Phylogeny  
Belongs to the TK group, RTK family, VEGF receptor (type V) sub-family (Stuttfeld & Ballmer-Hofer, 2009). Orthologues are reported in human, mouse, rat, chicken, Xenopus, and zebrafish. A single ancestral VEGFR-like receptor (D-VEGFR/PVR) is present in Drosophila, indicating early duplication/triplication events in vertebrate evolution (Shibuya & Claesson-Welsh, 2006; Stuttfeld & Ballmer-Hofer, 2009; Gordon et al., 2013).

Reaction Catalyzed  
ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (Roskoski, 2008).

Cofactor Requirements  
Catalysis requires Mg²⁺ for ATP phosphate coordination (Roskoski, 2008).

Substrate Specificity  
Autophosphorylation occurs on Y1230, Y1231, Y1265, Y1337 and Y1363 in VEGFR3 homodimers; in VEGFR3–VEGFR2 heterodimers only Y1230, Y1231 and Y1265 are modified (Lee et al., 2025). Phospho-Y1337 creates an SH2 docking site for SHC/GRB2 (Asthana, 2019). No consensus exogenous substrate motif has been defined (Roskoski, 2008).

Structure  
• Extracellular region comprises seven Ig-like domains; proteolytic cleavage within domain 5 leaves two disulphide-linked fragments that influence ligand access (Shibuya & Claesson-Welsh, 2006).  
• Single transmembrane helix (residues 776–797) followed by a juxtamembrane segment (798–844) (Roskoski, 2008).  
• Cytoplasmic portion contains a split, bilobed kinase domain; key catalytic residues include Lys868 (β3), Glu885 (αC), Asp1028 (HRD), and Asp1046 (DFG) (Roskoski, 2008).  
• Activation-segment phosphorylation stabilises the active conformation; overall folding is inferred from the closely related VEGFR2 because no FLT4 crystal structure is currently available (Roskoski, 2008).

Regulation  
• Ligand-induced autophosphorylation on Y1230/Y1231/Y1265/Y1337/Y1363 activates the receptor (Lee et al., 2025).  
• Heterodimerisation with VEGFR2 suppresses Y1337 and Y1363 phosphorylation, altering signalling specificity (Roskoski, 2008).  
• Integrin engagement activates c-Src, which can phosphorylate VEGFR3 independently of ligand binding (Asthana, 2019).  
• Extracellular cleavage in Ig-domain 5 modulates ligand responsiveness (Shibuya & Claesson-Welsh, 2006; Lee et al., 2025).  
• Alternative splicing yields a shorter C-terminal isoform lacking several autophosphorylation sites and displaying reduced signalling (Roskoski, 2008).

Function  
Expression – Broad endothelial expression during embryogenesis; post-natally restricted mainly to lymphatic endothelium, fenestrated capillaries and selected veins (Shibuya & Claesson-Welsh, 2006; Taipale et al., 1999).  
Upstream activators – VEGF-C and VEGF-D homodimers bind Ig-domains 1–2 and promote receptor dimerisation (Shibuya & Claesson-Welsh, 2006; Taipale et al., 1999).  
Downstream signalling – Phospho-Y1337 recruits SHC/GRB2 to trigger the RAS-MAPK cascade; PI3K-AKT supports survival; PKC contributes to ERK activation (Asthana, 2019; VEGF-A/VEGFRs system, 2022).  
Physiological roles – Essential for embryonic vascular remodelling (Vegfr3-null mice die at E9.5–E11) (Roskoski, 2008; Taipale et al., 1999); governs lymphangiogenesis, endothelial migration and sprouting in adult tissues (Shibuya, 2001; VEGF-A/VEGFRs system, 2022). Forms heterodimers with VEGFR2 to modulate KDR signalling output (Lee et al., 2025).

Inhibitors  
Small-molecule TKIs with activity toward VEGFR3 include MAZ51, tivozanib, axitinib, vandetanib and sorafenib; multi-targeted agents such as sunitinib and sorafenib inhibit VEGFR1-3 and PDGFRs (Asthana, 2019; Roskoski, 2008). Soluble receptor “ligand traps” that sequester VEGF-C/D act as decoy inhibitors (Lee et al., 2025).

Other Comments  
Loss-of-function FLT4 mutations cause congenital lymphoedema 1 (Milroy disease); >58 pathogenic variants, mainly kinase-domain missense changes, are reported (Gordon et al., 2013). The Chy mouse p.Ile1053Phe allele mirrors the human phenotype, and a recessive p.Ser1235Cys mutation produces mild hereditary lymphoedema (Melikhan-Revzin et al., 2015).

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