## Phylogeny

The PIM kinase family belongs to the CAMK (Ca²⁺/calmodulin-dependent protein kinase) group of the human kinome on the basis of catalytic-domain sequence homology and phylogenetic analysis (Manning et al., 2002).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Bogusz et al., 2017; Bullock et al., 2009; Zhang et al., 2018).

## Cofactor Requirements

Mg²⁺ (Bogusz et al., 2017; Bullock et al., 2009; Iyer et al., 2017).

## Substrate Specificity

PIM1 shows a strong preference for substrates that contain a basic residue three positions N-terminal to the phosphorylation site, with Arg at P-3 being a defining determinant (Johnson et al., 2023).

## Structure

PIM1 adopts the canonical bi-lobed protein-kinase fold with an N-terminal β-sheet-rich lobe (residues 37–122) and a predominantly α-helical C-terminal lobe (residues 126–305) joined by a short hinge (residues 123–125). The ATP pocket is bordered by a glycine-rich loop (residues 44–52) and an activation segment (residues 185–204). Key elements include the C-helix, DFG motif and a hydrophobic spine (Bullock et al., 2009; Bogusz et al., 2017). A unique Pro123 in the hinge substitutes for the usual main-chain hydrogen-bond donor, altering ATP interactions (Bogusz et al., 2017; Kumar et al., 2005; Merkel et al., 2012). Crystal structures show PIM1 in a constitutively active conformation that does not require activation-loop phosphorylation (Bullock et al., 2009; Merkel et al., 2012).

## Regulation

Enzymatic activity is constitutive; control occurs mainly through transcription and protein stability (Bogusz et al., 2017; Unknown authors, 2019). Cytokine- and growth-factor-driven JAK-STAT and NF-κB pathways up-regulate PIM1 expression (Bogusz et al., 2017). The protein has a short half-life (< 5 min) and is degraded via the ubiquitin–proteasome system; Hsp90 stabilises whereas Hsp70 promotes degradation (Merkel et al., 2012). PP2A-mediated dephosphorylation enhances ubiquitylation and turnover (Merkel et al., 2012; Nock et al., 2023). Autophosphorylation may aid stability, and phosphorylation at Tyr218 by ETK increases catalytic activity (Merkel et al., 2012).

## Function

PIM1 is a proto-oncogenic serine/threonine kinase that supports cell survival and proliferation. It is normally expressed at low levels but is frequently over-expressed in haematopoietic and several solid tumours (Bogusz et al., 2017; Bullock et al., 2009).  
Major substrates and downstream effects:  
• MYC (Ser62, Ser329) – stabilisation and enhanced transcriptional activity (Bogusz et al., 2017; Zhang et al., 2018).  
• BAD (Ser112) and ASK1 – inhibition of apoptosis (Bullock et al., 2009; Merkel et al., 2012).  
• p21^Cip1/WAF1, Cdc25A, histone H3 (Ser10) – promotion of cell-cycle progression (Bullock et al., 2009; Unknown authors, 2021).  
• PRAS40 – modulation of mTOR signalling (Merkel et al., 2012).  
• ABC transporters (e.g., BCRP/ABCG2) – contribution to drug resistance (Merkel et al., 2012; Lee et al., 2013).

## Inhibitors

Most reported inhibitors are ATP-competitive and recognise the active ATP pocket (Merkel et al., 2012; Bogusz et al., 2017). Compounds that have progressed to clinical trials include SGI-1776, AZD1208 and LGH447 (Zhang et al., 2018; Unknown authors, 2015). CX-6258 is a potent pan-PIM/Flt-3 inhibitor (Bogusz et al., 2017). Additional chemotypes encompass imidazo[1,2-b]pyridazines, organoruthenium complexes and pyridones (Bullock et al., 2009; Lee et al., 2013). Off-target inhibitors with significant PIM1 activity include CX-4945, Ro-3306 and LY294002 (Bogusz et al., 2017; Unknown authors, 2009).

## Other Comments

PIM1 was originally identified as a proviral integration site for Moloney leukaemia virus and cooperates with MYC to accelerate tumorigenesis. Over-expression correlates with poor prognosis and chemoresistance in acute myeloid/lymphoid leukaemias, diffuse large B-cell lymphoma and prostate, breast and pancreatic cancers (Bogusz et al., 2017; Zhang et al., 2018). Aberrant somatic hypermutations are reported in non-Hodgkin’s lymphoma (Kumar et al., 2005). The mild phenotype of Pim1-knockout mice suggests an acceptable therapeutic window for pharmacological inhibition (Bogusz et al., 2017).

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