcellular targeting, as the N-myristoylation of cyclin Y directs the complex to the plasma membrane, a feature that is uncommon in classical cell cycle CDKs (alonso2021caracterizacióndecdk1418 pages 114-118, alonso2021caracterizacióndecdk1418a pages 32-35). Furthermore, CDK14 contains a PFTAIRE motif (in some reports distinguished as a variant of the PCTAIRE motif), which is a signature sequence that distinguishes it from other CDKs and contributes to its unique regulatory and substrate recognition properties (mikolcevic2012orphankinasesturn pages 1-2).

## 6. Regulation

The activation and regulation of CDK14 are multi-layered and critically dependent on its interaction with regulatory proteins and post-translational modifications. The primary mode of activation is through binding to cyclin Y, which leads to a conformational change and subsequent activation of the kinase catalytic domain (alonso2021caracterizacióndecdk1418 pages 114-118, alonso2021caracterizacióndecdk1418a pages 32-35). Cyclin Y binds through conserved regions in both its own cyclin box and complementary regions in CDK14. In addition to cyclin binding, phosphorylation events are involved in the fine-tuning of CDK14 activity. Although specific phosphorylation sites on CDK14 have been less thoroughly characterized compared to classical CDKs, evidence indicates that phosphorylation by other kinases (for example, PKA-mediated events observed in related CDKs) might modulate its association with cyclin Y or other cofactors (alonso2021caracterizacióndecdk1418a pages 29-32). CDK14 activity may also be regulated by interactions with scaffold proteins such as 14-3-3 proteins, which in some contexts bind phosphorylated residues and further modulate kinase activity, stability, and subcellular distribution (alonso2021caracterizacióndecdk1418 pages 114-118). Finally, there is emerging evidence that CDK14 can participate in feedback loops whereby it phosphorylates its regulatory partners (e.g., influencing cyclin Y stability via formation of phospho-degron motifs), thus ensuring tight control over its own activity during the cell cycle (alonso2021caracterizacióndecdk1418a pages 41-44).

## 7. Function

CDK14 functions as a key serine/threonine kinase involved in several critical cellular processes, particularly those associated with the regulation of the cell cycle and signaling pathways. One of its best characterized roles is in the regulation of the Wnt signaling pathway. By phosphorylating the extracellular receptor co‐factor LRP6 at Ser-1490 during the G2/M phase, CDK14 primes LRP6 for subsequent activation events. This phosphorylation is crucial for the propagation of the canonical Wnt/β-catenin signaling cascade, which is pivotal to cell fate determination, proliferation, and developmental processes (alonso2021caracterizacióndecdk1418 pages 114-118, alonso2021caracterizacióndecdk1418a pages 38-41). Moreover, CDK14 has been implicated in cell cycle regulation beyond its effect on Wnt signaling. It may exert its influence by phosphorylating substrates such as RB1, which is a central regulator of G1/S transition, although this activity has so far been demonstrated largely in vitro and awaits further in vivo confirmation (alonso2021caracterizacióndecdk1418 pages 35-38).  
In addition to its role in cell cycle control, CDK14 is suggested to play roles in specialized processes such as meiosis and neuronal differentiation. Its tissue expression pattern, with notable expression in postmitotic differentiated neuronal cells and reproductive tissues, supports the idea that CDK14 functions outside of classical mitotic regulation. For instance, in neuronal systems, CDK14 may regulate aspects of polarized protein trafficking and neurite outgrowth, thereby contributing to proper neuronal function and development (alonso2021caracterizacióndecdk1418 pages 114-118, mikolcevic2012orphankinasesturn pages 6-8). Furthermore, emerging data indicate that CDK14 might be involved in the modulation of insulin-responsive glucose transport, acting indirectly as a negative regulator of glucose receptor trafficking, and thus may have metabolic implications (alonso2021caracterizacióndecdk1418 pages 41-44). Finally, in the context of cancer, aberrant expression or dysregulation of CDK14 has been linked with enhanced cell motility, migration, and invasion. In hepatocellular carcinoma (HCC) and other malignancies such as gastric and cutaneous melanoma, elevated CDK14 expression correlates with more aggressive tumor phenotypes and metastasis rather than with direct alterations in proliferation, highlighting its potential as a therapeutic target to interfere with tumor metastasis and invasion (alonso2021caracterizacióndecdk1418 pages 41-44, ferguson2019discoveryofcovalent pages 1-3).

## 8. Other Comments

Currently, selective pharmacological inhibitors directed against CDK14 are not as well developed as those for other cell cycle CDKs (e.g., CDK4/6 inhibitors). Recent research, however, has provided promising leads with the development of covalent inhibitors that target unique residues such as Cys218 located in the hinge region of CDK14; these inhibitors demonstrate pan‐TAIRE family specificity and serve as valuable chemical probes for dissecting CDK14 function (ferguson2019discoveryofcovalent pages 1-3, ferguson2019discoveryofcovalent pages 3-4). Disease associations for CDK14 extend primarily to oncogenesis, with its hyperactivity and overexpression implicated in metastatic features of cancers – for instance, correlating with poor prognosis in cutaneous melanoma and hepatocellular carcinoma (alonso2021caracterizacióndecdk1418 pages 41-44). Mutational analyses and loss-of-function studies further suggest that CDK14, while not critical for basal cell viability in many adult tissues, may contribute to tumor invasion and metastasis by modulating actin cytoskeletal dynamics as well as through its regulation of Wnt signaling. Additionally, its role in neuronal and reproductive tissues continues to stimulate research into its potential involvement in neurodegenerative conditions and reproductive disorders. Ongoing studies aim to better define its substrate repertoire, activation mechanisms, and the precise interplay between its phosphorylation activity and downstream cellular functions. As new selective inhibitors are refined, further research will likely elucidate CDK14’s full clinical relevance and help in designing therapeutic strategies that target its activity with minimal side effects (alonso2021caracterizacióndecdk1418 pages 114-118, ferguson2019discoveryofcovalent pages 12-13).

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