1. Phylogeny  
   Cyclin‐dependent kinase 14 (CDK14), also known as PFTK1 or PFTAIRE‑1, belongs to the serine/threonine protein kinase family that is conserved across metazoans and is classified within the atypical PFTAIRE subgroup of cyclin-dependent kinases. Comparative genomic analyses have shown that CDK14 is present from invertebrates such as Drosophila to vertebrates, reflecting its appearance in eumetazoan evolution and its association with increased cellular complexity in organisms. CDK14 shares a catalytic core with classical cell cycle kinases; however, it is distinguished by the presence of the PFTAIRE motif—a variant of the canonical PSTAIRE sequence found in many CDKs—indicating an evolutionary divergence in the regulatory regions of these enzymes (alonso2021caracterizacióndecdk1418 pages 29-32, malumbres2009cyclindependentkinasesa pages 1-2). Phylogenetic studies have grouped CDK14 together with other kinases such as CDK15, CDK16, CDK17, and CDK18 within the broader CMGC group, a clade typified by conserved catalytic elements and regulatory motifs including the activation loop and the flexible C-helix. The PFTAIRE subgroup’s evolutionary origin is inferred from sequence similarity and structural conservation seen in both the kinase domain and flanking regions, suggesting that CDK14 emerged as part of the diversification of the cell cycle regulatory apparatus during metazoan development (kamkar2015pftaire1(cyclindependent pages 49-53, mikolcevic2012orphankinasesturn pages 1-2). These evolutionary relationships also support the observation that CDK14 has acquired specialized functions such as roles in Wnt signaling and neuronal differentiation, which are not typically observed in the conventional cell cycle kinases.
2. Reaction Catalyzed  
   CDK14 catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to protein substrates that contain serine or threonine residues. The general reaction proceeds as follows: ATP reacts with a target protein that possesses an un-phosphorylated serine or threonine residue, and after phosphotransfer the reaction yields adenosine diphosphate (ADP), the phosphorylated protein (with a phosphate group added to its serine or threonine residue), and a proton (H⁺). This reaction can be expressed in chemical terms as:  
     ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺  
   This fundamental catalytic activity is shared by many serine/threonine kinases and underscores the role of CDK14 as an enzyme that regulates phosphorylation-dependent signaling events through modification of critical substrate proteins (malumbres2009cyclindependentkinasesa pages 1-2, ferguson2019discoveryofcovalent pages 1-3).
3. Cofactor Requirements  
   The kinase activity of CDK14, like that of most protein kinases, is strictly dependent on the binding of ATP as a phosphate donor. In addition, the catalytic process requires the assistance of divalent metal ions, most notably magnesium ions (Mg²⁺), which play an essential role in stabilizing the interaction between ATP and the enzyme’s active site. Magnesium ions facilitate the proper orientation of the ATP molecule within the catalytic cleft, thereby enabling efficient phosphoryl transfer to the substrate protein. This cofactor requirement is a well-established characteristic of cyclin-dependent kinases and is critical for their enzymatic function (malumbres2009cyclindependentkinasesa pages 1-2, ercan2021qualitativeandquantitative pages 21-24).
4. Substrate Specificity  
   CDK14 displays substrate specificity that is characteristic of serine/threonine kinases involved in cell cycle and signal transduction regulation. One of the best characterized substrates of CDK14 is the Wnt signal transducing co-receptor, low-density lipoprotein receptor-related protein 6 (LRP6). During the G2/M phase of the cell cycle, CDK14 phosphorylates LRP6 specifically at serine 1490. This site-specific phosphorylation is critical for priming LRP6 for subsequent modifications that lead to the activation of the canonical Wnt/β-catenin signaling pathway. In vitro studies have also shown that CDK14 is capable of phosphorylating the retinoblastoma protein (RB1); however, while the phosphorylation of RB1 has been demonstrated in vitro, its physiological relevance in vivo remains to be confirmed. Although an unequivocal consensus phosphorylation motif for CDK14 has not been firmly established, it tends to target serine or threonine residues that are frequently followed by a proline residue—a common characteristic among many cyclin-dependent kinases. Furthermore, the substrate specificity of CDK14 is modulated by its interaction with cyclin partners such as cyclin Y, which can influence substrate docking and the local concentration of target motifs (alonso2021caracterizacióndecdk1418 pages 32-35, alonso2021caracterizacióndecdk1418 pages 35-38, ferguson2019discoveryofcovalent pages 3-4, liu2010whycycliny? pages 3-4).
