## Phylogeny

• Orthologs: Saccharomyces cerevisiae Arg82/Ipk2, Dictyostelium discoideum IpkA/B, Drosophila melanogaster IPMK, Arabidopsis thaliana AtIPMK, Mus musculus Ipmk, Homo sapiens IPMK (shears2019inositolphosphatekinases pages 1-3, saiardi2018microbialinositolpolyphosphate pages 16-21, unknownauthors2009structuralstudiesof pages 18-24).  
• Kinome placement: Atypical protein kinase class, PDKG-InsPK subfamily within the inositol-phosphate-kinase clade (shears2019inositolphosphatekinases pages 3-4).  
• Evolutionary relationship: Yeast, plant and human IPMK catalytic cores superimpose with RMSD ≈1 Å and share the two-lobe protein-kinase fold common to IP3K and IP6K families (unknownauthors2009structuralstudiesof pages 63-69, shears2019inositolphosphatekinases pages 12-17).

## Reaction Catalyzed

Ins(1,4,5)P₃ + ATP → ADP + Ins(1,3,4,5)P₄ (sowd2024ipmkregulateshdac3 pages 1-4)  
Ins(1,3,4,5)P₄ + ATP → ADP + Ins(1,3,4,5,6)P₅ (sowd2024ipmkregulateshdac3 pages 1-4)  
Ins(1,3,4,6)P₄ + ATP → ADP + Ins(1,3,4,5,6)P₅ (unknownauthors2003functionalstudiesof pages 14-18)  
PtdIns(4,5)P₂ + ATP → ADP + PtdIns(3,4,5)P₃ (malabanan2016inositolpolyphosphatemultikinase pages 3-4)

## Cofactor Requirements

Catalysis requires two Mg²⁺ ions that coordinate the nucleotide α-phosphate within the catalytic cleft (wang2017structuralfeaturesof pages 3-5, shears2019inositolphosphatekinases pages 12-17).

## Substrate Specificity

• Broad specificity toward soluble inositol phosphates; highest activity for Ins(1,4,5)P₃ and Ins(1,3,4,5)P₄, with additional turnover of Ins(1,3,4,6)P₄ and Ins(1,4,5,6)P₄ (sowd2024ipmkregulateshdac3 pages 1-4, unknownauthors2003functionalstudiesof pages 14-18).  
• Exhibits lipid 3-kinase activity toward nuclear PtdIns(4,5)P₂ (malabanan2016inositolpolyphosphatemultikinase pages 3-4).  
• Substrate discrimination is conferred by an electropositive pocket in the divergent C-lobe; no peptide consensus motif has been identified, reflecting preference for small inositol substrates (shears2019inositolphosphatekinases pages 1-3, malabanan2016inositolpolyphosphatemultikinase pages 3-4).

## Structure

• Domain organisation: Single kinase domain (residues 50-416) composed of an N-lobe β-sheet with αC-helix and a predominantly α-helical C-lobe connected by a short hinge (wang2017structuralfeaturesof pages 1-2).  
• 3D structures: Human IPMK catalytic core with flavonoid inhibitor (PDB 4O4E, 2.4 Å); yeast IPMK (PDB 2IF8, 2.0 Å); Arabidopsis IPMK (PDB 4FRF) (gu2019inhibitionofinositol pages 6-8, malabanan2016inositolpolyphosphatemultikinase pages 9-13).  
• Catalytic motifs: VAIK Lys75 anchors ATP; HRD Asp144 acts as catalytic base; DFG-like Asp385 chelates Mg²⁺, forming part of the regulatory spine with αC-helix Glu131 (wang2017structuralfeaturesof pages 3-5).  
• Activation segment: Residues 161-190 contain Tyr191, the glucose-regulated phosphorylation site (malabanan2016inositolpolyphosphatemultikinase pages 9-13).  
• Unique elements: “IP loop” and a proline-rich loop reposition Arg82/Gln78 for substrate contact; these inserts are absent from canonical protein kinases (shears2019inositolphosphatekinases pages 3-4, wang2017structuralfeaturesof pages 3-5).  
• AlphaFold model AF-Q8NFU5-F1 reproduces the two-lobe architecture and positions the IP loop consistent with crystal structures (shears2019inositolphosphatekinases pages 3-4).

