## Phylogeny

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) belongs to the receptor tyrosine kinase (RTK) group, ROR subfamily, within the kinome classification of Manning et al. (Unknown Authors, 2021). Human ROR1 shares ~50 % overall sequence identity with human ROR2 and ~99 % identity within the kringle domain with its Mus musculus orthologue; additional orthologues occur in Rattus norvegicus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans, the latter encoding the catalytically active CAM-1 kinase (Bainbridge et al., 2014; Qi et al., 2018; Guarino et al., 2022). Comparative biochemical work shows that, unlike CAM-1, human ROR1 and ROR2 have lost robust phosphotransfer activity and function as pseudokinases (Bainbridge et al., 2014).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine O-phosphate; catalytic efficiencies of the isolated ROR1 kinase domain are 100- to 1000-fold lower than canonical RTKs (Bainbridge et al., 2014).

## Cofactor Requirements

Divalent Mg²⁺ or Mn²⁺ ions are required for any detectable in-vitro phosphorylation (Bainbridge et al., 2014).

## Substrate Specificity

No consensus phospho-acceptor motif has been defined. Purified ROR1 neither autophosphorylates its activation-loop tyrosines nor phosphorylates generic tyrosine-containing peptides under standard assay conditions (Bainbridge et al., 2014; Unknown Authors, 2021).

## Structure

Domain organisation: Ig-like domain – Frizzled-like cysteine-rich domain (CRD) – kringle domain – single transmembrane helix – intracellular pseudokinase domain – serine/threonine-rich region – proline-rich region – second serine/threonine-rich region (Bainbridge et al., 2014; Guarino et al., 2022).  
Ectodomain: the human kringle domain adopts the canonical triple-loop kringle fold at 1.4 Å resolution and presents a basic protein-interaction surface (Guarino et al., 2022).  
Pseudokinase domain: crystallography and HDX-MS reveal an inactive conformation with an occluded ATP pocket, displaced αC-helix and autoinhibitory positioning of Tyr554 within a YxxxYY motif; Met527 serves as the gatekeeper residue (Sheetz et al., 2020).  
Type-II inhibitors (ponatinib, GZD824) induce ~20° N-lobe rotation, stabilising a DFG-out-like state and exposing latent druggable conformations (Sheetz et al., 2020).

## Regulation

• Lyn kinase phosphorylates intracytoplasmic residues, recruiting c-CBL and regulating receptor surface dynamics during chemotaxis of chronic lymphocytic leukaemia (CLL) cells (Dave et al., 2022).  
• Constitutive tyrosine phosphorylation is detected in CLL, indicating trans-phosphorylation in vivo (Wei et al., 2024).  
• WNT5A stimulation yields <1 % activation-loop phosphorylation, underscoring minimal intrinsic autophosphorylation (Bainbridge et al., 2014).  
• Binding of ponatinib or GZD824 allosterically locks the pseudokinase in an inactive conformation (Sheetz et al., 2020).

## Function

Expression: high during embryogenesis and in immature B-cell precursors; low in most adult tissues but markedly up-regulated in CLL, mantle-cell lymphoma, acute lymphoblastic leukaemia, triple-negative breast cancer, lung adenocarcinoma, and multiple solid tumours (Guarino et al., 2022; Gupta et al., 2023; Wei et al., 2024).

Ligand-mediated signalling and interacting partners:  
– CRD binds WNT5A, suppressing WNT3A/β-catenin and activating non-canonical NF-κB pathways (Bainbridge et al., 2014).  
– ROR1 forms complexes with EGFR/ERBB3 to sustain PI3K-AKT-mTOR signalling in lung adenocarcinoma (Liu et al., 2015).  
– IGFBP5 engagement promotes a ROR1–ERBB2 complex that enhances CREB signalling in glioblastoma (Wei et al., 2024).  
– A ROR1–HER3–lncRNA axis modulates Hippo-YAP signalling in bone-metastasis models (Gupta et al., 2023).  
– ROR1 stabilises GRB2, driving ERK/c-Fos activation and glioma stem-cell maintenance (Zhu et al., 2025).

Loss-of-function: RNAi or pharmacological down-regulation decreases PI3K/AKT/mTOR activity, arrests proliferation and induces apoptosis in lung and breast cancer models (Liu et al., 2015; Gupta et al., 2023).

## Inhibitors

Ponatinib and GZD824 (type-II ATP-competitive binders), KAN0441571C, CID1261330, ARI-1 and the natural product strictinin all exhibit cytotoxic activity toward ROR1-positive cancer cells (Sheetz et al., 2020; Gupta et al., 2023; Wei et al., 2024; Fultang et al., 2019).

## Other Comments

High tumoural ROR1 expression correlates with larger tumour size, advanced stage and poor prognosis in breast cancer, lung adenocarcinoma and glioblastoma (Gupta et al., 2023; Liu et al., 2015; Zhu et al., 2025). Restoration of canonical catalytic motifs fails to rescue kinase activity, confirming pseudokinase status (Bainbridge et al., 2014). Antibody-based therapeutics, bispecific T-cell engagers and switchable CAR-T cells targeting ROR1 ectodomain epitopes are under active development (Sheetz et al., 2020; Qi et al., 2018).

## 9. References

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