## Phylogeny

– Human TBK1 shares 99 % amino-acid identity with its murine ortholog, illustrating strong conservation across mammals (revach2020targetingtankbindingkinase pages 1-3).  
– The kinase is assigned to the non-canonical IκB-kinase (IKK-related) subfamily within the CAMK-like group and clusters most closely with IKKε, with 49 % identity in the kinase domain (xiang2021tankbindingkinase1 pages 1-2).  
– Sequence identity with canonical IKKα/IKKβ is ~28–35 %, indicating early divergence inside the broader IKK clade (tu2013structureandubiquitinationdependent pages 2-4, larabi2013crystalstructureand pages 1-2).  
– Orthologous proteins are reported across vertebrates; the dimer interface residues and regulatory lysines are conserved from fish to mammals (tu2013structureandubiquitinationdependent pages 4-5).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + phosphoprotein-L-Ser/Thr (ma2012molecularbasisof pages 1-1).

## Cofactor Requirements

Catalytic turnover requires ATP binding in the active site; activity of this Ser/Thr kinase is divalent-cation dependent, although the specific metal (Mg²⁺ versus Mn²⁺) is not detailed in the cited excerpts (revach2020targetingtankbindingkinase pages 14-15).

## Substrate Specificity

– Kinase-domain peptide profiling indicates preference for a bulky hydrophobic residue (Leu/Ile) at the +1 position, yielding a φ-X-S/T-φ consensus (helgason2013recentinsightsinto pages 3-5).  
– Structural analyses corroborate broad tolerance elsewhere in the motif, rationalising phosphorylation of diverse substrates bearing the hydrophobic +1 residue (ma2012molecularbasisof pages 5-6).

## Structure

– Domain organisation: kinase domain (1-307), ubiquitin-like domain (ULD, 310-385), scaffold/dimerisation domain (SDD, 407-657), C-terminal adaptor-binding tail (657-729) (revach2020targetingtankbindingkinase pages 1-3).  
– Full-length crystal structures reveal a back-to-back homodimer in which each KD-ULD-SDD trio forms an elongated subunit; the interface clamps but does not occlude the active sites (tu2013structureandubiquitinationdependent pages 2-4).  
– Activation loop (Leu164-Gly199) is disordered in the apo state; trans-autophosphorylation of Ser172 orders the loop and locks the C-helix via a Glu55-Lys38 salt bridge and Arg54/Arg134/Arg162 contacts (xiang2021tankbindingkinase1 pages 1-2).  
– An activation-loop-swapped dimer captured in PDB 4EUT/4EUU supports the trans-phosphorylation mechanism (ma2012molecularbasisof pages 1-1).  
– Inhibitor-bound structures (e.g., BX795, amlexanox) show a conserved hinge hydrogen bond with Cys89 and pocket plasticity accommodating diverse chemotypes (xiang2021tankbindingkinase1 pages 9-10).  
– The ULD E355/R357 “EGR” motif forms salt bridges with SDD residue R547; mutations on either side disrupt dimer stability and abolish activation (tu2013structureandubiquitinationdependent pages 4-5).

## Regulation

Phosphorylation  
– Ser172 autophosphorylation is indispensable for catalytic competence (larabi2013crystalstructureand pages 1-2).  
– Tyr179 phosphorylation by Src enhances activation (zhao2019tankbindingkinase1 pages 7-10).  
– Ser716 phosphorylation by PKCθ modulates downstream signal amplitude (revach2020targetingtankbindingkinase pages 3-4).  
– Ser527 phosphorylation by DYRK2 earmarks TBK1 for proteasomal turnover (zhao2019tankbindingkinase1 pages 7-10).  
Dephosphorylation  
– PPM1B, PP4, Cdc25A and PPM1A remove pSer172, providing negative feedback (revach2020targetingtankbindingkinase pages 14-15).  
Ubiquitination  
– K63-linked poly-ubiquitination on Lys30 and Lys401 by TRAF-family E3 ligases (MIB1, MIB2, RNF128, RNF144B, RNF41) is essential for activation; CYLD and USP2b reverse this modification (revach2020targetingtankbindingkinase pages 3-4).  
– K48-linked chains target TBK1 for degradation (revach2020targetingtankbindingkinase pages 3-4).  
SUMOylation  
– Lys694 SUMOylation augments antiviral signalling (revach2020targetingtankbindingkinase pages 3-4).  
Higher-order Assembly  
– K63-Ub chains plus adaptor proteins TANK, NAP1 and SINTBAD drive clustering, positioning kinase domains for trans-autophosphorylation (tu2013structureandubiquitinationdependent pages 8-9).

## Function

– Constitutive expression in most tissues; elevated in immune cells, hepatocytes and multiple tumour types (hui2025tankbindingkinase1 pages 1-2).  
Upstream pathways  
– Activated downstream of TLR3/4-TRIF, RIG-I/MAVS and cGAS-STING sensors (revach2020targetingtankbindingkinase pages 3-4).  
Core adaptors/interactors  
– TANK, NAP1, SINTBAD, TRAF3, TRAF2, STING, OPTN and NDP52 coordinate localisation and pathway selection (helgason2013recentinsightsinto pages 1-2).  
Key substrates  
– IRF3, IRF7, STING Ser366, RIPK1, Rab7, PLK1, CEP170, NUMA, AKT (revach2020targetingtankbindingkinase pages 27-29, unknownauthors2020regulationofintracellular pages 66-69, revach2020targetingtankbindingkinase pages 6-7).  
Signalling outputs  
– Type I interferon induction, NF-κB activation, selective autophagy/mitophagy, modulation of apoptosis–necroptosis decisions, and support of KRAS-driven oncogenic survival via the RalB–Sec5 axis (tu2013structureandubiquitinationdependent pages 2-4).

## Inhibitors

– BX795, IC₅₀ ≈ 1 nM, co-crystal PDB 4IW0, multi-kinase profile (revach2020targetingtankbindingkinase pages 27-29).  
– MRT67307, IC₅₀ 19 nM, selective versus canonical IKKs (tu2013structureandubiquitinationdependent pages 4-5).  
– GSK8612, highly selective with in-vivo efficacy (revach2020targetingtankbindingkinase pages 23-27).  
– Amlexanox, IC₅₀ 0.85 µM, co-crystal PDB 5W5V (xiang2021tankbindingkinase1 pages 9-10).  
– CYT387/Momelotinib, IC₅₀ 58 nM (revach2020targetingtankbindingkinase pages 27-29).  
– Cmpd1, IC₅₀ 1 nM (revach2020targetingtankbindingkinase pages 27-29).  
– BAY-985, IC₅₀ 2 nM, limited pharmacokinetics (xiang2021tankbindingkinase1 pages 9-10).  
– Compound II and DMXD-011 exhibit anti-inflammatory efficacy in pre-clinical models (hui2025tankbindingkinase1 pages 12-14).

## Other Comments

– Germline deletion in mice is embryonic-lethal owing to hepatocyte apoptosis, underscoring essential developmental roles (revach2020targetingtankbindingkinase pages 6-7).  
– ALS/FTD-linked variants (e.g., K38D, S172A, G175S, CCD2 deletions) impair dimerisation, autophosphorylation or adaptor binding, leading to defective autophagy and neuroinflammation (umair2021impactofsingle pages 1-2, foster2020alsassociatedtbk1variant pages 1-2, oakes2017tbk1anew pages 1-2).  
– Hyper-activated TBK1 sustains survival of KRAS-mutant lung and pancreatic cancers, representing a synthetic-lethal vulnerability (tu2013structureandubiquitinationdependent pages 2-4).

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