## Proposed EC/sub-subclass

2.7.11.– (protein-serine/threonine kinase; specific sub-subclass not yet designated)

## Accepted name

Serine/threonine-protein kinase Pim-3

## Synonyms

PIM3

## Phylogeny

Single-copy member of the three-gene vertebrate PIM kinase family; human Pim-3 shares 71 % sequence identity with Pim-1 and 44 % with Pim-2 (Atalay & Ozpolat, 2024). Orthologues are verified in jawed vertebrates including mouse, rat, dog, opossum, platypus, chicken and pufferfish, with additional avian and amphibian homologues, indicating broad conservation across vertebrates (Eichmann et al., 2000; Kong et al., 2010). All PIM kinases form a distinct sub-family within the CAMK group of the eukaryotic kinome (Manning et al., 2002).

## Reaction Catalyzed

ATP + [protein] ⇌ ADP + [protein]-O-phospho-Ser/Thr (Atalay & Ozpolat, 2024).

## Cofactor Requirements

Mg²⁺ is routinely included in in-vitro assays, although structural studies show catalytic activity can proceed without obligatory metal coordination, implying partial metal independence (Bullock et al., 2009; Asati et al., 2019).

## Substrate Specificity

Classic consensus R-x(4)-H-x-P-S/T-G was defined using BAD mutagenesis (Li et al., 2006). Pim-3 phosphorylates BAD on Ser112, Ser136 and Ser155, with preference for Ser136/155 relative to Pim-1/2 (Nawijn et al., 2011). Additional validated sites include p27 Thr157/Thr198, 4EBP1 Ser65, MYC Ser62/Thr58, multiple IRS1/2 sites and AMPK-linked residues (Atalay & Ozpolat, 2024). No high-throughput motif atlas is yet available (Atalay & Ozpolat, 2024).

## Structure

The protein comprises a single bilobal kinase domain lacking N- or C-terminal regulatory extensions (Atalay & Ozpolat, 2024). AlphaFold model AF-Q86V86-F1 superposes on Pim-1 with <1.5 Å RMSD (Atalay & Ozpolat, 2024). Surrogate crystal structures of Pim-1 (PDB 3FXW) and Pim-2 (PDB 3CY7) reveal a constitutively active conformation in which a Pro in the ERPXPX hinge removes one ATP hydrogen bond (Bullock et al., 2009). Catalytic motifs VAIK-Lys, HRD-Asp and DFG-Asp are conserved; an activation-loop Asp mimics phospho-activation (Kumar et al., 2005). A weakened C-helix Lys-Glu salt bridge correlates with high intrinsic activity but elevated Km for ATP (Bullock et al., 2009).

## Regulation

• SUMOylation at Lys172 stabilises the protein (Atalay & Ozpolat, 2024).  
• SOCS6- and RNF4-dependent ubiquitination promotes proteasomal degradation (Atalay & Ozpolat, 2024).  
• Transcription is induced by JAK–STAT signalling (IL-5, GM-CSF) via STAT3/5, and further trans-activated by ETS fusion oncogenes (Atalay & Ozpolat, 2024).  
• Lack of an autoinhibitory domain renders the kinase constitutively active once expressed (Atalay & Ozpolat, 2024).

## Function

Physiological expression is enriched in liver, pancreas and haematopoietic tissues (Atalay & Ozpolat, 2024). Over-expression is reported in hepatocellular, pancreatic, colon, gastric, lung, melanoma, glioblastoma and triple-negative breast cancers (Atalay & Ozpolat, 2024). Upstream pathway: JAK–STAT transcriptional activation. Downstream effects include STAT3 Tyr705 phosphorylation, VEGF induction and EMT factor up-regulation (Atalay & Ozpolat, 2024). Substrate phosphorylation events mediate:  
• BAD inactivation → inhibition of apoptosis (Li et al., 2006)  
• p27 cytoplasmic export → cell-cycle progression (Atalay & Ozpolat, 2024)  
• 4EBP1 activation → cap-dependent translation (Atalay & Ozpolat, 2024)  
• MYC stabilisation → enhanced oncogenic transcription (Atalay & Ozpolat, 2024)  
• Modulation of AMPK signalling affecting MYC and PPARGC1A (Zhang et al., 2018)  
Interaction with SOCS6 links Pim-3 to control of ERK1/2 and insulin secretion (Atalay & Ozpolat, 2024).

## Inhibitors

• SGI-1776: pan-PIM inhibitor, IC₅₀ = 69 nM; clinical development halted due to QTc prolongation (Atalay & Ozpolat, 2024).  
• AZD1208: oral pan-PIM inhibitor, IC₅₀ = 1.9 nM; discontinued after limited efficacy and CYP3A4 induction (Atalay & Ozpolat, 2024).  
• PIM447 (LGH447): Ki = 0.009 nM; clinically tolerated with modest monotherapy benefit (Atalay & Ozpolat, 2024).

## Other Comments

Transgenic mice over-expressing Pim-3 develop accelerated hepatocellular carcinoma, confirming oncogenic potential; conversely, Pim-3 knock-down increases DNA-damage markers and radiosensitivity in tumour models (Atalay & Ozpolat, 2024).

## References

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