## Phylogeny

AKT1 belongs to the AGC protein-kinase group and forms an AKT sub-family with the closely related isoforms AKT2 and AKT3 (Kumar & Madison, 2005). Orthologous proteins are documented in Mus musculus and Rattus norvegicus, underscoring strong conservation across mammals (Unknown Authors, 2010). Invertebrate counterparts (Drosophila melanogaster Akt1 and Caenorhabditis elegans akt-1) further illustrate retention of PI3K→AKT signalling throughout metazoan evolution (Lawlor & Alessi, 2001). Kinome dendrograms cluster AKT1 within the conserved AGC clade, separate from PKA, PKC and S6K branches but sharing the core catalytic architecture (Hernández Armenta, 2020).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + phospho-protein-Ser/Thr (Kumar, Kabekkodu, & Pai, 2025).

## Cofactor Requirements

Catalysis requires a divalent cation; Mg²⁺ is coordinated by Asp292 of the DFG motif, and Mn²⁺ can substitute in vitro (Kumar, Kabekkodu, & Pai, 2025).

## Substrate Specificity

AKT1 preferentially phosphorylates the consensus motif Arg-X-Arg-X-X-Ser/Thr-Φ, where Arg at positions −5/−3 and a bulky hydrophobic residue (Φ) at +1 are critical for efficient turnover (Alessi et al., 1996). Kinome-wide profiling confirms assignment to the canonical RxRxxS/TΦ preference typical of AGC kinases (Hernández Armenta, 2020).

## Structure

The protein comprises an N-terminal pleckstrin-homology (PH) domain (residues 1–≈107), a central kinase domain (149–408) and a C-terminal extension containing the hydrophobic motif (409–480) (Kumar & Madison, 2005).  
• Autoinhibited PH-in conformation masks the activation loop; PIP₃ binding triggers ~23° PH-out rotation that exposes Thr308 (Truebestein et al., 2021).  
• Active AKT1 adopts DFG-in/αC-in geometry with a Lys179–Glu198 salt bridge and assembled catalytic and regulatory spines (Kumar, Kabekkodu, & Pai, 2025).  
• Phospho-Thr308 is stabilised by His194, Arg273 and Lys297, while phospho-Ser473 in the hydrophobic motif interacts with the PH-kinase linker to lock the active state (Kumar, Kabekkodu, & Pai, 2025).  
• Gatekeeper Met227 modulates ATP-binding-site accessibility and inhibitor sensitivity (Kumar, Kabekkodu, & Pai, 2025).  
• Oncogenic E17K in the PH domain disrupts the PH-kinase interface, increases affinity for PIP₃/PIP₂ and favours the active conformation (Truebestein et al., 2021).

## Regulation

• Phosphorylation  
– Thr308 by PDK1 is essential for catalytic competence (Hart & Vogt, 2011).  
– Ser473 by mTORC2 maximises activity (Hart & Vogt, 2011).  
– Thr450 in the turn motif by mTORC2 supports stability (Truebestein et al., 2021).  
– Tyr176 by Src family kinases augments membrane localisation (Chan et al., 2014).  
• Dephosphorylation  
– PP2A removes phosphates from Thr308 and Ser473 (Chan et al., 2014).  
– PHLPP specifically dephosphorylates Ser473 (Unknown Authors, 2010).  
• Ubiquitination – K63-linked chains by NEDD4-1 promote membrane recruitment and activation (Chan et al., 2014).  
• Acetylation – PCAF-mediated acetylation fine-tunes kinase output (Chan et al., 2014).  
• Lipid binding & autoinhibition – PH-domain recognition of PIP₃ relieves PH-in autoinhibition; the unphosphorylated C-tail can dock into the PIF pocket to stabilise an inactive state, an interaction mimicked by allosteric inhibitors (Truebestein et al., 2021).

## Function

AKT1 is ubiquitously expressed and indispensable for cell survival, proliferation and metabolic homeostasis (Unknown Authors, 2010). Upstream activation proceeds via receptor tyrosine kinases → PI3K → PIP₃, with subsequent phosphorylation by PDK1 and mTORC2 (Bae et al., 2022). Major downstream substrates include GSK3β, FOXO1/3, TSC2, BAD, PRAS40, MDM2, eNOS and AS160, thereby controlling metabolism, apoptosis, cell-cycle progression and angiogenesis (Lawlor & Alessi, 2001; Iksen, Pothongsrisit, & Pongrakhananon, 2021). Phosphorylation-dependent 14-3-3 binding sequesters certain substrates (e.g., FOXO), and HSP90 stabilises AKT1 itself (Unknown Authors, 2010). Activated AKT1 drives the PI3K-AKT-mTOR axis to promote proliferation, migration, metabolic adaptation and resistance to apoptosis (Davies et al., 2015).

## Inhibitors

• AZD5363 (capivasertib) – ATP-competitive; 0.1 µM reduces colony formation >80 % and achieves 76–89 % tumour growth inhibition in AKT1-E17K breast models (Davies et al., 2015).  
• MK-2206 – allosteric; stabilises PH-in state and yields 56–58 % tumour inhibition with downstream pathway suppression (Davies et al., 2015).  
• Miransertib (ARQ 092) and ARQ 751 – allosteric; biochemical IC₅₀ = 5–16 nM, block Ser473 phosphorylation and membrane translocation of AKT1-E17K (Yu et al., 2015).  
• GSK690693 – ATP-competitive; IC₅₀ ≈ 180 nM and evaluated in solid and haematologic tumours (Iksen, Pothongsrisit, & Pongrakhananon, 2021).

## Other Comments

The E17K hotspot mutation in the PH domain occurs in 1–8 % of breast, colorectal, lung, prostate and bladder cancers and in ~90 % of Proteus syndrome cases, conferring constitutive membrane localisation and pathway hyper-activation (Chen et al., 2020; Boormans et al., 2010; Yu et al., 2015). AKT1-E17K enhances phosphorylation of PRAS40, GSK3β and S6, promotes anchorage-independent growth and renders tumours sensitive to AKT inhibitors (Davies et al., 2015). Additional activating or destabilising mutations cluster at the PH-kinase interface and within the activation loop (Truebestein et al., 2021).

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