## Proposed EC/sub-subclass:

Not yet assigned

## Accepted name:

Leukocyte tyrosine kinase

## Synonyms:

LTK; leukocyte tyrosine kinase receptor

## Phylogeny

• Receptor tyrosine kinase (RTK) of the insulin-receptor family, ALK/LTK sub-family (unknownauthors2015diversityofreceptor, pp. 51-56).  
• Cytoplasmic kinase domain shares ≈ 79 % amino-acid identity with anaplastic lymphoma kinase (ALK), consistent with a recent gene-duplication event (Centonze et al., 2019, pp. 15-18).  
• Mammalian orthologues have lost the N-terminal MAM and LDLa modules retained in non-mammalian species; TNF-like (TG) and EGF-like segments remain conserved (Katic & Priscan, 2023, pp. 1-2).  
• Verified orthologues: Homo sapiens, Mus musculus, Danio rerio, Xenopus tropicalis, Gallus gallus (Centonze et al., 2019, pp. 15-18).

## Reaction catalysed

protein-L-tyrosine + ATP ⇄ protein-L-tyrosine-phosphate + ADP + H⁺ (Roll & Reuther, 2012, pp. 1-2).

## Cofactor requirements

Activity is presumed, in line with other RTKs, to require Mg²⁺ or Mn²⁺; no dedicated biochemical study is available (Nadendla et al., 2025, pp. 18-19; Farhan, 2020, pp. 4-6).

## Substrate Specificity

• Position-scanning peptide libraries place LTK among tyrosine kinases that prefer acidic residues at −3/−1 and a hydrophobic residue at +1 relative to the target Tyr (Nadendla et al., 2025, pp. 18-19).  
• Strong bias toward the first Tyr in Y-x-x-x-Y-Y motifs, matching cellular data (Roll & Reuther, 2012, pp. 12-13).  
• Confirmed cellular substrate: Sec12 phosphorylated at Y10 and Y177, regulating COPII vesicle formation (Centonze et al., 2019, pp. 18-20).

## Structure

• Domain architecture: signal peptide 1-16 – extracellular TG supradomain 17-424 – single transmembrane helix 425-449 – cytoplasmic kinase domain 450-864 (unknownauthors2023subcellularlocalizationand, pp. 12-15).  
• Ectodomain crystal structure (PDB 7NX1) shows a composite TG fold with pGII helices forming the ligand-binding surface (De Munck et al., 2021, pp. 13-17).  
• Catalytic core contains conserved VAIK (K567), HRD (H648-R650-D651) and DFG (D666-F667-G668) motifs; autophosphorylation occurs at Y672 within the activation loop (unknownauthors2023subcellularlocalizationand, pp. 39-44).  
• Activating mutations F568L (αC helix) and R669Q (DFG+1) lie adjacent to regulatory motifs (Roll & Reuther, 2012, pp. 12-13).  
• AlphaFold model AF-P29376 confirms intact regulatory and catalytic spines typical of active RTKs (unknownauthors2023subcellularlocalizationand, pp. 12-15).

## Regulation

• Autophosphorylation on Y672 is required for full activity and is detected mainly at the Golgi (unknownauthors2023subcellularlocalizationand, pp. 39-44).  
• N-glycosylation at N257, N380 and N412 influences receptor maturation, Golgi localisation and ligand responsiveness; the N257Q/N380Q/N412Q mutant abolishes FAM150A-induced activation (unknownauthors2023subcellularlocalizationand, pp. 39-44).  
• Extracellular ligands FAM150A (Augmentor-β) and FAM150B (Augmentor-α) trigger receptor dimerisation and kinase activation (Zhang et al., 2014, pp. 1-2; unknownauthors2023subcellularlocalizationand, pp. 12-15).  
• Ubiquitination by the E3 ligase CBL regulates receptor turnover (Nadendla et al., 2025, pp. 18-19).  
• Spatial control: activation requires an intact Golgi; Brefeldin A or FLI-06 block activation by disrupting Golgi integrity or ER export (unknownauthors2023subcellularlocalizationand, pp. 50-54).

## Function

• Expression: highly expressed in pre-B/B lymphocytes, brain, placenta and plasmacytoid dendritic cells (Roll & Reuther, 2012, pp. 1-2; Zhang et al., 2014, pp. 3-4).  
• Substrates / partners: Sec12 (direct substrate) (Centonze et al., 2019, pp. 18-20); ERGIC-53 (stable complex) (unknownauthors2023subcellularlocalizationand, pp. 24-30); adaptor proteins IRS-1, Shc and PI3K bind NPXY motifs Y485/Y862 and Y753 (unknownauthors2023subcellularlocalizationand, pp. 12-15).  
• Downstream signalling: activates MAPK, PI3K/AKT and JAK/STAT cascades upon ligand binding or activating mutations (Roll & Reuther, 2012, pp. 13-14; unknownauthors2023subcellularlocalizationand, pp. 15-20).  
• Cellular role: phosphorylation of Sec12 boosts COPII budding, expands ER exit-site number and accelerates ER-to-Golgi transport (Centonze et al., 2019, pp. 1-4).

## Inhibitors

• Crizotinib inhibits wild-type and F568L-mutant LTK, suppressing STAT5, AKT and ERK signalling and blocking soft-agar colony growth (Roll & Reuther, 2012, pp. 13-14).  
• Ceritinib and Alectinib block autophosphorylation and impair secretory-pathway functions at ~1 µM in cells (Centonze et al., 2019, pp. 15-18; unknownauthors2023subcellularlocalizationand, pp. 15-20).

## Other Comments

• Disease links: over-expression or activating mutations associated with acute myeloid leukaemia and increased metastatic risk in non-small-cell lung cancer (Nadendla et al., 2025, pp. 18-19).  
• Gain-of-function polymorphism near the PI3K-binding site enhances B-cell activation and predisposes to systemic lupus erythematosus (unknownauthors2023subcellularlocalizationand, pp. 15-20).  
• Catalogue of oncogenic mutations includes F568L, R669Q, P116S, G310E, A432T, V480I, R608*, Y616*, Q717K, many of which cluster near catalytic motifs and increase kinase activity (Roll & Reuther, 2012, pp. 12-13; Palmer & Hallberg, 2015, pp. 15-18).

## References

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