## Phylogeny

• Member of the WEE kinase family within the atypical CMGC branch; closest paralogues are WEE1 and WEE2 (schmidt2017regulationofg2m pages 5-9).  
• Verified metazoan orthologs include Xenopus laevis Myt1 controlling oocyte G2 arrest (ruiz2010atwostepinactivation pages 1-2) and Drosophila melanogaster Myt1 required for spermatocyte progression (varadarajan2016myt1inhibitionof pages 13-13).  
• Additional orthologs cited in comparative analyses are Saccharomyces cerevisiae Swe1, Mus musculus Pkmyt1 and Danio rerio pkmyt1, underscoring conservation across eukaryotes (schmidt2017regulationofg2m pages 5-9).  
• Functional redundancy with WEE1 is documented in human and fly models, indicating a shared evolutionary checkpoint role (schmidt2017regulationofg2m pages 3-5).

## Reaction Catalyzed

ATP + [CDK1]-Thr14 → ADP + [CDK1]-Thr14-P; a lower-efficiency parallel reaction targets Tyr15 on the same CDK1/cyclin B complex (schmidt2017regulationofg2m pages 1-3, platzer2018identificationofpkmyt1 pages 1-2).

## Cofactor Requirements

Catalytic activity is ATP-dependent; no divalent cation requirement beyond the canonical Mg²⁺ used by protein kinases has been explicitly reported (rohe2012invitroand pages 1-2).

## Substrate Specificity

• Exhibits strict preference for the full-length CDK1/cyclin B complex; a series of synthetic peptides were not phosphorylated in vitro (rohe2012invitroand pages 2-3).  
• A fluorescence-polarization assay identified the peptide EFS247–259 as a minimal acceptor, indicating limited peptide tolerance under optimized conditions (platzer2018identificationofpkmyt1 pages 9-10).  
• Dual-specificity phosphorylation of Thr14 and Tyr15 is observed, with kinetic preference for Thr14 (schmidt2017regulationofg2m pages 5-9).  
• No consensus linear motif has been defined in the available literature (rohe2012invitroand pages 2-3).

## Structure

• Domain organisation:  
– N-terminal single-pass membrane anchor localises the protein to ER/Golgi membranes (schmidt2017regulationofg2m pages 3-5).  
– Central bilobal kinase domain (~residues 75–362) contains all catalytic elements; isolated domain is catalytically inactive without flanking regions (rohe2012invitroand pages 1-2).  
– C-terminal regulatory tail mediates high-affinity binding to CDK1 complexes (schmidt2017regulationofg2m pages 3-5).  
• Nine crystal structures are available (PDB: 3P1A, 5VCV, 5VCW, 5VCX, 5VCY, 5VCZ, 5VD0, 5VD1, 5VD3) resolving apo and inhibitor-bound conformations (platzer2018identificationofpkmyt1 pages 6-9).  
• Key catalytic and regulatory features:  
– Lys139–Glu157 salt bridge aligns the β3 strand with the C-helix (schmidt2017regulationofg2m pages 5-9).  
– Gatekeeper Thr178 opens an accessible hydrophobic back pocket absent in WEE1 (schmidt2017regulationofg2m pages 5-9).  
– Hinge residue Cys190 provides the principal hydrogen-bond anchor for ATP and most inhibitors (platzer2018identificationofpkmyt1 pages 6-9).  
– DFG motif Asp251-Phe252-Gly253 coordinates Mg²⁺/ATP and marks the activation loop (schmidt2017regulationofg2m pages 5-9).  
– P-loop Ser120 permits close approach of threonine substrates, rationalising dual specificity (schmidt2017regulationofg2m pages 5-9).

## Regulation

• Auto-inhibitory phosphorylation by active CDK1/cyclin B down-regulates PKMYT1 at mitotic entry (schmidt2017regulationofg2m pages 3-5).  
• Polo-like kinase 1 phosphorylates PKMYT1 to accelerate G2 checkpoint recovery (schmidt2017regulationofg2m pages 3-5).  
• MEK1-dependent phosphorylation promotes Golgi membrane fragmentation during prophase (schmidt2017regulationofg2m pages 15-17).  
• In Xenopus oocytes, sequential phosphorylation by CDK1/XRINGO followed by p90Rsk at Thr453, Ser472, Ser475, Ser492, and Ser504 abolishes CDK1 binding and completes inactivation (ruiz2010atwostepinactivation pages 1-2).  
• Substrate binding increases ATP affinity, indicating substrate-induced ordering of the active site (platzer2018identificationofpkmyt1 pages 9-10).

## Function

• Acts as the principal membrane-bound inhibitor of CDK1/cyclin B, enforcing the G2/M checkpoint (schmidt2017regulationofg2m pages 1-3).  
• ER/Golgi localisation via its N-terminal anchor is essential for coordinating organelle fragmentation and reassembly during mitosis (schmidt2017regulationofg2m pages 3-5, zhu2017structuralbasisof pages 1-2).  
• Over-expression in pancreatic ductal adenocarcinoma correlates with poor prognosis and represents a CRISPR-defined genetic dependency (huang2025discoveryofcmnpd31124 pages 1-2, huang2025discoveryofcmnpd31124 pages 14-14).  
• Promotes proliferation and apoptosis resistance in gastric cancer cells (zhang2020<p>pkmyt1promotesgastric pages 11-11).  
• Synthetic-lethal interaction with WEE1 loss has been demonstrated in glioblastoma stem-like cells (schmidt2017regulationofg2m pages 17-17).  
• Upstream regulators: Plk1 and MEK1 (schmidt2017regulationofg2m pages 3-5, schmidt2017regulationofg2m pages 15-17).  
• Primary downstream substrate: CDK1; no additional substrates are firmly validated in the cited literature (rohe2012invitroand pages 2-3).

## Inhibitors

• PD0166285, a pyridopyrimidine, IC₅₀ ≈ 7 nM (schmidt2017regulationofg2m pages 9-11).  
• Dasatinib (IC₅₀ ≈ 130 nM) and Bosutinib (IC₅₀ ≈ 350 nM) bind the ATP site but lack selectivity (schmidt2017regulationofg2m pages 9-11).  
• RP-6306, a selective, orally bioavailable inhibitor advancing through pre-clinical evaluation (huang2025discoveryofcmnpd31124 pages 14-14).  
• CMNPD31124, a marine indole alkaloid with nanomolar affinity in PDAC models (huang2025discoveryofcmnpd31124 pages 14-14).  
• MK-1775, a WEE1-selective diaminopyrimidine, shows moderate off-target inhibition of PKMYT1 (platzer2018identificationofpkmyt1 pages 10-11).  
• Kinase-focused screens identified additional diaminopyrimidine, azastilbene and 4-aminoquinoline scaffolds with sub-micromolar potency (platzer2018identificationofpkmyt1 pages 6-9, najjar2019computeraideddesignsynthesis pages 1-6).

## Other Comments

• Cancer cells harbouring p53 defects rely on the PKMYT1-mediated G2 checkpoint, offering a therapeutic window for combination with DNA-damaging agents (schmidt2017regulationofg2m pages 9-11).  
• PKMYT1 displays a low small-molecule hit rate (~4 %), complicating selective inhibitor discovery (schmidt2017regulationofg2m pages 9-11).  
• Elevated expression is reported in colorectal, hepatocellular and non-small cell lung cancers, linking PKMYT1 to diverse oncogenic contexts (zhang2020<p>pkmyt1promotesgastric pages 8-11).

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