## Phylogeny

MAST4 belongs to the MAST subfamily within the AGC serine/threonine kinase superfamily and is one of four mammalian paralogs (MAST1-4) that diverged early from the MAST-like (MASTL) lineage (lemke2025mastkinases’function pages 2-4). Orthologous tri-domain MAST kinases (DUF1908-kinase-PDZ) are conserved in invertebrates, including the Drosophila homolog Dop and related worm kinases, while protist and plant precursors retain only the DUF1908 domain (lemke2025mastkinases’function pages 4-6, rumpf2023microtubuleassociatedserinethreonine(mast) pages 14-16). Sequence analysis places MAST4 closest to MAST3; all four human paralogs share identical catalytic core motifs and an extended activation segment (~37 aa) (lemke2025mastkinases’function pages 17-18).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (sakaji2023mast4promotesprimary pages 3-5, rumpf2023microtubuleassociatedserinethreonine(mast) pages 1-2).

## Cofactor Requirements

Catalysis requires a divalent metal ion coordinated by the DFG^522-524 loop; Mg²⁺ has been demonstrated for related AGC kinases and inferred for MAST4 (sakaji2023mast4promotesprimary pages 3-5, rumpf2023microtubuleassociatedserinethreonine(mast) pages 1-2).

## Substrate Specificity

Experimentally validated substrates  
• Dynein light-chain Tctex-1, Thr94 (sakaji2023mast4promotesprimary pages 1-2).  
• FOXO3 transcription factor, regulatory Ser/Thr sites leading to inactivation (fujiwaratani2024nuclearmast4suppresses pages 5-8).  
• Sox9 transcription factor, Ser494 (lemke2025mastkinases’function pages 6-8).  
A consensus phosphorylation motif for MAST4 has not been defined; large-scale mapping studies have yet to report a preferred sequence context (lemke2025mastkinases’function pages 12-14).

## Structure

Domain organisation (2 434 aa) (sakaji2023mast4promotesprimary pages 2-3)  
N-terminal DUF1908 (regulatory/interaction) – central AGC kinase domain – C-terminal PDZ domain, flanked by intrinsically disordered regions (lemke2025mastkinases’function pages 17-18).  
Key catalytic elements  
• RD motif R503-D504-K^506 (catalysis) (sakaji2023mast4promotesprimary pages 3-5).  
• DFG^522-524 loop (metal binding) (sakaji2023mast4promotesprimary pages 3-5).  
• Autophosphorylation site Thr^535 in the activation segment (sakaji2023mast4promotesprimary pages 3-5).  
3-D architecture  
AlphaFold modeling shows a canonical bilobal kinase fold with an extended activation loop and conserved hydrophobic spine; domain alignments reveal near-identity of the ATP pocket across MAST1-4 (karpov2024predictionofproteinligand pages 1-2, lemke2025mastkinases’function pages 4-6). Pocket mapping identifies multiple conserved ligandable surfaces beyond the ATP cleft (karpov2024predictionofproteinligand pages 2-5). The DUF domain folds into an α-helical barrel predicted to mediate protein interactions (lemke2025mastkinases’function pages 4-6).

## Regulation

Post-translational modifications  
• Autophosphorylation at Thr^535 is required for full catalytic activity (sakaji2023mast4promotesprimary pages 3-5).  
• Multiple phospho-Ser/Thr sites in the DUF1908 and C-terminal regions create docking motifs for 14-3-3 proteins identified in interactome data (lemke2025mastkinases’function pages 8-11).  
Transcriptional / post-transcriptional control  
• miR-582-5p directly represses MAST4 mRNA; reduced miR-582-5p elevates MAST4 in gemcitabine-resistant pancreatic cancer cells (fujiwaratani2024nuclearmast4suppresses pages 5-8).  
Subcellular localisation  
• Serum stimulation targets MAST4 to basal bodies and axonemes in ciliated cells (sakaji2023mast4promotesprimary pages 6-7).  
• In gemcitabine-resistant PDAC cells, MAST4 accumulates in the nucleus and complexes with AKT3 (fujiwaratani2024nuclearmast4suppresses pages 9-12).

## Function

Expression pattern  
MAST4 exhibits the lowest baseline expression among MAST paralogs; protein is detectable in cytoplasm of brain, esophagus and bladder epithelia and in ciliated retinal pigment epithelial cells (lemke2025mastkinases’function pages 6-8). Nuclear over-expression is observed in pancreatic ductal adenocarcinoma (fujiwaratani2024nuclearmast4suppresses pages 8-9).  
Biological roles  
• Ciliary dynamics: phosphorylates Tctex-1 to activate Cdc42 and Rab5, driving serum-induced primary ciliary resorption during G1-S and G2-M transitions (sakaji2023mast4promotesprimary pages 6-7).  
• Chemoresistance: nuclear MAST4 interacts with AKT3, enhances FOXO3 phosphorylation and promotes gemcitabine resistance in PDAC cells (fujiwaratani2024nuclearmast4suppresses pages 5-8, fujiwaratani2024nuclearmast4suppresses pages 9-12).  
• Skeletal differentiation: phosphorylates Sox9 Ser494, leading to its degradation and favouring osteogenic differentiation of mesenchymal stromal cells (lemke2025mastkinases’function pages 6-8).  
Interactome highlights  
Tctex-1, AKT3, FOXO3, 14-3-3 proteins, Cdc42, Rab5 (sakaji2023mast4promotesprimary pages 6-7, fujiwaratani2024nuclearmast4suppresses pages 5-8, lemke2025mastkinases’function pages 8-11).

## Inhibitors

AX13587 inhibits MAST4 kinase activity in cell-based assays, reducing phosphorylation of AKT3 and FOXO3 and restoring gemcitabine sensitivity in pancreatic cancer models (fujiwaratani2024nuclearmast4suppresses pages 8-9). Structural analysis shows the ATP pocket is highly conserved across MAST kinases, potentially limiting selectivity of ATP-competitive compounds (karpov2024predictionofproteinligand pages 2-5).

## Other Comments

Disease associations  
• High nuclear MAST4 correlates with poor overall survival and chemoresistance in pancreatic ductal adenocarcinoma (fujiwaratani2024nuclearmast4suppresses pages 8-9).  
• MAST4 up-regulation contributes to osteolytic lesions in multiple myeloma via estrogen-responsive signalling (lemke2025mastkinases’function pages 6-8).  
• Point mutation I898T in the catalytic hydrophobic-motif is linked to neurodevelopmental disability and predicts reduced kinase activity (lemke2025mastkinases’function pages 11-12).  
• Co-over-expression of MAST4 and Tctex-1 has been reported in breast cancer (sakaji2023mast4promotesprimary pages 7-8).  
• Impaired ciliary disassembly due to loss of MAST4 activity is implicated in ciliopathy-related pathologies (sakaji2023mast4promotesprimary pages 1-2).

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