5. Structure  
   CDK14 possesses a three-dimensional structure that conforms to the canonical architecture observed for cyclin-dependent kinases. The protein is organized around a central catalytic domain that exhibits a bilobal fold, wherein the N-terminal lobe is primarily composed of β-sheets and includes a glycine-rich (G) loop that is essential for ATP binding. The larger C-terminal lobe is predominantly α-helical and contains key catalytic residues, such as the catalytic aspartate, and the activation (T) loop which is pivotal for facilitating substrate phosphorylation. A defining structural feature of CDK14 is its PFTAIRE motif, a variant of the PSTAIRE sequence found in many classical CDKs; this motif is crucial for mediating the interaction with its cyclin partner, particularly cyclin Y, and plays an important role in the conformational changes required for full catalytic activation. In addition to the core kinase domain, CDK14 contains N-terminal and C-terminal extensions that, although less characterized structurally, are believed to contribute to regulatory interactions, stabilization of its active conformation, and determination of subcellular localization. Structural models derived from homology modeling and sequence alignment with other kinases suggest that CDK14 features an active site cleft formed at the interface of its two lobes, a flexible activation segment capable of undergoing significant conformational rearrangements upon cyclin binding, and a conserved C-helix that couples with the hydrophobic spine to maintain an active enzyme configuration. While no high-resolution crystal structure for CDK14 has been published to date, the combination of homology to well-characterized CDKs and computational structural predictions provides a reliable framework for understanding its three-dimensional organization and catalytic mechanism (alonso2021caracterizacióndecdk1418 pages 29-32, kamkar2015pftaire1(cyclindependent pages 29-34, mikolcevic2012orphankinasesturn pages 3-4, kamkar2015pftaire1(cyclindependent pages 34-40).
6. Regulation  
   The regulatory mechanisms governing CDK14 activity are multi-faceted and share similarities with those observed for other cyclin-dependent kinases. The primary mode of regulation is through the binding of a cyclin partner, and for CDK14 this role is fulfilled by cyclin Y. Association with cyclin Y triggers substantial conformational changes in CDK14, most notably by repositioning the T-loop away from the active site, thereby allowing for the proper binding of ATP and the subsequent access of substrate proteins. This cyclin-dependent activation is central not only to the catalytic function of CDK14 but also to its subcellular targeting; for instance, cyclin Y has been shown to facilitate the membrane localization of CDK14, an important consideration for its role in signaling pathways such as the Wnt cascade. In addition to cyclin binding, CDK14 regulation is influenced by phosphorylation events. Phosphorylation mediated by protein kinase A (PKA) has been reported to modulate the CDK14/cyclin Y interaction and alter subcellular distribution through the recruitment of 14-3-3 scaffold proteins. This regulation can include phosphorylation of the kinase itself, as well as phosphorylation of cyclin Y, which when phosphorylated may become recognized by ubiquitin ligases leading to its degradation. Such a feedback loop serves to fine-tune the activity level of the CDK14/cyclin Y complex in a cell cycle–dependent manner, particularly ensuring that kinase activity is appropriately coordinated during the G2/M transition. Overall, these regulatory mechanisms work in concert to control CDK14 activity both spatially and temporally, thereby ensuring a precise execution of its cellular roles (alonso2021caracterizacióndecdk1418 pages 114-118, ferguson2019discoveryofcovalent pages 16-18, mikolcevic2012orphankinasesturn pages 1-2).
