## Phylogeny

• Serine/threonine-protein kinase 17B (STK17B/DRAK2) belongs to the death-associated protein kinase (DAPK) family nested within the Ca²⁺/calmodulin-dependent kinase (CAMK) group of the human kinome (farag2019death‐associatedproteinkinase pages 1-2, picado2020achemicalprobe pages 18-19).  
• The closest human paralog is STK17A (DRAK1); more distant paralogs are DAPK1, DAPK2 and DAPK3, which share the conserved catalytic domain but differ in extra-catalytic regions (farag2019death‐associatedproteinkinase pages 2-4, picado2020achemicalprobe pages 18-19).  
• Vertebrate orthologs are conserved (e.g., mouse Stk17b, zebrafish stk17b), and the Drosophila kinase Drak functions as an invertebrate ortholog, underscoring evolutionary conservation of this apoptosis-related clade (chen2019drakstk17adrivesneoplastic pages 9-14).  
• Curated kinome resources flag STK17B as an understudied CAMK/DAPK sub-branch member, guiding prioritisation for chemical-biology efforts (moret2020aresourcefor pages 7-10).

## Reaction Catalyzed

ATP + [protein]-L-Ser/Thr → ADP + [protein]-O-phospho-L-Ser/Thr (farag2019death‐associatedproteinkinase pages 4-6).

## Cofactor Requirements

Catalytic activity requires divalent cations, preferentially Mg²⁺ or Mn²⁺ (scheuplein2024evaluationofstk17b pages 1-2).

## Substrate Specificity

• Direct substrate: myosin light chain 2 (MLC2) phosphorylated on Ser19, providing a pharmacodynamic read-out (scheuplein2024evaluationofstk17b pages 1-2).  
• Additional validated substrate: serine/arginine-rich splicing factor 6 (SRSF6) identified by phosphoproteomics (scheuplein2024evaluationofstk17b pages 13-13).  
• Autophosphorylation occurs on Thr180 within the activation loop, a hallmark regulatory site (scheuplein2024evaluationofstk17b pages 13-13).  
• High-throughput motif profiling has not yet defined a consensus recognition motif for STK17B (scheuplein2024evaluationofstk17b pages 13-13).

## Structure

• Architecture: single N-terminal kinase domain (~residues 1–270) followed by a C-terminal tail containing two predicted nuclear-localisation signals; no CaM-binding region (farag2019death‐associatedproteinkinase pages 4-6).  
• Crystal structures: apo form (PDB 3LM5) and inhibitor-bound forms (PDB 6Y6F, 6Y6H) reveal the canonical bilobal fold and an atypical, ligand-dependent P-loop that adopts “open” and “folded” conformations (picado2020achemicalprobe pages 7-8, serafim2021chemicalprobesfor pages 10-14).  
• Catalytic features: Lys62 (β3) forms a salt bridge with Glu80 (αC); conserved DFG motif Asp166-Phe167-Gly168 coordinates Mg²⁺; hinge residue Ala113 anchors ATP/inhibitors; activation loop Thr180 is the primary regulatory phosphosite (picado2020achemicalprobe pages 7-8).  
• A family-specific 12-residue “basic loop” mediates dimerisation and promotes autophosphorylation without directly contacting substrates (farag2019death‐associatedproteinkinase pages 4-6).  
• Inhibitor binding induces P-loop folding over the ligand, generating extensive contacts with Arg41 and Lys62, which underlies high selectivity over STK17A (picado2020achemicalprobe pages 7-8).

## Regulation

• Autophosphorylation on Thr180 activates catalytic function (scheuplein2024evaluationofstk17b pages 13-13).  
• Protein kinase D phosphorylates Ser351 downstream of Ca²⁺/ROS signalling, modulating activity (scheuplein2024evaluationofstk17b pages 13-13, zheng2022newinsightsinto pages 4-5).  
• Ubiquitination events regulate protein stability, although the responsible E3 ligases remain unidentified (scheuplein2024evaluationofstk17b pages 13-13).  
• The proto-oncogene MYB represses STK17B transcription; MYB knock-down elevates STK17B levels and triggers caspase-9-dependent apoptosis (zheng2022newinsightsinto pages 4-5).  
• Ca²⁺ influx after T-cell receptor stimulation induces mitochondrial ROS, activating PKD and thereby STK17B, integrating calcium signalling with kinase activation (zheng2022newinsightsinto pages 4-5).  
• Ligand-induced folding of the P-loop constitutes an allosteric mechanism that occludes ATP binding and locks the enzyme in an inactive, inhibitor-bound state (picado2020achemicalprobe pages 7-8).

## Function

• Highest expression in developing and mature lymphocytes, particularly T and B cells (scheuplein2024evaluationofstk17b pages 1-2, zheng2022newinsightsinto pages 8-10).  
• Sets the activation threshold for T-cell receptor signalling; genetic loss sensitises T cells to suboptimal stimulation and enhances cytokine release (scheuplein2024evaluationofstk17b pages 1-2).  
• Acts as a positive regulator of apoptosis, partly through phosphorylation of myosin light chains (picado2020achemicalprobe pages 18-19).  
• In hepatocytes, STK17B limits phosphorylation of SRSF6, contributing to non-alcoholic fatty liver disease pathology (scheuplein2024evaluationofstk17b pages 13-13).  
• Promotes autophagy-mediated degradation of TRAF6, thereby restraining cervical cancer cell growth and metastasis (zheng2022newinsightsinto pages 4-5).  
• Upstream regulators include Ca²⁺/PKD and MYB; downstream effectors encompass caspase-9 and cytoskeletal contractility via MLC2 (zheng2022newinsightsinto pages 4-5, scheuplein2024evaluationofstk17b pages 1-2).

## Inhibitors

• Thieno[2,3-d]pyrimidine probe 11s: K\_d = 5.6 nM, enzyme IC₅₀ = 34 nM, >100-fold selective over STK17A; selectivity driven by folded P-loop interactions (picado2020achemicalprobe pages 7-8).  
• Precursor analog 18: K\_d = 3.8 nM, ~60-fold selectivity versus STK17A (serafim2021chemicalprobesfor pages 10-14).  
• Negative control compound 19g: >100-fold weaker binding, confirms structure–activity determinants (picado2020achemicalprobe pages 7-8).  
• 5-Arylthieno[2,3-b]pyridine compound 13: enzyme IC₅₀ = 0.86 µM, K\_d = 9 nM; dual DRAK1/2 activity (farag2019death‐associatedproteinkinase pages 22-23).  
• Optimised analog 14: enzyme IC₅₀ = 29 nM with reduced family selectivity (farag2019death‐associatedproteinkinase pages 22-23).  
• Indirubin-3′-monoxime derivative 15 represents a distinct chemotype with reported DRAK2 inhibition (farag2019death‐associatedproteinkinase pages 22-23).  
• Multi-target agent nintedanib binds DRAK2 with K\_d = 670 nM, illustrating the liability of promiscuous kinase inhibitors (farag2019death‐associatedproteinkinase pages 26-28).

## Other Comments

• Disease links include autoimmune pathologies, type 1 diabetes, non-alcoholic fatty liver disease, chronic lymphocytic leukaemia, breast cancer and cervical cancer (zheng2022newinsightsinto pages 8-10, serafim2021chemicalprobesfor pages 10-14).  
• STK17B-deficient mice display enhanced T-cell apoptosis yet show resistance to organ-specific autoimmunity, highlighting its immunoregulatory role (picado2020achemicalprobe pages 18-19).  
• No recurrent cancer-associated point mutations with functional annotation have been reported to date (scheuplein2024evaluationofstk17b pages 13-13).

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