Phylogeny  
• Member of the Tyrosine Kinase (TK) group, ErbB sub-family, clustering with EGFR/HER1, HER2 and HER3; cytoplasmic domain shares ≈79 % identity with EGFR (el‐gamal2021areviewof pages 1-3, el‐gamal2021areviewof pages 3-4).  
• Vertebrate orthologs include Mus musculus Erbb4, whose genetic ablation causes embryonic cardiac and neural defects (monsey2010her4andher2neu pages 1-2).

Reaction Catalyzed  
• ATP + protein-L-tyrosine → ADP + protein-L-tyrosine-phosphate (qiu2008mechanismofactivation pages 6-7).

Cofactor Requirements  
• Catalytic activity requires divalent cations; in vitro assays employ 10 mM Mn²⁺ for optimal phosphorylation (qiu2008mechanismofactivation pages 6-7).

Substrate Specificity  
• The kinase phosphorylates generic tyrosine-containing peptides; no strict consensus motif was defined in biochemical assays (qiu2008mechanismofactivation pages 6-7).

Structure  
• Domain organization: ectodomain with four β-hairpin subdomains and a cleavage-prone JM-a stalk, single transmembrane helix, intracellular juxtamembrane segment, bilobed kinase domain, C-terminal tail bearing multiple Tyr sites (el‐gamal2021areviewof pages 1-3, rio2000tumornecrosisfactorαconverting pages 1-2).  
• Crystal structures of the isolated kinase (PDB complexes with AMP-PNP and lapatinib) reveal canonical N- and C-lobes, an activation loop adopting active or inactive conformations, and a drug-occupied ATP pocket (qiu2008mechanismofactivation pages 6-7).  
• Active signaling requires asymmetric C-lobe/N-lobe dimers analogous to EGFR; dimerization is cooperative and concentration-dependent (monsey2010her4andher2neu pages 1-2).  
• Catalytic elements: Lys726 (β3) anchors ATP, Asp836 (HRD) is catalytic base, Phe837 stabilizes the regulatory spine, Thr771 and Met774 line the adenine pocket (sahu2017identificationandcharacterization pages 1-3).  
• JM-a–specific sequence confers susceptibility to TACE cleavage, a property absent in other ErbBs (rio2000tumornecrosisfactorαconverting pages 1-2).

Regulation  
• Ligand binding by NRG1-4, BTC, EREG or HBEGF induces homo- or heterodimerization followed by trans-autophosphorylation (el‐gamal2021areviewof pages 3-4).  
• Principal autophosphorylation sites: Y984, Y1056, Y1188 (ojala2024recurrentcancerassociatederbb4 pages 34-35).  
• ERK-mediated feedback phosphorylation attenuates signaling (el‐gamal2021areviewof pages 24-25).  
• Proteolytic control: JM-a isoform is sequentially cleaved by TACE and γ-secretase, releasing a nuclear intracellular domain that chaperones STAT5A (rio2000tumornecrosisfactorαconverting pages 1-2, maatta2006proteolyticcleavageand pages 13-13).  
• Heterodimerization with HER2 markedly enhances kinase activity; co-expression with HER3 amplifies downstream Akt and ERK phosphorylation (monsey2010her4andher2neu pages 1-2, wandinger2016quantitativephosphoproteomicsanalysis pages 5-7).  
• Cancer-associated mutations such as K935I, Y285C and D595V increase dimerization, phosphorylation and intracellular-domain release (el‐gamal2021areviewof pages 6-7).

Function  
• Widely expressed in fetal heart, nervous system, basal epidermis, skeletal muscle neuromuscular junctions, adult cardiomyocytes and mammary epithelium (el‐gamal2021areviewof pages 3-4).  
• Essential for cardiac trabeculation, neural crest migration, axon guidance, mammary differentiation and lactation (el‐gamal2021areviewof pages 1-3).  
• Activates PI3K/AKT and MAPK cascades; NRG1-stimulated homodimers induce BRCA1 and G2/M checkpoint, slowing proliferation in breast cancer cells (el‐gamal2021areviewof pages 7-9).  
• Co-expression with HER3 enhances Akt-Ser474 and MEK/ERK phosphorylation upon NRG1 stimulation (wandinger2016quantitativephosphoproteomicsanalysis pages 5-7).  
• Nuclear intracellular domain partners with STAT5A to regulate gene transcription (maatta2006proteolyticcleavageand pages 13-13).

Inhibitors  
• Lapatinib – reversible; Ki = 347 nM (bose2009theerbbkinase pages 19-19).  
• Gefitinib – reversible; Ki = 1.1 µM (bose2009theerbbkinase pages 19-19).  
• Erlotinib – reversible; Ki = 1.5 µM (bose2009theerbbkinase pages 19-19).  
• Canertinib – irreversible; IC₅₀ = 14 nM (sahu2017identificationandcharacterization pages 9-11).  
• Ibrutinib – irreversible covalent inhibitor with HER4 activity (el‐gamal2021areviewof pages 15-17).  
• AC-480 (BMS-599626) – reversible; IC₅₀ = 190 nM (el‐gamal2021areviewof pages 15-17).  
• Pyrotinib – irreversible pan-HER inhibitor retaining HER4 affinity (el‐gamal2021areviewof pages 22-24).  
• Imidazo[2,1-b]thiazole derivatives (Compound I IC₅₀ = 15.24 nM; Compound II IC₅₀ = 17.70 nM) show >60-fold selectivity across 63 kinases (el‐gamal2021areviewof pages 15-17, el‐gamal2021areviewof pages 22-24).

Other Comments  
• Context-dependent roles: phosphorylated HER4 associates with poor prognosis in glioblastoma, melanoma and gastric cancer (el‐gamal2021areviewof pages 7-9, el‐gamal2021areviewof pages 27-28).  
• Higher HER4 expression predicts favorable outcome in bladder and hormone-sensitive prostate cancers (el‐gamal2021areviewof pages 6-7, el‐gamal2021areviewof pages 27-28).  
• Recurrent activating mutations confer resistance to targeted therapies (ojala2024recurrentcancerassociatederbb4 pages 34-35).

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