## Regulation

Post-translational modifications  
• Tyr191 phosphorylation increases after glucose stimulation; Y191F prevents this modification without affecting catalytic turnover (bang2012ampactivatedproteinkinase pages 3-4).  
• Ser/Thr phosphorylation is detected but unchanged by glucose (bang2012ampactivatedproteinkinase pages 2-3).  
• Upstream tyrosine kinase remains unidentified (bang2012ampactivatedproteinkinase pages 3-4).

Allosteric and protein-protein regulation  
• Binding to nuclear receptor SF-1 lowers k\_cat but improves K\_M for PtdIns(4,5)P₂ phosphorylation (malabanan2016inositolpolyphosphatemultikinase pages 9-13).  
• N-terminal residues 1-60 bind mTORC1, stabilising the complex independently of kinase activity (malabanan2016inositolpolyphosphatemultikinase pages 3-4).  
• Phospho-Tyr191 enhances binding to AMPKα2 via regions encoded by exon 4 and exon 6 (bang2012ampactivatedproteinkinase pages 2-3).

## Function

Expression  
• High expression in intestinal ileum and notable levels in spleen and skeletal muscle; localisation in both nucleus and cytoplasm (guha2020lossofpi3kinase pages 6-9).  
• Predominantly nuclear localisation in diverse cell types (unknownauthors2012investigationsofinositol pages 14-20).

Biological roles and interacting partners  
• Epigenetic control: IPMK-derived Ins(1,4,5,6)P₄, InsP₅ and InsP₆ are obligatory cofactors for HDAC3; IPMK knockout elevates histone H4 acetylation (sowd2024ipmkregulateshdac3 pages 4-10).  
• Energy sensing: Phospho-Tyr191 IPMK binds AMPKα2, modulating Thr172 phosphorylation in a glucose-dependent manner (bang2012ampactivatedproteinkinase pages 2-3).  
• Nutrient signalling: N-terminal interaction stabilises mTORC1, coupling amino-acid availability to TOR signalling (malabanan2016inositolpolyphosphatemultikinase pages 3-4).  
• Autophagy initiation: Required for AMPK-dependent ULK1 activation and transcription of autophagy genes during liver regeneration (guha2019ipmkmediatesactivation pages 18-20).  
• Programmed necrosis: InsP₅/InsP₆ produced by IPMK bind MLKL, releasing the N-terminal auto-inhibitory segment (malabanan2016inositolpolyphosphatemultikinase pages 9-13).  
• Transcriptional scaffolding: Yeast Arg82/Ipk2 integrates into the ArgR-Mcm1 complex independent of kinase activity to regulate arginine-responsive genes (unknownauthors2003functionalstudiesof pages 14-18).

## Inhibitors

• Flavonoid derivative “compound 1” (UNC7437): IC₅₀ = 26 ± 1.2 nM against human IPMK; binding mode resolved in PDB 4O4E (gu2019inhibitionofinositol pages 6-8).  
• Second-generation inhibitor UNC9750 (“compound 15”): improved mouse pharmacokinetics and selectively lowers cellular InsP₅ at sub-µM concentrations (zhou2024designsynthesisand pages 3-7).

## Other Comments

• Global Ipmk knockout in mice is embryonic-lethal with neural-tube defects (unknownauthors2009structuralstudiesof pages 18-24).  
• Loss of kinase activity reduces proliferation of PTEN-deficient U251-MG glioblastoma cells (sowd2024ipmkregulateshdac3 pages 1-4).  
• Germline IPMK mutations are associated with small intestinal carcinoid tumours (zhou2024designsynthesisand pages 27-28).

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