## Phylogeny

AAK1 is a serine/threonine kinase assigned to the numb-associated kinase (NAK) family within the human kinome (wells2019achemicalprobe pages 6-7).  
Within this family it shares 50 % overall and 74 % kinase-domain identity with its closest paralog BMP2K/BIKE (wells2019achemicalprobe pages 1-2).  
Vertebrate orthologs are documented in mouse, rat and zebrafish (huang2023currentthoughtson pages 1-3).  
Invertebrate counterparts include Drosophila melanogaster NAK and Caenorhabditis elegans SEL-5 (huang2023currentthoughtson pages 1-3).  
Fungal homologs Ark1 and Prk1 from Saccharomyces cerevisiae show ~38 % identity to the human kinase domain, reflecting an evolutionarily conserved endocytic kinase lineage (huang2023currentthoughtson pages 1-3).  
AAK1 was originally isolated as an Ark-related kinase that binds the α-adaptin ear domain (conner2002identificationofan pages 2-3).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-L-Ser/Thr-phosphate (conner2002identificationofan pages 6-7).

## Cofactor Requirements

Enzymatic assays were performed in the presence of Mg²⁺, indicating a requirement for divalent magnesium ions (agajanian2019wntactivatesthe pages 22-23).

## Substrate Specificity

Phosphoproteomic profiling defined a preference for threonine within motifs containing a hydrophobic residue at −3 and a small residue at +1 (johnson2023anatlasof pages 4-5).  
The canonical I/L-X-X-Q-X-T-G motif was derived from the AP2M1 Thr156 site (conner2002identificationofan pages 7-7).  
Validated cellular targets include AP2M1 Thr156, AP1M1 Thr154 and NUMB Thr102 (huang2023currentthoughtson pages 3-4).

## Structure

AAK1 contains an N-terminal bilobal kinase domain (~residues 25–396), a glutamine/proline/alanine-rich middle segment and a C-terminal region with DPF, NPF and DLL motifs that bind adaptor proteins and clathrin (conner2002identificationofan pages 2-3).  
Crystal structures of the kinase domain (e.g., PDB 4WSQ) reveal a canonical active site with a Lys49-Glu65 salt bridge, an ordered activation loop and a complete regulatory spine (yoshida2024developmentofa pages 5-7).  
Co-crystal complexes with 3-acylaminoindazole probes show an active C-helix orientation and classical hinge interactions (wells2019achemicalprobe pages 6-7).  
Docking of TIM-098a demonstrates hydrogen bonds to Cys129 and Gln133 and hydrophobic contact with Leu52 in the ATP pocket, rationalising selectivity (yoshida2024developmentofa pages 5-7).

## Regulation

AAK1 undergoes autophosphorylation and displays a reversible phosphorylation cycle in nerve terminals (conner2002identificationofan pages 3-5).  
Association with assembled clathrin allosterically activates the kinase and enhances AP2M1 phosphorylation (abdelmagid2017inhibitorsofadaptorassociated pages 1-2).  
WNT stimulation of LRP6 activates AAK1, establishing a negative feedback loop on β-catenin signalling (agajanian2019wntactivatesthe pages 22-23).  
C-terminal DPF/NPF motifs engage the α-adaptin ear domain, recruiting AAK1 to nascent clathrin-coated pits (conner2002identificationofan pages 3-5).

## Function

AAK1 is broadly expressed and enriched at presynaptic terminals and the leading edge of migrating HeLa cells (conner2002identificationofan pages 3-5).  
Phosphorylation of AP2M1 Thr156 stabilises the open+ conformation of AP-2, increases affinity for YxxΦ sorting motifs and accelerates clathrin-mediated endocytosis (siao2023phosphorylationofadaptor pages 1-4).  
AAK1 phosphorylates NUMB Thr102, redirecting NUMB to endosomes and modulating Notch signalling (huang2023currentthoughtson pages 3-4).  
Interaction with LRP6 and subsequent phosphorylation promote LRP6 internalisation, attenuating canonical WNT/β-catenin signalling (agajanian2018aak1inhibitswnt pages 1-5).  
The kinase functions as a host factor for hepatitis C, dengue, Ebola and SARS-CoV-2, facilitating adaptor-dependent viral entry (huang2023currentthoughtson pages 5-6).

## Inhibitors

SGC-AAK1-1 inhibits AAK1 with a biochemical IC50 of 31 nM and possesses narrow kinome selectivity (wells2019achemicalprobe pages 1-2).  
TIM-098a shows an in-vitro IC50 of 0.24 µM and suppresses cellular AP2M1 phosphorylation with an IC50 of 0.87 µM (yoshida2024developmentofa pages 1-2).  
Multi-target kinase inhibitors such as sunitinib and baricitinib inhibit AAK1 and display antiviral efficacy against SARS-CoV-2 (huang2023currentthoughtson pages 5-6).

## Other Comments

AAK1 knockout mice are resistant to neuropathic pain, underscoring analgesic potential for AAK1 inhibition (abdelmagid2017inhibitorsofadaptorassociated pages 1-2).  
Polymorphisms in AAK1 are associated with earlier Parkinson’s disease onset (abdelmagid2017inhibitorsofadaptorassociated pages 1-2).  
AAK1 dysfunction is implicated in amyotrophic lateral sclerosis and bipolar disorder (wells2019achemicalprobe pages 6-7).  
Inhibition of AAK1-dependent endocytosis mitigates amyloid-β-induced axonal degeneration in Alzheimer’s disease models (abdelmagid2017inhibitorsofadaptorassociated pages 2-3).

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