## Phylogeny

• Human PIM3 is one of three paralogous PIM kinases and shares 71 % identity with PIM1 and 44 % with PIM2 (atalay2024pim3kinasea pages 2-4).  
• Confirmed orthologs exist in mouse, rat, dog, opossum, platypus, chicken and pufferfish, demonstrating conservation across jawed vertebrates (kong2010acceleratedevolutionof pages 2-2).  
• Additional evidence identifies avian and amphibian homologues, supporting broad vertebrate retention of the Pim3 gene (eichmann2000developmentalexpressionof pages 1-2).  
• All PIM kinases cluster within the CAMK group as a distinct PIM sub-family in the kinome classification of Manning et al. 2002 (manning2002theproteinkinase pages 1-2).

## Reaction Catalyzed

ATP + [protein] ⇌ ADP + [protein]-O-phospho-Ser/Thr (atalay2024pim3kinasea pages 11-13).

## Cofactor Requirements

• Kinase assays routinely include Mg²⁺, indicating functional dependence in vitro (bullock2009crystalstructureof pages 6-7).  
• Structural analyses report catalytic activity without obligatory metal coordination, suggesting partial metal independence (asati2019pimkinaseinhibitors pages 2-3).

## Substrate Specificity

• Johnson 2023 did not profile PIM3; therefore no atlas motif is available (atalay2024pim3kinasea pages 16-17).  
• Classical motif preference is R-x(4)-H-x-P-S/T-G, defined using BAD mutagenesis (li2006pim3aprotooncogene pages 4-5).  
• PIM3 efficiently phosphorylates BAD at Ser112, Ser136 and Ser155, with a bias toward Ser136/155 relative to PIM1/2 (nawijn2011forbetteror pages 7-8).  
• Verified additional substrates include p27 Thr157/Thr198, 4EBP1 Ser65, MYC Ser62/Thr58, IRS1/2 sites, and AMPK-linked sites (atalay2024pim3kinasea pages 8-10).

## Structure

• The protein comprises a single bilobal serine/threonine kinase domain lacking regulatory extensions (atalay2024pim3kinasea pages 2-4).  
• AlphaFold model AF-Q86V86-F1 reproduces the canonical kinase fold with <1.5 Å RMSD to PIM1 (atalay2024pim3kinasea pages 10-11).  
• Surrogate crystal structures PIM1 (PDB 3FXW) and PIM2 (PDB 3CY7) reveal a constitutively active conformation with a Pro in the ERPXPX hinge that removes one ATP hydrogen bond (bullock2009crystalstructureof pages 1-2).  
• Key catalytic residues align with the VAIK-Lys, HRD-Asp and DFG-Asp motifs and an activation loop Asp that mimics phosphorylation (kumar2005crystalstructuresof pages 8-9).  
• The C-helix Lys-Glu salt bridge is weakened, correlating with high intrinsic activity yet elevated Km for ATP (bullock2009crystalstructureof pages 2-3).

## Regulation

• SUMOylation at Lys172 enhances protein stability (atalay2024pim3kinasea pages 10-11).  
• SOCS6- and RNF4-mediated ubiquitination target the kinase for proteasomal degradation (atalay2024pim3kinasea pages 11-13).  
• Transcription is induced by JAK-STAT signaling downstream of IL-5 or GM-CSF, with STAT3/5 promoter binding (atalay2024pim3kinasea pages 16-17).  
• ETS oncogenic fusion proteins further transactivate the PIM3 promoter (atalay2024pim3kinasea pages 16-17).  
• Absence of an autoinhibitory domain renders the enzyme constitutively active once expressed (atalay2024pim3kinasea pages 2-4).

## Function

• Physiological expression occurs in liver, pancreas and hematopoietic tissues (atalay2024pim3kinasea pages 16-17).  
• Tumor overexpression is documented in hepatocellular, pancreatic, colon, gastric, lung, melanoma, glioblastoma and triple-negative breast cancers (atalay2024pim3kinasea pages 4-5).  
• Upstream pathway: JAK-STAT activates transcription; downstream pathway: STAT3 Tyr705 phosphorylation, VEGF induction and EMT factor up-regulation (atalay2024pim3kinasea pages 4-5).  
• BAD phosphorylation releases BCL-XL and blocks apoptosis (li2006pim3aprotooncogene pages 3-3).  
• p27 phosphorylation drives cytoplasmic export and cell-cycle progression (atalay2024pim3kinasea pages 8-10).  
• 4EBP1 phosphorylation stimulates cap-dependent translation and growth (atalay2024pim3kinasea pages 8-10).  
• MYC phosphorylation stabilizes the transcription factor and augments oncogenic transcription (atalay2024pim3kinasea pages 6-8).  
• The kinase modulates AMPK signaling, influencing MYC and PPARGC1A levels (zhang2018pimkinaseas pages 2-4).  
• SOCS6 interaction represses ERK1/2, linking PIM3 to insulin-secretion control (atalay2024pim3kinasea pages 11-13).

## Inhibitors

• SGI-1776: pan-PIM inhibitor, IC₅₀ = 69 nM for PIM3; development stopped after QTc prolongation (atalay2024pim3kinasea pages 10-11).  
• AZD1208: oral pan-PIM inhibitor, IC₅₀ = 1.9 nM for PIM3; discontinued due to limited efficacy and CYP3A4 induction (atalay2024pim3kinasea pages 11-13).  
• PIM447 (LGH447): Ki = 0.009 nM for PIM3; clinically tolerated with modest monotherapy benefit (atalay2024pim3kinasea pages 11-13).

## Other Comments

• Transgenic mice overexpressing Pim3 develop accelerated hepatocellular carcinoma, confirming oncogenic potential (atalay2024pim3kinasea pages 16-17).  
• PIM3 knock-down increases DNA damage markers and enhances radiosensitivity in tumor models (atalay2024pim3kinasea pages 14-16).

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