## Phylogeny

STK33 orthologs are found in Homo sapiens (UniProt Q9BYT3) and Mus musculus; deletion in mice causes male infertility (Ku et al., 2024). A more ancient ortholog is present in the sea-anemone genome, indicating that the lineage arose ≥ 700 Myr ago (Goyal et al., 2009). Sequence analyses place the catalytic domain within the Ca²⁺/calmodulin-dependent protein-kinase (CAMK) group, yet the protein lacks the canonical CaM-binding and C-terminal regulatory regions, defining it as an atypical CAMK-group kinase (Mujica et al., 2001). Large-scale kinome surveys corroborate CAMK placement but show that STK33 forms a discrete clade outside established CaMK subfamilies (Bradham et al., 2006). The closest vertebrate paralog, STK35L1, shares ~28 % catalytic-domain identity and arose later in evolution, underscoring early divergence of the STK33 branch (Goyal et al., 2009).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-O-phospho-Ser/Thr (Babij et al., 2011).

## Cofactor Requirements

Kinase assays employ standard Ser/Thr-kinase buffers with ATP; specific divalent-cation requirements have not been reported (Babij et al., 2011).

## Substrate Specificity

• Phosphorylates sperm fibrous-sheath proteins AKAP3 and AKAP4 during spermatogenesis (Ku et al., 2024).  
• Targets the N-terminal head domain of vimentin (Chen & Li, 2016).  
• In vitro, efficiently phosphorylates a p70S6K-derived peptide, whereas histone H3, MBP and PLK-derived peptides are not modified under identical conditions (Babij et al., 2011).  
A global consensus motif has not been defined and systematic substrate-atlas data are currently unavailable.

## Structure

The protein consists solely of a classical bi-lobed Ser/Thr kinase domain (Ku et al., 2024). A 2.7 Å crystal structure of the human catalytic domain bound to inhibitor CDD-2211 (PDB 8VF6) reveals two monomers per asymmetric unit that form a segment-exchange dimer in which activation-loop residues 273–283 of one protomer dock onto helices αE/αG of the partner (Ku et al., 2024). Canonical catalytic motifs (VAIK Lys145, HRD triad, DFG) are intact (Babij et al., 2011). The activation loop is partly disordered yet participates in dimerization; no CaM-binding helix or C-terminal autoregulatory tail is present, consistent with sequence analysis (Mujica et al., 2001).

## Regulation

• Autophosphorylates on Ser/Thr residues; precise sites remain unmapped (Chen & Li, 2016).  
• HSP90 chaperoning maintains protein stability under hypoxia, sustaining HIF-1α/VEGF signalling (Liu et al., 2017).  
• NFYB transcriptionally up-regulates STK33, contributing to chemoresistance in diffuse large B-cell lymphoma (Feng et al., 2021).  
• One study reports Ca²⁺/calmodulin-dependent activation (Chen & Li, 2016); however, the absence of a CaM-binding sequence challenges this mechanism (Mujica et al., 2001).

## Function

Expression is highest in testis, particularly in spermatogenic epithelium; lower levels occur in lung epithelium, alveolar macrophages, retinal horizontal cells and embryonic neural tissue (Chen & Li, 2016).  
• Reproduction: essential for spermatid differentiation and flagellar assembly via phosphorylation of AKAP3/AKAP4; knockout males are infertile (Ku et al., 2024).  
• Cytoskeleton: phosphorylation of vimentin modulates intermediate-filament dynamics (Chen & Li, 2016).  
• Oncogenic signalling:  
– Activates PI3K/AKT/mTOR to promote proliferation and survival in pancreatic neuroendocrine tumours (Zhou et al., 2020).  
– Drives EMT, invasion and p38-MAPK activation in large-cell lung cancer (Wang et al., 2015).  
– Supports hypoxia-induced HIF-1α/VEGF angiogenic programmes via HSP90 (Liu et al., 2017).  
– Enhances RPS6/BAD and ERK pathways, mediating cisplatin resistance (Feng et al., 2021).  
KRAS-synthetic-lethality screens were not confirmed; STK33 is dispensable for viability of KRAS-mutant cell lines (Babij et al., 2011).

## Inhibitors

• CDD-2211: sub-nanomolar ATP-site inhibitor; co-crystal structure available (Ku et al., 2024).  
• ML280: IC₅₀ ≈ 0.27 µM with high kinase selectivity (Unknown Authors, 2014).  
• ML281: IC₅₀ ≈ 0.014 µM, improved potency over ML280 (Unknown Authors, 2014).  
• Additional HTS compounds with IC₅₀ < 10 nM have been reported (Babij et al., 2011).

## Other Comments

Loss of STK33 causes male infertility in mice (Ku et al., 2024). Elevated expression correlates with advanced stage, tumour size, lymph-node metastasis and reduced disease-free survival in pancreatic neuroendocrine tumours; over-expression also promotes progression of large-cell lung carcinoma and cisplatin resistance in diffuse large B-cell lymphoma (Wang et al., 2015; Zhou et al., 2020; Feng et al., 2021).

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