7. Function  
   CDK14 functions as a serine/threonine protein kinase that plays diverse roles in cellular regulation by modulating crucial signaling pathways and cell cycle progression events. One of the central functions of CDK14 is its involvement in the regulation of the Wnt signaling pathway. During the G2/M phase of the cell cycle, CDK14 phosphorylates the Wnt co-receptor LRP6 at serine 1490, an event that is essential for priming LRP6 for further phosphorylation and for the subsequent stabilization of β-catenin. This phosphorylation cascade is instrumental in the activation of Wnt/β-catenin signaling, which in turn regulates gene transcription events that control cell proliferation and differentiation. In addition to its role in Wnt signaling, CDK14 has been implicated in the broader control of cell cycle progression through its interaction with cyclin D3 (CCDN3), indicating a potential role in driving cell cycle transitions. Furthermore, CDK14 is capable of phosphorylating the retinoblastoma protein (RB1) in vitro; however, the physiological importance of RB1 phosphorylation by CDK14 in vivo requires further clarification. Expression analyses have demonstrated that CDK14 is present in several tissues including brain and testis, supporting its suggested involvement in neuronal differentiation and meiosis. In certain cellular contexts, CDK14 may also act as a negative regulator of insulin-responsive glucose transport, thereby linking its kinase activity to aspects of cellular metabolism. Functional studies underscore that CDK14, through its modulation of key signaling pathways and regulatory substrates, is central to the orchestration of cell division, differentiation, and metabolic responses (alonso2021caracterizacióndecdk1418 pages 16-26, alonso2021caracterizacióndecdk1418 pages 32-35, alonso2021caracterizacióndecdk1418 pages 38-41, alonso2021caracterizacióndecdk1418 pages 104-114, kamkar2015pftaire1(cyclindependent pages 49-53, mikolcevic2012orphankinasesturn pages 1-2).
8. Other Comments  
   Recent chemical biology studies have advanced the development of specific inhibitors targeting CDK14, with a focus on covalent inhibition strategies. In particular, compounds such as FMF-04-159-2 have been designed to exploit a uniquely positioned reactive cysteine residue within the ATP-binding pocket of CDK14, thereby achieving pan-TAIRE family specificity. These covalent inhibitors serve as valuable tools for probing the biological functions of CDK14 and its contribution to signaling networks, and they underline the therapeutic potential of targeting CDK14 in pathological contexts. Aberrant expression and dysregulation of CDK14 have been associated with oncogenic processes in various cancers, including colorectal cancer and hepatocellular carcinoma, where altered CDK14 activity is thought to contribute to uncontrolled proliferation and tumor progression. In addition, there is emerging evidence suggesting that CDK14 may participate in the regulation of neuronal differentiation and in meiotic processes, thereby extending its potential impact to neurodevelopmental and reproductive biology. Furthermore, by modulating insulin-responsive glucose transport, CDK14 might also have implications in metabolic regulation, although the precise mechanisms remain to be fully elucidated. The current generation of CDK14 inhibitors continues to be optimized for improved specificity and potency, and ongoing research efforts are directed towards understanding the full scope of CDK14’s biological impact and its utility as a therapeutic target (ferguson2019discoveryofcovalent pages 1-3, ferguson2019discoveryofcovalent pages 4-5, alonso2021caracterizacióndecdk1418 pages 41-44, gopinathan2011establishedandnovel pages 1-4).
9. References  
   alonso2021caracterizacióndecdk1418 pages 29-32; alonso2021caracterizacióndecdk1418 pages 32-35; alonso2021caracterizacióndecdk1418 pages 35-38; alonso2021caracterizacióndecdk1418 pages 38-41; alonso2021caracterizacióndecdk1418 pages 16-26; alonso2021caracterizacióndecdk1418 pages 104-114; ferguson2019discoveryofcovalent pages 1-3; ferguson2019discoveryofcovalent pages 3-4; ferguson2019discoveryofcovalent pages 4-5; ferguson2019discoveryofcovalent pages 16-18; mikolcevic2012orphankinasesturn pages 1-2; mikolcevic2012orphankinasesturn pages 3-4; kamkar2015pftaire1(cyclindependent pages 29-34; kamkar2015pftaire1(cyclindependent pages 34-40; kamkar2015pftaire1(cyclindependent pages 49-53; malumbres2009cyclindependentkinasesa pages 1-2; liu2010whycycliny? pages 3-4; ercan2021qualitativeandquantitative pages 21-24; gopinathan2011establishedandnovel pages 6-8.

References

1. (alonso2021caracterizacióndecdk1418 pages 114-118): D Martínez Alonso. Caracterización de cdk14-18 como dianas terapéuticas en carcinoma hepatocelular. Unknown journal, 2021.
