## Phylogeny

Aurora kinase C (AURKC) belongs to the Aurora sub-family within the CMGC group of the human kinome. It clusters most closely with its paralogue AURKB and more distantly with AURKA (Vats et al., 2025; Moura, 2016). Orthologues have been reported in Mus musculus, Rattus norvegicus, Danio rerio and Xenopus laevis, whereas a single ancestral Ipl1 fulfils the Aurora role in Drosophila melanogaster and Saccharomyces cerevisiae (Willems et al., 2018; Vats et al., 2025).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (Unknown Authors, 2021).

## Cofactor Requirements

Catalysis requires divalent Mg²⁺ or Mn²⁺ ions (Abdul Azeez et al., 2019).

## Substrate Specificity

AURKC prefers the motif R/K/N-X-S/T-Φ (Φ = hydrophobic residue), resembling AURKB preference (Abdul Azeez et al., 2019). Verified cellular substrates include histone H3 S10/S28, INCENP S893/S894, BIRC5/Survivin, and TACC1 S228 (Abdul Azeez et al., 2019; Sarı & Özsoy, 2024).

## Structure

The protein comprises a short N-terminal segment (~1–38 aa), a bilobal catalytic domain (39–290 aa) and a C-terminal tail with an internal RxxL D-box (291–306 aa) (Vats et al., 2025). Crystal structures of fully active human AURKC bound to phosphorylated INCENP (PDB 6GR8, 6GR9; 1.75 Å) reveal an ordered activation loop in the DFG-in state, with pThr198 anchored by three arginines (Abdul Azeez et al., 2019). The INCENP TSSxxW motif embraces both faces of the αC helix; Trp897 stacks against His97 and His190, completing the regulatory spine. Lack of Met249 prevents the domain-swap dimer seen in AURKB, favouring a monomeric configuration (Abdul Azeez et al., 2019).

## Regulation

• Autophosphorylation on Thr198 is essential for activity (Abdul Azeez et al., 2019).  
• Binding of phosphorylated INCENP (S893/S894) re-orders the αC helix and hydrophobic spine, markedly increasing k\_cat; alanine substitution at either site elevates K\_M and lowers catalytic efficiency (Abdul Azeez et al., 2019).  
• PLK1 controls Chromosomal Passenger Complex (CPC) localisation, thereby influencing spatial activation of AURKC during cell division (Santos et al., 2011).  
• Methylation of INCENP Arg887 weakens binding and down-regulates kinase activity (Abdul Azeez et al., 2019).  
• An internal RxxL D-box (but no KEN or DAD/A motifs) suggests APC/C-Cdh1-mediated proteolysis distinct from AURKA/B (Vats et al., 2025; Lindon et al., 2016).  
• Allosteric activation is achieved through binding of phosphorylated INCENP, which locks the kinase in the active conformation (Abdul Azeez et al., 2019).

## Function

AURKC is most abundant in testis germ cells, with lower basal expression in placenta, lung, bladder and skeletal muscle (Sarı & Özsoy, 2024). As the catalytic core of the CPC (with INCENP, BIRC5 and CDCA8), it governs chromosome alignment, kinetochore–microtubule attachment, spindle-assembly checkpoint function and cytokinesis in mitosis and meiosis (Unknown Authors, 2021; Goldenson & Crispino, 2015). AURKC is largely redundant with AURKB and can compensate for AURKB loss in mitotic cells (Goldenson & Crispino, 2015). Downstream phosphorylation of histone H3 facilitates chromatin condensation, while phosphorylation of TACC1 promotes spindle stability, supporting faithful chromosome segregation (Sarı & Özsoy, 2024; Abdul Azeez et al., 2019).

## Inhibitors

• VX-680 (tozasertib): IC₅₀ = 4.6 nM; crystal structure shows ATP-site binding that partially disrupts INCENP contacts (Kovacs et al., 2023; Abdul Azeez et al., 2019).  
• BRD-7880: nanomolar affinity for Aurora B/C; binds the hinge region while preserving the INCENP interface, retaining the active conformation (Abdul Azeez et al., 2019).  
• CCT137690: IC₅₀ = 19 nM (Kovacs et al., 2023).

## Other Comments

Germline mutations Y248*, W279* and c.T1093C in AURKC cause macrozoospermia and male infertility (Sarı & Özsoy, 2024; Santos et al., 2011; Moraes et al., 2024). Over-expression of AURKC has been detected in several epithelial cancers, suggesting oncogenic potential (Sarı & Özsoy, 2024).

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