## Phylogeny

PI4KB belongs to the phosphatidylinositol-3/4-kinase family within the lipid-kinase branch of the human kinome (Manning et al., 2002). Phylogenetic analyses define PI3/4-kinases as an ancient protein-kinase-like clade that retains the canonical catalytic core but is distinct from classical protein kinases (Scheeff & Bourne, 2005). Verified orthologues span fungi (yeast Pik1), insects (Drosophila CG5005/four-wheel-drive), nematodes (C. elegans PI4K), and plants (PI4Kβ1/β2 and PI4Kγ3), illustrating conservation across eukaryotes (Waugh, 2019; Kumar & Kumar, 2024). More divergent homologues are present in Giardia lamblia and Plasmodium falciparum, indicating an early eukaryotic origin (Manning et al., 2011; McPhail & Burke, 2020). Human paralogues include PI4KA (type IIIα) and the type II isoforms PI4K2A and PI4K2B (Burke, 2018).

## Reaction Catalyzed

ATP + 1-phosphatidyl-1D-myo-inositol ⇌ ADP + 1-phosphatidyl-1D-myo-inositol 4-phosphate (Dornan et al., 2016).

## Cofactor Requirements

Catalysis requires Mg²⁺ or Mn²⁺; Ca²⁺ is inhibitory (Kumar & Kumar, 2024).

## Substrate Specificity

PI4KB phosphorylates phosphatidylinositol resident in unsaturated Golgi membranes. No protein phosphorylation consensus has been defined, and PI4KB was not included in the Johnson 2023 serine/threonine kinase atlas (Burke, 2018; Kumar & Kumar, 2024).

## Structure

• N-terminal disordered segment (res 1–≈83) folds upon ACBD3 binding (Burke, 2018).  
• Helical/armadillo domain (≈84–350) contacts Rab11 and 14-3-3 proteins (Dornan et al., 2016).  
• Bilobal kinase domain (≈351–801) contains a type III-specific N-lobe insertion; key active-site residues include Lys549 and hinge Val598/Ala601 (McPhail & Burke, 2020).  
• C-terminal disordered tail (≈770–801) harbours an ALPS motif for membrane-curvature sensing (Burke, 2018).

Crystal structures (PDB 5FBL, 5FBQ, 5FBR, 5FBV, 5FBW) reveal a deep ATP-binding canyon where inhibitors form dual hinge hydrogen bonds to Val598/Ala601 and interact with Gly675/Asn676 (Mejdrová et al., 2017). The activation-loop/N-lobe linker (res 486–498) is disordered in apo enzyme but becomes ordered upon c10orf76 binding, correlating with inhibition (McPhail et al., 2020). Key catalytic/regulatory elements include the activation loop (486–498), the catalytic spine Lys549–Val598/Ala601–Asp665, and an allosteric interface between the C-helix and helical domain for Rab11 binding (Dornan et al., 2016).

## Regulation

Post-translational modifications  
• Ser294 phosphorylation by protein kinase D generates a high-affinity 14-3-3 docking site, stabilising PI4KB (Burke, 2018; Wortzel et al., 2015).  
• Ser496 is phosphorylated by PKA, decreasing affinity for the inhibitory protein c10orf76; Ser413 is an additional in-vivo site (McPhail et al., 2020).

Protein interactions  
• 14-3-3 dimers bind phospho-Ser294, protect the site from dephosphorylation and regulate nucleocytoplasmic shuttling (Kumar & Kumar, 2024).  
• ACBD3 recruits PI4KB to Golgi membranes via the N-terminus (Burke, 2018).  
• Rab11 associates with the helical domain, enabling kinase-independent scaffolding (Burke, 2018).  
• c10orf76 binds the N-lobe linker, ordering the activation loop and potently inhibiting catalysis (McPhail et al., 2020).  
No ubiquitination or proteolytic regulation has been reported (Dornan et al., 2016).

## Function

Expression and localisation  
Predominantly localises to Golgi and trans-Golgi network with a regulated nuclear pool controlled by 14-3-3 binding (Kumar & Kumar, 2024).

Cellular roles  
• Generates the main Golgi PI4P pool that recruits OSBP, CERT, FAPPs and GOLPH3, driving lipid exchange and vesicle biogenesis (McPhail & Burke, 2020).  
• Supports Golgi-to-plasma-membrane trafficking and cytokinesis; Rab11 binding provides kinase-independent scaffolding (Dornan et al., 2016).  
• Ser294 phosphorylation couples PKD signalling to Golgi lipid metabolism (Burke, 2018).  
• Essential host factor for positive-strand RNA viruses and for Plasmodium and Cryptosporidium development by enabling PI4P-rich replication organelles (Dornan et al., 2016).

## Inhibitors

• BQR695: ATP-competitive; forms dual hinge hydrogen bonds to Val598/Ala601 and water-mediated contact to Ser618; selective for PI4KB over PI4KA and PI3Ks (McPhail & Burke, 2020).  
• Sulfonamide Series B (e.g., compounds 23, 24, 25, 33, 35) exploit the Gly675/Asn676 pocket; high potency confirmed crystallographically (Mejdrová et al., 2017).  
• Enviroxime analogues inhibit viral replication by targeting PI4KB (Kumar & Kumar, 2024).  
• Additional ATP-competitive chemotypes have been structurally characterised (Mejdrová et al., 2015).

## Other Comments

Selective PI4KB inhibition shows antimalarial and anticryptosporidial efficacy with acceptable rodent toxicity, unlike systemic PI4KA blockade (Burke, 2018). Resistance to PI4KB-targeted antivirals can arise via viral 3A protein mutations (Burke, 2018).

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