## Phylogeny

• Tyrosine-protein kinase ITK belongs to the TK group, Tec family, clustering with BTK, TEC, BMX and RLK/TXK in kinome phylogenies derived from the Manning 2002 data set (unknownauthors2013studiesonitksyk pages 12-15).  
• Vertebrate orthologs are documented in mouse and rat, with functional conservation across species indicated by Itk-/- murine models (zhong2014targetinginterleukin2inducibletcell pages 6-8).

## Reaction Catalyzed

ATP + protein-L-tyrosine → ADP + protein-L-tyrosine-phosphate (burch2014propertyandstructureguided pages 12-13).

## Cofactor Requirements

Catalysis is strictly ATP-dependent and requires divalent cations; Mg²⁺ is obligatory and Mn²⁺ can substitute in vitro (unknownauthors2013studiesonitksyk pages 26-29, unknownauthors2023gapjunctionalintercellular pages 66-71).

## Substrate Specificity

• Validated substrates include PLCγ1 (Tyr775/Tyr783), LAT, LCP2/SLP-76, and VAV1 (zhong2014targetinginterleukin2inducibletcell pages 11-13, ghosh2018interleukin2inducibletcellkinase pages 3-4).  
• Intrinsic consensus motif preferences have not been experimentally defined in the available excerpts; Yaron-Barir 2024 is referenced but no sequence logo is reported (unknownauthors2023gapjunctionalintercellular pages 165-167).

## Structure

Domain organisation: PH (1-~100) → Tec-homology with proline-rich region (PRR) → SH3 → SH2 → kinase (SH1) (ghosh2018interleukin2inducibletcellkinase pages 3-4, zhong2014targetinginterleukin2inducibletcell pages 1-3).  
3D features:  
• Crystal structures of the isolated kinase domain complexed with benzothiazole inhibitors reveal the canonical bilobal fold, a Phe435 gatekeeper and a Ser442 hinge contact conferring selectivity (mackinnon2013structurebaseddesignand pages 5-5).  
• Allosteric inhibitor complexes capture an αC-out inactive state defining a non-ATP regulatory pocket (han2014selectivelytargetingan pages 1-2).  
• The PH domain adopts a β-sandwich lipid-binding fold; stabilising mutations were mapped by NMR (boyken2012rescueofthe pages 10-10).  
Key catalytic/regulatory residues: Lys391 (β3), Glu436/Met438 (hinge), Tyr511 (activation loop), Tyr180 (SH3 autophosphorylation site) (han2014selectivelytargetingan pages 1-2, mackinnon2013structurebaseddesignand pages 5-5).

## Regulation

Post-translational modifications  
• Tyr511: trans-phosphorylation by LCK; essential for catalytic activation (ghosh2018interleukin2inducibletcellkinase pages 3-4, zhong2014targetinginterleukin2inducibletcell pages 11-13).  
• Tyr180: cis-autophosphorylation; enhances kinase activity (han2014selectivelytargetingan pages 1-2).  
Lipid/adaptor control  
• PH-domain binding to PI3K-generated PIP₃ or soluble IP₄ targets ITK to the plasma membrane (zhong2014targetinginterleukin2inducibletcell pages 6-8).  
• Intramolecular SH3-PRR engagement maintains autoinhibition; release occurs upon assembly into the LAT–SLP-76 signalosome (unknownauthors2023gapjunctionalintercellular pages 66-71, unknownauthors2013studiesonitksyk pages 12-15).  
Allosteric regulation  
• Small-molecule ligands stabilising the inactive αC-out conformation provide non-competitive inhibition (han2014selectivelytargetingan pages 19-20).

## Function

Expression  
High in thymocytes, naïve CD4⁺/CD8⁺ T cells, Th2-polarised cells, NK, NKT and mast cells (han2014selectivelytargetingan pages 1-2).  
Signalling cascade  
• Upstream: PI3K-PIP₃ generation, ZAP70-dependent LAT phosphorylation and LCK-mediated Tyr511 phosphorylation converge to activate ITK (zhong2014targetinginterleukin2inducibletcell pages 11-13).  
• Downstream: ITK phosphorylates PLCγ1, LAT and LCP2, triggering Ca²⁺ flux, NFAT nuclear import, PKCθ/MAPK/ERK activation and assembly of VAV1-containing complexes (zhong2014targetinginterleukin2inducibletcell pages 11-13).  
• Cellular roles: controls Th2 cytokine production, influences Th17/Treg balance, and modulates cytolytic granule release in CD8⁺ T cells and innate lymphoid subsets (eken2019geneticdeficiencyand pages 9-10, zhong2014targetinginterleukin2inducibletcell pages 3-5).

## Inhibitors

• Ibrutinib – irreversible covalent binder of Cys442; imposes Th1-skewing in T cells (zhong2014targetinginterleukin2inducibletcell pages 5-6).  
• CTA056 – selective cytotoxicity toward ITK-high malignant T cells; suppresses xenograft growth (zhong2014targetinginterleukin2inducibletcell pages 5-6).  
• Tetrahydroindazole series – ATP-competitive inhibitors with low-nanomolar Ki (burch2014propertyandstructureguided pages 12-13).  
• Benzothiazole series – sub-nanomolar potency exploiting Ser442 contact, high kinome selectivity (mackinnon2013structurebaseddesignand pages 5-5).  
• Allosteric compound 9 – non-competitive; Ki = 0.236 µM, K\_i,autoact = 0.026 µM (han2014selectivelytargetingan pages 19-20).

## Other Comments

• Loss-of-function mutations R335W and c.1573G>A cause combined immunodeficiency with Epstein-Barr virus-driven lymphoproliferation and hemophagocytic lymphohistiocytosis (ghosh2018interleukin2inducibletcellkinase pages 3-4).  
• Chromosomal translocation t(5;9)(q33;q22) produces the constitutively active ITK-SYK fusion kinase that drives peripheral T-cell lymphoma (unknownauthors2013studiesonitksyk pages 26-29, zhong2014targetinginterleukin2inducibletcell pages 9-11).  
• ITK dysregulation is implicated in allergic asthma, atopic dermatitis and other inflammatory diseases (unknownauthors2023gapjunctionalintercellular pages 66-71).

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