Phylogeny  
The kinase belongs to the AGC group, DMPK/ROCK/MRCK sub-family (Manning et al., 2002). Within the human kinome its closest paralogues are MRCKα (≈ 85 % identity in the catalytic domain) and MRCKγ (≈ 72 %) (Unbekandt & Olson, 2014). Orthologues are present in mouse (Cdc42bpb), zebrafish (cdc42bpb), fruit-fly (Genghis Khan) and C. elegans (MRCK-1) (Unbekandt & Olson, 2014). The kinase shares ~45–50 % catalytic-domain identity with ROCK1/2, reflecting divergence among Rho-GTPase effector kinases (Ruscetta et al., 2023).

Reaction Catalyzed  
ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (Unbekandt & Olson, 2014).

Cofactor Requirements  
Activity requires Mg²⁺; Mn²⁺ can substitute in vitro (Unbekandt et al., 2020).

Substrate Specificity  
Peptide studies indicate a preference for basic residues at positions −3/−2 and exclusion of acidic side chains, giving an R/K-x-x-S/T consensus (Johnson et al., 2023).

Structure  
The protein is modular: N-terminal capped-helix bundle → kinase domain → coiled-coil/kinase-inhibitory motif (KIM) → C1 → PH → CNH → CRIB (Zhao & Manser, 2015). Crystal structures of the catalytic domain (apo or ADP-bound; PDB 4UAK) show an active conformation that does not require activation-loop phosphorylation (Unbekandt et al., 2020). Complexes with selective inhibitors (BDP5290, BDP9066, BDP8900; PDB 4UAL, 5OTF, 5OTE) reveal hinge contacts to Asp154/Tyr156; the Thr137 gatekeeper and a conserved water complete the catalytic spine (Ruscetta et al., 2023). Lys105 coordinates the ATP β-phosphate, while the ordered activation loop and aligned αC-helix lock the enzyme in a catalytically competent geometry (Unbekandt et al., 2020). N-terminal dimerisation helices form stable dimers and higher-order tetramers in solution (Zhao & Manser, 2015).

Regulation  
• Recruitment of the CRIB domain to membrane-bound CDC42-GTP is the principal activator (Leung et al., 1998).  
• An autoinhibitory KIM within the coiled-coil suppresses catalysis until conformationally released (Zhao & Manser, 2015).  
• Binding of diacylglycerol or phorbol esters to the C1 domain increases activity ~3-fold (Zhao & Manser, 2015).  
• Autophosphorylation at Thr1108 occurs in cis and serves as a pharmacodynamic marker without altering turnover (Unbekandt et al., 2020).  
• Substrate-directed feedback: phosphorylation of MYPT1 Thr697/Thr855 inhibits myosin phosphatase, reinforcing contractility (Zhao & Manser, 2015).

Function  
Transcript levels are ubiquitous but highest in brain; overall abundance generally exceeds that of MRCKγ (Unbekandt et al., 2020). Upstream inputs are CDC42-GTP (primary) and Rac1-GTP (secondary) via the CRIB motif (Ruscetta et al., 2023). Verified substrates/partners include:  
– MYL9/MLC2 Ser19/Thr18 to drive actomyosin contractility (Unbekandt & Olson, 2014).  
– MYPT1 Thr654/Thr697/Thr855 to inhibit myosin phosphatase (Zhao & Manser, 2015).  
– PPP1R12C, LIMK1/2 (via FAM89B), and the MYO18A–LURAP1 complex (Ruscetta et al., 2023).  
Biological roles encompass epithelial polarisation, lamellipodial protrusion, cell migration, phagocytosis and cancer cell invasion (Unbekandt & Olson, 2014).

Inhibitors  
Potent ATP-competitive inhibitors include BDP5290 (Ki ≈ 4 nM, > 40-fold selectivity vs. ROCK), BDP8900 and BDP9066 (sub-nanomolar, 5OTF structure) (Ruscetta et al., 2023; Unbekandt et al., 2018). DJ4 is a dual MRCK/ROCK inhibitor (IC₅₀ ≈ 0.1 µM), while chelerythrine acts non-competitively (IC₅₀ ≈ 1.8 µM). ROCK inhibitors fasudil and Y-27632 inhibit MRCKβ with lower potency (Zhao & Manser, 2015).

Other Comments  
Gene amplification or over-expression correlates with aggressive ovarian, breast, cutaneous squamous carcinoma and glioma; pharmacological inhibition suppresses invasion and tumour growth in pre-clinical models (Ruscetta et al., 2023; Unbekandt et al., 2018). Autophosphorylation at Thr1108 (MRCKβ) and Ser1003 (MRCKα) serve as biomarkers of inhibitor engagement (Unbekandt et al., 2020).

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