## Phylogeny

• Member of the GRK4 subfamily (GRK4, GRK5, GRK6) within the AGC serine/threonine kinase superfamily (gurevich2012gproteincoupledreceptor pages 2-4, homan2014structuralinsightsinto pages 1-2).  
• Orthologs documented in human (GRK6), mouse (Grk6) and rat (Grk6); these species are routinely used in comparative GRK lineage studies (komolov2018gproteincoupledreceptor pages 14-15, gurevich2012gproteincoupledreceptor pages 27-28).  
• Diverges from the GRK2/3 branch by lacking a pleckstrin-homology domain and by being insensitive to Gβγ subunits (gurevich2012gproteincoupledreceptor pages 13-15).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-L-Ser/Thr-phosphate (cato2021theopenquestion pages 2-4).

## Cofactor Requirements

No divalent-cation dependence is explicitly reported in the referenced sources (gurevich2012gproteincoupledreceptor pages 2-4).

## Substrate Specificity

• Efficiently phosphorylates Ser/Thr residues located in the third intracellular loop or C-terminal tail of agonist-occupied GPCRs (chaudhary2020roleofgrk6 pages 1-3, pitcher1998gprotein–coupledreceptor pages 3-5).  
• Peptide library screening indicates preference for basic residues immediately N-terminal to the phospho-acceptor (Komolov2018gproteincoupledreceptor pages 3-4).  
• Catalytic efficiency is markedly higher for full-length activated receptors than for isolated peptides, underscoring receptor-driven allosteric activation (komolov2018gproteincoupledreceptor pages 3-4).  
• Documented physiological substrates include D₂-like dopamine receptors, CXCR4, P2Y1, P2Y12, PAR4 and BLT1 (gurevich2012gproteincoupledreceptor pages 25-27, chaudhary2020roleofgrk6 pages 1-3).

## Structure

• Domain organisation: N-terminal basic amphipathic helix (~20 aa) required for receptor/phospholipid engagement; regulator of G-protein signalling homology (RH) domain (~140 aa) that scaffolds the kinase core; bilobal kinase domain (~270 aa) related to PKA but active without activation-loop phosphorylation; C-terminal amphipathic helix harbouring palmitoylation sites that drive membrane anchoring (homan2014structuralinsightsinto pages 1-2, cato2021theopenquestion pages 2-4).  
• Crystal structures capture two conformational states:  
– Open, inactive apo form with an extensive RH-domain dimer interface (komolov2018gproteincoupledreceptor pages 14-15).  
– Closed, active-like form bound to the adenosine analogue sangivamycin that orders the N-terminal α-helix and the active-site-tether (AST) loop (cato2021theopenquestion pages 2-4).  
• A sulfate anion observed in the catalytic cleft maps a basic pocket proposed to cooperate with PIP₂ during membrane docking (homan2014structuralinsightsinto pages 5-6).  
• The activation loop adopts a catalytically competent alignment without phosphorylation, consistent with the GRK family mechanism (homan2014structuralinsightsinto pages 1-2).  
• The C-terminal helix toggles between membrane insertion and packing against the small lobe to stabilise the active conformation (homan2014structuralinsightsinto pages 5-6).

## Regulation

• Membrane association is mediated by electrostatic contacts of the N-terminal helix with anionic phospholipids (PIP₂, phosphatidylserine) and by palmitoylated residues in the C-terminal helix (cato2021theopenquestion pages 2-4, homan2014structuralinsightsinto pages 1-2).  
• Agonist-bound GPCRs serve as allosteric activators, triggering kinase-domain closure even in the absence of receptor phospho-acceptor sites (cato2021theopenquestion pages 2-4).  
• GRK6 is not activated by Gβγ subunits, distinguishing it from GRK2/3 (gurevich2012gproteincoupledreceptor pages 13-15).  
• Ca²⁺·calmodulin modulates kinase activity, although precise mechanistic details remain unresolved (cato2021theopenquestion pages 2-4).

## Function

• Expression: ubiquitous; predominant GRK isoform in adult rat brain and abundantly expressed in platelets and hematopoietic cells (gurevich2012gproteincoupledreceptor pages 27-28, chaudhary2020roleofgrk6 pages 1-3).  
• Platelet signalling: limits Gq- and Gi-mediated aggregation; Grk6⁻/⁻ mice exhibit enhanced Akt, ERK and PKCδ phosphorylation, potentiated aggregation and shortened bleeding times (chaudhary2020roleofgrk6 pages 1-3).  
• Immune regulation: restrains CXCR4-dependent neutrophil retention and dampens chemokine-driven acute inflammation; knockout exacerbates experimental colitis with elevated granulocyte infiltration (gurevich2012gproteincoupledreceptor pages 25-27).  
• Neuromodulation: contributes to desensitisation of D₂-like dopamine receptors in striatum (gurevich2012gproteincoupledreceptor pages 27-28).  
• Mechanistic outcome: receptor phosphorylation promotes β-arrestin recruitment, terminating G-protein signalling and initiating receptor internalisation (chaudhary2020roleofgrk6 pages 1-3, cato2021theopenquestion pages 2-4).

## Inhibitors

• Sangivamycin and related adenosine analogues bind the ATP pocket and stabilise the closed conformation in crystal structures; biochemical potency against GRK6 was not quantified in the cited work (cato2021theopenquestion pages 2-4).  
• No selective, cell-permeable GRK6 inhibitors have been reported in peer-reviewed literature (komolov2018gproteincoupledreceptor pages 3-4).

## Other Comments

• Grk6⁻/⁻ mice display heightened thrombus formation, indicating an antithrombotic role for the kinase (chaudhary2020roleofgrk6 pages 1-3).  
• Dysregulated GRK6 expression has been associated with heart failure, depression and Parkinson’s disease in broader GRK surveys (gurevich2012gproteincoupledreceptor pages 1-2).

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