## Phylogeny

• Member of the tyrosine-kinase (TK) group, Eph receptor family, EphB subfamily (manning2002theproteinkinase pages 3-3).  
• One of four catalytically active human EphB receptors (EphB1–EphB4) (overman2014completingthestructural pages 1-2).  
• Closest human paralogs: EPHB1, EPHB2 and EPHB4, generated by vertebrate-specific gene duplications (unknownauthors2010theephephringene pages 16-18).  
• Orthologs include mouse EphB3 and chicken EphB3, each retaining nanomolar affinity for ephrin-B3 (bergemann1998ephrinb3aligand pages 3-5).  
• Conserved across jawed vertebrates following the two early whole-genome duplication events (brunet2016wholegenomeduplications pages 6-7).  
• Invertebrate genomes such as Drosophila and Caenorhabditis contain a single Eph receptor, underscoring vertebrate expansion of the family (manning2002theproteinkinase pages 3-3).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-L-tyrosine phosphate (overman2014completingthestructural pages 7-9).

## Cofactor Requirements

No metal-ion cofactor requirement is reported in the available sources (overman2014completingthestructural pages 7-9).

## Substrate Specificity

A consensus phosphorylation motif has not been defined; in vitro assays reveal a subtly altered substrate preference compared with other EphB kinases (overman2013biochemicalandbiophysical pages 9-10).

## Structure

Domain organisation  
• Extracellular region comprising a globular ligand-binding domain, a cysteine-rich/EGF module and two fibronectin type III repeats (unknownauthors2005structurefunctionand pages 42-45).  
• Single-pass transmembrane helix (unknownauthors2005structurefunctionand pages 42-45).  
• Cytoplasmic segment containing a juxtamembrane region with regulatory tyrosines, a protein-tyrosine-kinase domain, a sterile-α-motif (SAM) and a C-terminal PDZ-binding motif (unknownauthors2005structurefunctionand pages 45-48).

Kinase domain crystallography  
• Crystal structure solved at 2.2 Å after introduction of the stabilising A899P mutation, which increases yield and thermostability without altering ligand binding (overman2014completingthestructural pages 2-4).  
• Classical bilobed kinase fold with a partially ordered activation loop; an activation-loop tyrosine occupies the substrate groove in the apo state, suggesting a cis-autophosphorylation mechanism (overman2014completingthestructural pages 7-9).  
• Catalytic HRD motif (Asp758–Arg762) and the invariant lysine for ATP coordination are intact, whereas the DFG motif adopts an inactive orientation in the solved structure (overman2014completingthestructural pages 7-9).

Unique structural features  
• Hinge-region Cys717 (Gly in other EphB kinases) constricts the solvent channel and determines a distinct inhibitor profile (overman2013biochemicalandbiophysical pages 7-8, overman2014completingthestructural pages 7-9).  
• Wild-type protein exhibits temperature-dependent salting-out, a property abrogated by the A899P mutation (overman2014completingthestructural pages 7-9).

## Regulation

Post-translational modifications  
• Ligand-induced oligomerisation triggers trans- and cis-autophosphorylation on juxtamembrane, kinase-domain and SAM-domain tyrosines, creating SH2 docking sites (kung2016developmentofspecific pages 1-3, unknownauthors2005structurefunctionand pages 45-48).  
• Cytoplasmic phosphatase SHP2 dephosphorylates the receptor, dampening signalling output (unknownauthors2005structurefunctionand pages 42-45).

Conformational/allosteric control  
• Higher-order clustering of receptor ectodomains and lateral Eph–Eph interactions potentiate activation (unknownauthors2005structurefunctionand pages 42-45).  
• Activation-loop positioning observed crystallographically supports internal cis-regulation prior to ligand-stimulated phosphorylation (overman2014completingthestructural pages 7-9).

## Function

Expression  
• Strong expression along the midline of the developing neural tube (bergemann1998ephrinb3aligand pages 2-3).  
• mRNA present in neonatal and adult central nervous system tissues, including spinal cord (zhi2012ephrinb3(ephb3) pages 4-4).

Physiological roles  
• Cooperates with EPHB2 to guide corpus callosum and anterior commissure axons during brain development (bergemann1998ephrinb3aligand pages 2-3).  
• Facilitates adult axonal plasticity and promotes regrowth after central nervous system injury (zhi2012ephrinb3(ephb3) pages 4-4).  
• Regulates cell protrusion, migration, proliferation and fate determination in diverse cellular contexts (kung2016developmentofspecific pages 1-3, overman2013biochemicalandbiophysical pages 1-2).

Upstream ligand  
• Binds ephrin-B3 with nanomolar affinity and displays limited interaction with other ephrin-B ligands (bergemann1998ephrinb3aligand pages 3-5).

Signalling partners  
• Interacts with the Ras-binding adaptor AF6 (stringer2016epha3(ephreceptor pages 7-8).  
• Downstream effectors include Src-family kinases, PI3K, MAPKs, Rho-family GTPases, FAK, paxillin and p130Cas (unknownauthors2005structurefunctionand pages 42-45).

## Inhibitors

• Electrophilic quinazoline inhibitors form a covalent bond with Cys717, conferring potent, selective EphB3 inhibition and enabling chemoproteomic target engagement (kung2016developmentofspecific pages 1-3).  
• Broad-spectrum ATP-competitive inhibitors (CMPD1, CMPD2, Dasatinib, Afatinib, Sorafenib, Sunitinib) are less potent against EphB3; the C717G mutation restores inhibitor sensitivity (overman2013biochemicalandbiophysical pages 7-8, overman2014completingthestructural pages 7-9).

## Other Comments

• Dysregulated EPHB3 activity shows context-dependent roles in cancer, acting as a tumour suppressor in colon and non-small-cell lung cancer while promoting invasion in prostate cancer (kung2016developmentofspecific pages 1-3, overman2013biochemicalandbiophysical pages 1-2).  
• The availability of isozyme-selective covalent inhibitors provides a tool for mechanistic dissection of these divergent oncogenic versus tumour-suppressive functions (kung2016developmentofspecific pages 1-3).

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