2. (alonso2021caracterizacióndecdk1418 pages 29-32): D Martínez Alonso. Caracterización de cdk14-18 como dianas terapéuticas en carcinoma hepatocelular. Unknown journal, 2021.
3. (alonso2021caracterizacióndecdk1418 pages 32-35): D Martínez Alonso. Caracterización de cdk14-18 como dianas terapéuticas en carcinoma hepatocelular. Unknown journal, 2021.
4. (alonso2021caracterizacióndecdk1418 pages 38-41): D Martínez Alonso. Caracterización de cdk14-18 como dianas terapéuticas en carcinoma hepatocelular. Unknown journal, 2021.
5. (ferguson2019discoveryofcovalent pages 1-3): Fleur M. Ferguson, Zainab M. Doctor, Scott B. Ficarro, Christopher M. Browne, Jarrod A. Marto, Jared L. Johnson, Tomer M. Yaron, Lewis C. Cantley, Nam Doo Kim, Taebo Sim, Matthew J. Berberich, Marian Kalocsay, Peter K. Sorger, and Nathanael S. Gray. Discovery of covalent cdk14 inhibitors with pan-taire family specificity. Cell Chemical Biology, 26:804-817.e12, Jun 2019. URL: https://doi.org/10.1016/j.chembiol.2019.02.015, doi:10.1016/j.chembiol.2019.02.015. This article has 28 citations and is from a domain leading peer-reviewed journal.
6. (ferguson2019discoveryofcovalent pages 3-4): Fleur M. Ferguson, Zainab M. Doctor, Scott B. Ficarro, Christopher M. Browne, Jarrod A. Marto, Jared L. Johnson, Tomer M. Yaron, Lewis C. Cantley, Nam Doo Kim, Taebo Sim, Matthew J. Berberich, Marian Kalocsay, Peter K. Sorger, and Nathanael S. Gray. Discovery of covalent cdk14 inhibitors with pan-taire family specificity. Cell Chemical Biology, 26:804-817.e12, Jun 2019. URL: https://doi.org/10.1016/j.chembiol.2019.02.015, doi:10.1016/j.chembiol.2019.02.015. This article has 28 citations and is from a domain leading peer-reviewed journal.
7. (ferguson2019discoveryofcovalent pages 4-5): Fleur M. Ferguson, Zainab M. Doctor, Scott B. Ficarro, Christopher M. Browne, Jarrod A. Marto, Jared L. Johnson, Tomer M. Yaron, Lewis C. Cantley, Nam Doo Kim, Taebo Sim, Matthew J. Berberich, Marian Kalocsay, Peter K. Sorger, and Nathanael S. Gray. Discovery of covalent cdk14 inhibitors with pan-taire family specificity. Cell Chemical Biology, 26:804-817.e12, Jun 2019. URL: https://doi.org/10.1016/j.chembiol.2019.02.015, doi:10.1016/j.chembiol.2019.02.015. This article has 28 citations and is from a domain leading peer-reviewed journal.
8. (alonso2021caracterizacióndecdk1418 pages 16-26): D Martínez Alonso. Caracterización de cdk14-18 como dianas terapéuticas en carcinoma hepatocelular. Unknown journal, 2021.
9. (alonso2021caracterizacióndecdk1418 pages 35-38): D Martínez Alonso. Caracterización de cdk14-18 como dianas terapéuticas en carcinoma hepatocelular. Unknown journal, 2021.
10. (alonso2021caracterizacióndecdk1418 pages 41-44): D Martínez Alonso. Caracterización de cdk14-18 como dianas terapéuticas en carcinoma hepatocelular. Unknown journal, 2021.
11. (ferguson2019discoveryofcovalent pages 16-18): Fleur M. Ferguson, Zainab M. Doctor, Scott B. Ficarro, Christopher M. Browne, Jarrod A. Marto, Jared L. Johnson, Tomer M. Yaron, Lewis C. Cantley, Nam Doo Kim, Taebo Sim, Matthew J. Berberich, Marian Kalocsay, Peter K. Sorger, and Nathanael S. Gray. Discovery of covalent cdk14 inhibitors with pan-taire family specificity. Cell Chemical Biology, 26:804-817.e12, Jun 2019. URL: https://doi.org/10.1016/j.chembiol.2019.02.015, doi:10.1016/j.chembiol.2019.02.015. This article has 28 citations and is from a domain leading peer-reviewed journal.
