## Phylogeny

• Member of the AGC serine/threonine kinase superfamily, positioned within the PKN/PRK sub-family according to kinome phylogeny established by Manning et al. 2002 Science (hutchinson2013differentialbindingof pages 36-40).  
• Shares >80 % catalytic-domain identity with paralogs PKN2 and PKN3 and ~34 % identity with ROCK kinases, underscoring proximity to PKC-related branches (unknownauthors2020developmentofpkn2 pages 29-34).  
• Orthologs are conserved across all vertebrate classes and in Drosophila, reflecting preservation of Rho-effector function throughout metazoan evolution (arencibia2013agcproteinkinases pages 1-2).

## Reaction Catalyzed

ATP + [protein] Ser/Thr → ADP + [protein] phospho-Ser/Thr (arencibia2013agcproteinkinases pages 1-2).

## Cofactor Requirements

• Requires Mg²⁺ for catalytic phosphoryl transfer, as typical for AGC kinases (sophocleous2021thestructureand pages 14-15).

## Substrate Specificity

• Johnson 2023 Nature phospho-proteomics defined a consensus motif enriched for basic residues (Arg/Lys) at –3/–2 and hydrophobic residues at +1 relative to the phospho-Ser/Thr, characteristic of PKN1 substrates (sophocleous2021thestructureand pages 15-16).  
• Validated cellular substrates include VIM, neurofilament proteins (NEFH, NEFL, NEFM), MAPT/Tau (Ser575/637/669) and histone H3 (Thr11) (arencibia2013agcproteinkinases pages 1-2, ostrovskyi2016tofacitinibandanalogs pages 12-14).

## Structure

• Domain organisation: HR1a-HR1c antiparallel coiled-coil repeats (Rho-GTPase binding); C2-like lipid-regulated autoinhibitory segment; C-terminal serine/threonine kinase domain (mukai2003thestructureand pages 1-2).  
• Crystal structures: isolated kinase domain (PDB 4CRS) reveals canonical AGC fold with ordered activation segment; HR1a bound to RhoA (PDB 4OTC) defines effector interface (arencibia2013agcproteinkinases pages 1-2, hutchinson2013differentialbindingof pages 36-40).  
• Catalytic features: Lys644-Glu663 salt bridge, DFG motif (Asp711) coordinating Mg²⁺-ATP; activation loop phosphorylation site Thr774; hydrophobic motif Ser916 docks onto N-lobe hydrophobic groove, aligning the regulatory spine (sophocleous2021thestructureand pages 14-15).  
• Leucine-zipper-like ACC segment upstream of HR1 promotes oligomerisation and partner binding (mukai2003thestructureand pages 1-2).

## Regulation

• Phosphorylation  
– Thr774 in activation loop by PDK1: essential for catalytic activation (hutchinson2013differentialbindingof pages 36-40).  
– Ser916 within hydrophobic motif and additional Ser533/Ser537/Ser562 sites phosphorylated by CDK1 during mitosis, increasing activity independent of Thr774 status (unknownauthors2022phostagbasedscreensidentify pages 73-78).  
• Lipid binding  
– Phosphatidylinositol-4,5-bisphosphate, PI(3,4,5)P₃, cardiolipin and unsaturated fatty acids relieve C2-domain autoinhibition (lin2024lipidbindingregionswithin pages 11-11).  
• Small-GTPase interaction  
– RhoA, RhoB, Rac1 bind HR1 domains, triggering conformational activation and membrane recruitment (hutchinson2013differentialbindingof pages 36-40).  
• Proteolytic control  
– Limited proteolysis or caspase-3 cleavage generates constitutively active fragments under stress conditions (sophocleous2021thestructureand pages 16-17).

## Function

• Expression: ubiquitous with high protein levels in spleen, thymus, testes and neurons; overexpressed in prostate and ovarian carcinomas (mukai2003thestructureand pages 1-2, unknownauthors2022phostagbasedscreensidentify pages 78-82).  
• Cytoskeletal regulation: phosphorylates VIM and neurofilaments, inhibiting filament polymerisation and modulating cell shape/migration (arencibia2013agcproteinkinases pages 1-2).  
• Microtubule dynamics: phosphorylates MAPT/Tau at Ser575/637/669, reducing microtubule binding (arencibia2013agcproteinkinases pages 1-2).  
• Transcriptional co-activator: histone H3 Thr11 phosphorylation enables androgen-receptor-dependent gene activation (ostrovskyi2016tofacitinibandanalogs pages 12-14).  
• Signal transduction: operates downstream of ADRA1B to activate MAPK14/p38, integrating adrenergic signalling with stress responses (arencibia2013agcproteinkinases pages 1-2).  
• Neuronal survival: phosphorylation increase under hypoxia contributes to neurite stability and anti-apoptotic signalling (thauerer2014proteinkinasecrelated pages 2-3).

## Inhibitors

• Lestaurtinib (multi-target kinase inhibitor): low-micromolar IC₅₀ against PKN1 (arencibia2013agcproteinkinases pages 3-4).  
• Ro318220: broad AGC-kinase inhibitor exhibiting nanomolar potency on PKN1 in vitro (arencibia2013agcproteinkinases pages 3-4).  
• Tofacitinib: binds PKN1 with Kd ≈ 96 nM and cellular EC₅₀ ≈ 122 nM; analog compound 25 improves threefold selectivity (ostrovskyi2016tofacitinibandanalogs pages 12-14).

## Other Comments

• Disease links: promotes prostate cancer migration/metastasis and is implicated in ovarian cancer aggressiveness (sophocleous2021thestructureand pages 17-17, unknownauthors2022phostagbasedscreensidentify pages 78-82).  
• Neuropathology: dysregulated phosphorylation of neurofilaments and Tau connects PKN1 to ALS and Alzheimer’s disease pathways (thauerer2014proteinkinasecrelated pages 2-3).  
• Therapeutic targeting: siRNA nanotherapeutic Atu027 targeting PKN3 underscores the clinical interest in the PKN axis; analogous strategies are being explored for PKN1 (asquith2022identificationof4‐anilinoquin(az)oline pages 1-3).

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