Phylogeny  
• Homo sapiens TNK1 (Uniprot Q13470) is the human ortholog and reference sequence (ahmed2022thenoncatalyticregions pages 1-2).  
• Mus musculus Tnk1 (Uniprot Q9D0C6) is the mouse ortholog used for phospho-proteomic studies (unknownauthors2020discoveryofa pages 30-35).  
• Danio rerio tnk1a retains the proline-rich phospho-cluster corresponding to human S502 (unknownauthors2022examinationof1433 pages 59-63).  
• TNK1 and ACK1/TNK2 form the ACK subfamily within the Tyrosine Kinase (TK) group of the human kinome as classified in the Manning kinome framework (balasooriya2024integratingclinicalcancer pages 14-15, prietoechague2011regulationofackfamily pages 6-7).

Reaction Catalyzed  
ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (ahmed2022thenoncatalyticregions pages 1-2).

Cofactor Requirements  
• Catalysis requires Mg²⁺; Mn²⁺ also supports activity in vitro (chan2021tnk1isa pages 14-15, ahmed2022thenoncatalyticregions pages 8-9).

Substrate Specificity  
• Highest in-vitro turnover toward a WASP-derived PxxP peptide; Km = 214 µM (ahmed2022thenoncatalyticregions pages 1-2).  
• Secondary phosphorylation observed on an Abl YxxP peptide, indicating partial overlap with Abl-family motifs (ahmed2022thenoncatalyticregions pages 1-2).  
• Cellular tyrosine substrates include PLC-γ1 Y783 and STAT3 Y705, whereas STAT5 is not phosphorylated (unknownauthors2020discoveryofa pages 53-58).  
• Yeast phospho-proteomics defines a motif enriched in proline residues flanking pTyr and basic residues at +1/+2, consistent with P-x-x-pY-[K/R]-[K/R] (unknownauthors2016decipheringhumancytoplasmic pages 79-82).  
• The 2024 tyrosine-kinome atlas does not report intrinsic specificity data for TNK1; motif therefore remains experimentally defined as above (unknownauthors2020discoveryofa pages 35-40).

Structure  
• Domain organization: SAM 1-111; Kinase core 112-350 (activation-loop autophosphorylation site Y277); SH3 351-410; Proline-rich 411-589 containing 14-3-3 site S502; UBA 590-666 (chan2021tnk1isa pages 14-15, ahmed2022thenoncatalyticregions pages 8-9).  
• AlphaFold model AF-Q13470-F1 covers the full polypeptide and preserves canonical kinase features including β3 Lys, HRD274-276 catalytic triad, and DFG292-294 motif (ahmed2022thenoncatalyticregions pages 9-10, unknownauthors2022examinationof1433 pages 79-83).  
• UBA domain folds into a five-helix bundle that forms a high-affinity ubiquitin-binding pocket (chan2021tnk1isa pages 14-15).  
• No experimental crystal or cryo-EM structures have been reported to date (ahmed2022thenoncatalyticregions pages 9-10).

Regulation  
• Autophosphorylation at Y277 within the activation loop enhances catalytic activity (unknownauthors2022examinationof1433 pages 79-83).  
• MARK1-4 phosphorylate S502, creating a docking site for multiple 14-3-3 isoforms which sequester and inhibit TNK1 (unknownauthors2022examinationof1433 pages 59-63).  
• Loss of 14-3-3 binding (S502A or C-terminal truncation) induces cytosolic puncta and increases kinase signaling (unknownauthors2022examinationof1433 pages 70-75).  
• The C-terminal UBA domain binds K48-, K63-, and M1-linked poly-ubiquitin with nanomolar affinity; ubiquitin engagement is required for full activation (unknownauthors2020discoveryofa pages 44-48).  
• Y661 inside the UBA is a major phosphorylation site that modulates 14-3-3 and ubiquitin interactions (unknownauthors2022examinationof1433 pages 115-119).

Function  
• mRNA is ubiquitous in fetal tissues and restricted in adults to prostate, testis, ovary, colon, and small intestine; elevated expression is observed in AML, ALL, prostate and ovarian cancer cell lines (unknownauthors2020discoveryofa pages 13-17).  
• Upstream regulator: LKB1-activated MARK kinases mediate S502 phosphorylation (unknownauthors2022examinationof1433 pages 63-66).  
• Key interactors: 14-3-3 proteins (phospho-dependent binding), poly-ubiquitin chains (UBA-dependent), p62/SQSTM1, and TBK1 within ubiquitin condensates (unknownauthors2020discoveryofa pages 53-58, unknownauthors2022examinationof1433 pages 115-119).  
• Downstream signaling: phosphorylates PLC-γ1 and STAT3, negatively modulates Ras-RAF-MEK-ERK and NF-κB pathways, and enhances IFN-STAT1 antiviral signaling (unknownauthors2020tnk1inducesapoptosis pages 36-42, unknownauthors2020discoveryofa pages 53-58).

Inhibitors  
• TP-5801: ATP-competitive inhibitor; biochemical IC₅₀ = 1.4 nM, Ba/F3 cell growth IC₅₀ = 37-78 nM; oral dosing reduces tumor burden and prolongs survival in TNK1-driven mouse models (unknownauthors2020discoveryofa pages 53-58, unknownauthors2022amachinelearning pages 71-72).  
• (R)-9b exhibits micromolar inhibition in radiometric kinase assays (ahmed2022thenoncatalyticregions pages 8-9).

Other Comments  
• High TNK1 expression correlates with poor overall and relapse-free survival in ALL patient cohorts (unknownauthors2020discoveryofa pages 35-40).  
• A Hodgkin lymphoma-derived C-terminal truncation lacking the 14-3-3 binding region yields a hyperactive oncogenic variant (unknownauthors2020discoveryofa pages 13-17).  
• Whole-body Tnk1 knockout mice develop spontaneous lymphomas and carcinomas, indicating context-dependent tumor-suppressor functions (unknownauthors2020discoveryofa pages 13-17).

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