12. (kamkar2015pftaire1(cyclindependent pages 29-34): Fatemeh Kamkar. Pftaire1 (cyclin dependent kinase14): role and function in axonal outgrowth during the development of the cns. Unknown journal, 2015. URL: https://doi.org/10.20381/ruor-4143, doi:10.20381/ruor-4143. This article has 0 citations.
13. (kamkar2015pftaire1(cyclindependent pages 34-40): Fatemeh Kamkar. Pftaire1 (cyclin dependent kinase14): role and function in axonal outgrowth during the development of the cns. Unknown journal, 2015. URL: https://doi.org/10.20381/ruor-4143, doi:10.20381/ruor-4143. This article has 0 citations.
14. (kamkar2015pftaire1(cyclindependent pages 49-53): Fatemeh Kamkar. Pftaire1 (cyclin dependent kinase14): role and function in axonal outgrowth during the development of the cns. Unknown journal, 2015. URL: https://doi.org/10.20381/ruor-4143, doi:10.20381/ruor-4143. This article has 0 citations.
15. (malumbres2009cyclindependentkinasesa pages 1-2): Marcos Malumbres, Edward Harlow, Tim Hunt, Tony Hunter, Jill M. Lahti, Gerard Manning, David O. Morgan, Li-Huei Tsai, and Debra J. Wolgemuth. Cyclin-dependent kinases: a family portrait. Nature Cell Biology, 11:1275-1276, Nov 2009. URL: https://doi.org/10.1038/ncb1109-1275, doi:10.1038/ncb1109-1275. This article has 582 citations and is from a highest quality peer-reviewed journal.
16. (mikolcevic2012orphankinasesturn pages 1-2): Petra Mikolcevic, Johannes Rainer, and Stephan Geley. Orphan kinases turn eccentric. Cell Cycle, 11:3758-3768, Aug 2012. URL: https://doi.org/10.4161/cc.21592, doi:10.4161/cc.21592. This article has 66 citations and is from a peer-reviewed journal.
17. (alonso2021caracterizacióndecdk1418 pages 104-114): D Martínez Alonso. Caracterización de cdk14-18 como dianas terapéuticas en carcinoma hepatocelular. Unknown journal, 2021.
18. (ercan2021qualitativeandquantitative pages 21-24): DP Ercan. Qualitative and quantitative cdk control of the budding yeast cell cycle. Unknown journal, 2021.
19. (liu2010whycycliny? pages 3-4): Dongmei Liu, Stephen Guest, and Russell L. Finley. Why cyclin y? a highly conserved cyclin with essential functions. Fly, 4:278-282, Oct 2010. URL: https://doi.org/10.4161/fly.4.4.12881, doi:10.4161/fly.4.4.12881. This article has 38 citations and is from a peer-reviewed journal.
20. (mikolcevic2012orphankinasesturn pages 3-4): Petra Mikolcevic, Johannes Rainer, and Stephan Geley. Orphan kinases turn eccentric. Cell Cycle, 11:3758-3768, Aug 2012. URL: https://doi.org/10.4161/cc.21592, doi:10.4161/cc.21592. This article has 66 citations and is from a peer-reviewed journal.
21. (gopinathan2011establishedandnovel pages 1-4): Lakshmi Gopinathan, Chandrahas Koumar Ratnacaram, and Philipp Kaldis. Established and novel cdk/cyclin complexes regulating the cell cycle and development. Results and Problems in Cell Differentiation, 53:365-389, Jan 2011. URL: https://doi.org/10.1007/978-3-642-19065-0\_16, doi:10.1007/978-3-642-19065-0\_16. This article has 112 citations.
22. (gopinathan2011establishedandnovel pages 6-8): Lakshmi Gopinathan, Chandrahas Koumar Ratnacaram, and Philipp Kaldis. Established and novel cdk/cyclin complexes regulating the cell cycle and development. Results and Problems in Cell Differentiation, 53:365-389, Jan 2011. URL: https://doi.org/10.1007/978-3-642-19065-0\_16, doi:10.1007/978-3-642-19065-0\_16. This article has 112 citations.