Phylogeny  
PI5P4Kγ (PIP4K2C) is one of three PI5P4K isoforms (α, β, γ) restricted to metazoans and absent from unicellular eukaryotes (raghu2021emergingcellbiological pages 1-2). Orthologs are reported in Mus musculus (Pip4k2c) and Drosophila melanogaster (dPIP4K), indicating conservation within Bilateria (raghu2021emergingcellbiological pages 1-2). Within the human kinome, PI5P4Kγ belongs to the lipid-kinase branch as a type II phosphatidylinositol phosphate kinase, distinct from type I PIP5Ks (burke2023beyondpi3kstargeting pages 26-27, clarke2013evolutionarilyconservedstructural pages 11-12). Among mammalian PI5P4Ks, intrinsic catalytic efficiency decreases in the order α ≫ β ≫ γ (unknownauthors2020pip4khasa pages 21-28).

Reaction Catalyzed  
phosphatidyl-1D-myo-inositol-5-phosphate + ATP ⇄ phosphatidyl-1D-myo-inositol-4,5-bisphosphate + ADP (boffey2022developmentofselective pages 12-12).  
phosphatidyl-1D-myo-inositol-5-phosphate + GTP ⇄ phosphatidyl-1D-myo-inositol-4,5-bisphosphate + GDP (rooney2022theidentificationof pages 18-18).

Cofactor Requirements  
Catalysis requires Mg²⁺ ions (burke2023beyondpi3kstargeting pages 26-27).

Substrate Specificity  
PI5P4Kγ selectively phosphorylates phosphatidylinositol-5-phosphate with negligible activity toward PI3P or PI4P (unknownauthors2021investigatingtherole pages 32-34, raghu2021emergingcellbiological pages 4-5). The C-terminal activation loop dictates this lipid specificity; loop exchange with a type I kinase redirects the enzyme toward PI4P (unknownauthors2020pip4khasa pages 21-28). No peptide consensus motif applies because the kinase acts on lipid substrates.

Structure  
Crystal structure PDB 2GK9 reveals a bilobal protein-kinase core (≈1–404 aa) with an N-terminal extended β-sheet that mediates homodimerization; two dimers assemble into a tetramer with all catalytic clefts oriented on one face (unknownauthors2020pip4khasa pages 21-28). Canonical VAIK, HRD and DFG motifs are conserved, while a truncated activation loop (~25 aa) forms part of an allosteric pocket targeted by non-ATP-competitive inhibitors (boffey2022developmentofselective pages 12-12). AlphaFold model AF-Q8TBX8-F1 corroborates domain boundaries and highlights a reconfigured glycine-rich loop correlated with low catalytic turnover (boffey2022developmentofselective pages 12-12). The β-sheet interface generates a flat, positively charged membrane-binding surface characteristic of type II PIP kinases (unknownauthors2020pip4khasa pages 21-28).

Regulation  
• Phosphorylation by mTORC1 maintains basal mTORC1 signaling during nutrient starvation (burke2023beyondpi3kstargeting pages 26-27).  
• Additional activation-loop phosphorylation modulates catalytic output and localization (boffey2022developmentofselective pages 12-12).  
• GTP binding enhances activity relative to ATP, conferring guanine-nucleotide sensor capability (rooney2022theidentificationof pages 18-18).  
• PI5P4Kγ heterodimerizes with PI5P4Kα and PI5P4Kβ, tuning overall kinase activity (rooney2022theidentificationof pages 18-18).  
• Direct association with PIP5Ks suppresses PI(4,5)P₂ synthesis independently of its own catalysis (wang2019pip4kssuppressinsulin pages 5-10).  
• Non-ATP-competitive allosteric ligands stabilize an inactive activation-loop conformation (boffey2022developmentofselective pages 12-12).

Function  
Highest protein expression is detected in kidney nephron epithelial cells, with broader distribution across metabolic and immune tissues (clarke2015thefunctionof pages 9-9, burke2023beyondpi3kstargeting pages 26-27). By restraining PIP5Ks, PI5P4Kγ limits insulin-stimulated PI(3,4,5)P₃ production and downstream AKT activation, thereby negatively regulating insulin and PI3K-Akt signaling (wang2019pip4kssuppressinsulin pages 5-10). The kinase supports autophagosome biogenesis and sustains basal mTORC1 activity during starvation (boffey2022developmentofselective pages 12-12, burke2023beyondpi3kstargeting pages 26-27). Genetic ablation elevates mTOR signaling and provokes systemic inflammation, indicating a role in immune homeostasis (unknownauthors2020pip4khasaa pages 15-21). Pharmacological or genetic inhibition mitigates mutant huntingtin toxicity and can impair tumor cell survival, linking PI5P4Kγ to neurodegeneration and cancer biology (boffey2022developmentofselective pages 12-12).

Inhibitors  
• Non-ATP-competitive allosteric inhibitors with single-digit nanomolar IC₅₀ values have been developed (boffey2022developmentofselective pages 12-12).  
• A PI5P-site-directed inhibitor serves as an isoform-selective chemical probe (clarke2015thefunctionof pages 9-9).  
• Potent, selective and brain-penetrant tool molecules suitable for in-vivo studies are available (rooney2022theidentificationof pages 18-18).  
• PROTAC TMX-4153 induces selective degradation of PI5P4Kγ in leukemia cells (teng2023targetingthedark pages 5-7).  
• An additional high-affinity chemical probe has been reported (drewry2023identificationofa pages 17-17).

Other Comments  
Copy-number gains and transcriptional up-regulation of PIP4K2C are documented in several cancers, including gallbladder carcinoma (drewry2023identificationofa pages 17-17). Kinase-family studies also associate PIP4K2C genetic variation with oncogenic and autoimmune processes (burke2023beyondpi3kstargeting pages 26-27).

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