## Phylogeny

Orthologs: STK33 genes are present in Homo sapiens (UniProt Q9BYT3) and Mus musculus; mouse knockout causes male infertility (ku2024reversiblemalecontraception pages 2-4). A more ancient ortholog is detectable in the sea anemone genome, indicating emergence ≥700 Myr ago (goyal2009identifyingandcharacterizing pages 11-13).  
Kinome placement: Sequence analyses place the catalytic domain in the Ca²⁺/calmodulin-dependent protein kinase (CAMK) group, yet STK33 lacks the canonical CaM-binding and C-terminal regulatory segments typical of classical CaMK family members, defining it as an atypical CAMK-group kinase (mujica2001anovelserinethreonine pages 4-5). Large-scale kinome surveys corroborate CAMK-group assignment while noting that STK33 forms a discrete clade outside established CaMK subfamilies (bradham2006theseaurchin pages 2-3).  
Paralogy: The kinase shares 28 % identity within the catalytic domain to STK35L1, which arose later in vertebrate evolution, underscoring early divergence of the STK33 lineage (goyal2009identifyingandcharacterizing pages 11-13).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-O-phospho-Ser/Thr (babij2011stk33kinaseactivity pages 5-5).

## Cofactor Requirements

Experimental kinase assays employ standard serine/threonine kinase buffers with ATP; specific divalent-cation requirements are not explicitly reported (babij2011stk33kinaseactivity pages 5-5).

## Substrate Specificity

• Sperm fibrous-sheath scaffold proteins AKAP3 and AKAP4 are phosphorylated during spermatogenesis (ku2024reversiblemalecontraception pages 2-4).  
• Intermediate-filament protein vimentin/VIM is phosphorylated on its N-terminal head domain (chen2016researchprogressof pages 1-2).  
• In vitro the enzyme selectively phosphorylates a p70S6K-derived peptide, whereas histone H3, MBP, and PLK peptides are not substrates under identical conditions (babij2011stk33kinaseactivity pages 5-5).  
A consensus recognition motif has not been delineated; systematic substrate-atlas data are unavailable in the current literature.

## Structure

Domain architecture: STK33 consists solely of a classical bilobed serine/threonine kinase domain comprising an N-terminal β-sheet/αC lobe and a C-terminal α-helical lobe (ku2024reversiblemalecontraception pages 2-4).  
Crystal structure: The human kinase domain bound to inhibitor CDD-2211 has been solved at 2.7 Å resolution (PDB 8VF6). Two monomers per asymmetric unit form a segment-exchange dimer wherein activation-loop residues 273–283 of one protomer dock onto helices αE/αG of the partner (ku2024reversiblemalecontraception pages 2-4).  
Catalytic motifs: VAIK motif Lys145 (mutated to K145M for kinase-dead control), HRD catalytic triad, and DFG motif are intact (babij2011stk33kinaseactivity pages 3-4).  
Regulatory elements: The activation loop is partially disordered yet participates in dimerization; no CaM-binding helix or C-terminal autoregulatory tail is present, consistent with sequence analysis (mujica2001anovelserinethreonine pages 4-5). No AlphaFold model is discussed in current publications.

## Regulation

Autophosphorylation: STK33 undergoes serine/threonine autophosphorylation; specific sites remain unmapped (chen2016researchprogressof pages 1-2).  
Chaperone control: HSP90 maintains STK33 protein stability under hypoxic conditions, thereby supporting HIF-1α/VEGF signaling (liu2017stk33participatesto pages 13-14).  
Transcriptional control: NFYB up-regulates STK33 transcription, contributing to chemoresistance in diffuse large B-cell lymphoma (feng2021nfybpotentiatesstk33 pages 9-9).  
Calmodulin: One report describes Ca²⁺/calmodulin-dependent activation (chen2016researchprogressof pages 1-2); however, the absence of a CaM-binding segment in sequence and structure challenges this mechanism (mujica2001anovelserinethreonine pages 4-5).

## Function

Expression: Highest levels in testis, specifically spermatogenic epithelium; lower expression in lung epithelium, alveolar macrophages, retinal horizontal cells, and embryonic neural tissues (chen2016researchprogressof pages 1-2).  
Reproduction: STK33 is essential for spermatid differentiation and male fertility in mice by promoting sperm flagellar assembly via phosphorylation of AKAP3/AKAP4 (ku2024reversiblemalecontraception pages 2-4).  
Cytoskeleton: Phosphorylation of vimentin regulates intermediate-filament dynamics and cell morphology (chen2016researchprogressof pages 2-3).  
Oncogenic signaling:  
– Activates PI3K/AKT/mTOR signaling, enhancing proliferation and survival in pancreatic neuroendocrine tumours (zhou2020stk33promotesthe pages 19-21).  
– Drives epithelial–mesenchymal transition, invasion, and p38-MAPK activity in large-cell lung cancer (wang2015stk33playsan pages 8-9).  
– Supports HIF-1α-dependent angiogenic programs through HSP90 association (liu2017stk33participatesto pages 13-14).  
– Enhances RPS6/BAD and ERK signaling, mediating cisplatin resistance (feng2021nfybpotentiatesstk33 pages 9-9).  
KRAS context: Initial synthetic-lethal RNAi screens suggested dependency, yet comprehensive knock-down and inhibitor studies found STK33 dispensable for KRAS-mutant cell viability (babij2011stk33kinaseactivity pages 1-1).

## Inhibitors

CDD-2211: Sub-nanomolar ATP-site binder; co-crystal structure defines binding mode (ku2024reversiblemalecontraception pages 2-4).  
ML280: IC₅₀ ≈ 0.27 µM against purified STK33, high kinase selectivity (unknownauthors2014screenforinhibitors pages 1-5).  
ML281: IC₅₀ ≈ 0.014 µM, improved potency relative to ML280 (unknownauthors2014screenforinhibitors pages 1-5).  
High-throughput screening has identified additional compounds with IC₅₀ < 10 nM in enzymatic assays (babij2011stk33kinaseactivity pages 6-6).

## Other Comments

Male infertility: STK33 loss causes defective spermatid maturation and infertility in mice (ku2024reversiblemalecontraception pages 2-4).  
Cancer associations: Elevated STK33 expression correlates with advanced stage, larger tumour size, lymph-node metastasis, and reduced disease-free survival in pancreatic neuroendocrine tumours (zhou2020stk33promotesthe pages 23-25). Overexpression promotes progression of large-cell lung carcinoma (wang2015stk33playsan pages 1-1). NFYB-mediated activation contributes to cisplatin resistance in diffuse large B-cell lymphoma (feng2021nfybpotentiatesstk33 pages 9-9).

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