## Phylogeny

• One of three human Pim kinases (PIM1, PIM2, PIM3); family members are constitutively active serine/threonine protein kinases (le2015targetingpimkinases pages 1-2).  
• Shares 61 % amino-acid identity with PIM1 and ≈55 % with PIM3, underscoring close isoform relatedness (le2015targetingpimkinases pages 1-2, wang2021proteinkinasepim2 pages 1-3).  
• Gene is X-linked and encodes two major isoforms; absence of the C-terminal α-helix makes PIM2 the most divergent family member (nock2023pimkinasesimportant pages 5-6).  
• Orthologs are present in multiple vertebrate species, and functional redundancy with other Pim kinases has been demonstrated in murine systems (warfel2015pimkinase(and pages 1-7).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (le2015targetingpimkinases pages 1-2).

## Cofactor Requirements

• Catalysis is strictly Mg²⁺-dependent; no activating phosphorylation is required (arrouchi2019areviewon pages 2-4).

## Substrate Specificity

• Prefers basic consensus motifs typified by (K/R)₃-X-S/T-X; detailed sequence Lys/Arg-Lys/Arg-Arg-Lys/Arg-Leu-Ser/Thr-Xaa (arrouchi2019areviewon pages 2-4, unknownauthors2023pimkinasea pages 2-4).

## Structure

• Domain organisation: short proline-rich N-terminus followed by a single bilobal kinase domain; no regulatory domains (le2015targetingpimkinases pages 1-2, wang2021proteinkinasepim2 pages 1-3).  
• Active site architecture: conserved Lys67–Glu89 salt bridge, intact DFG motif, and constitutively ordered activation loop; no T-loop phosphorylation required for activity (le2015targetingpimkinases pages 1-2).  
• Hinge region contains Pro123, eliminating one canonical hinge hydrogen bond and widening the ATP pocket—feature exploited for inhibitor selectivity (arrouchi2019areviewon pages 2-4).  
• Crystal structures of Pim1 bound to ATP-competitive inhibitors reveal a conserved overall fold applicable to PIM2; e.g., CX-6258 co-crystal (bogusz2017structuralanalysisof pages 1-2).  
• Isoform variation: 34 kDa and 41 kDa splice products share an identical catalytic core (wang2021proteinkinasepim2 pages 1-3).  
• Structural divergence: PIM2 lacks the C-terminal α-helix present in PIM1, potentially influencing conformational dynamics and inhibitor sensitivity (nock2023pimkinasesimportant pages 5-6).

## Regulation

Post-translational  
• Rapid proteasomal turnover (half-life 5 min–1 h); degradation accelerated by PP2A and counteracted by HSP90/HSP70 chaperones (unknownauthors2019roleofpim pages 20-23).  
• Ubiquitinated under basal conditions yet not targeted for degradation; hypoxia-induced binding of the deubiquitinase USP28 stabilises the kinase (nock2023pimkinasesimportant pages 5-6).  
• Autophosphorylation occurs at Ser121 but is dispensable for catalytic activity (warfel2015pimkinase(and pages 1-7).

Transcriptional / translational  
• Promoter activation by STAT3 and STAT5 downstream of cytokine-driven JAK signalling, and by NF-κB; HIF-1α augments expression under hypoxia (wang2021proteinkinasepim2 pages 1-3, wang2021proteinkinasepim2 pages 3-5).  
• mRNA stability modulated by AU-rich 3′-UTR elements and microRNAs; long GC-rich 5′-UTR limits translation efficiency (unknownauthors2019roleofpim pages 20-23).

## Function

Expression pattern  
• Highest basal expression in thymus, bone-marrow-derived lymphoid cells and brain; low in most resting tissues (le2015targetingpimkinases pages 1-2, unknownauthors2019roleofpim pages 20-23).

Signalling roles  
• Cell-cycle progression: phosphorylates CDK2, p21^CIP1 (Thr145) and p27^KIP1 to drive G₁/S transition (wang2021proteinkinasepim2 pages 1-3).  
• Survival/apoptosis: phosphorylates BAD (Ser112) to release BCL-XL and stabilises MYC via Ser329 phosphorylation, enhancing MYC transcriptional output (warfel2015pimkinase(and pages 16-20, le2015targetingpimkinases pages 1-2).  
• Translational control: phosphorylates eIF4B to promote cap-dependent translation independently of mTORC1 (warfel2015pimkinase(and pages 16-20).  
• Metabolic regulation: phosphorylates PKM2 (Thr454) and HK2 (Ser473) and inhibits AMPKα1, thereby enhancing aerobic glycolysis (wang2021proteinkinasepim2 pages 3-5, unknownauthors2023pimkinasea pages 4-5).  
• Immune modulation: phosphorylates FOXP3, influencing regulatory T-cell function (wang2021proteinkinasepim2 pages 3-5).

## Inhibitors

• First-generation: SMI-4a, SMI-16a (wang2021proteinkinasepim2 pages 1-3).  
• Clinical/pre-clinical: SGI-1776, AZD1208, CX-6258, JP11646, DHPCC-9; PIM2 exhibits lower intrinsic sensitivity than PIM1/PIM3 (warfel2015pimkinase(and pages 1-7, bogusz2017structuralanalysisof pages 1-2, asati2019pimkinaseinhibitors pages 1-2, wang2021proteinkinasepim2 pages 11-12).

## Other Comments

• Over-expression correlates with poor prognosis in diffuse large B-cell lymphoma, multiple myeloma, acute myeloid leukaemia, hepatocellular carcinoma, prostate and colon cancers (asati2019pimkinaseinhibitors pages 1-2, warfel2015pimkinase(and pages 16-20, wang2021proteinkinasepim2 pages 11-12, arrouchi2019areviewon pages 2-4).

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