Chemical Inhibition of Protein Kinase D

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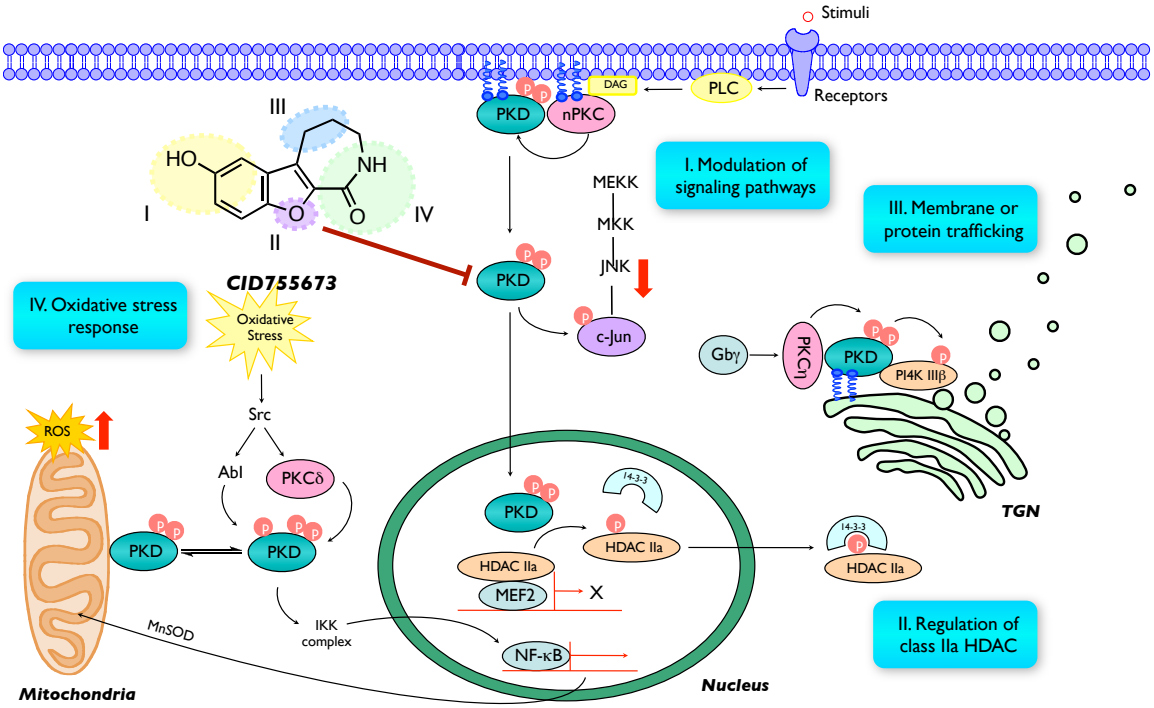
Protein kinase D (PKD) is a family of serine/threonine kinases related to PKC. Three isoforms, PKD1, PKD2, and PKD3, form a key component of the diacylglycerol network. This signaling pathway plays a critical role in the regulation of important cellular processes, including DNA synthesis, proliferation, survival, adhesion, invasion/migration, motility, and angiogenesis. PKD signaling has been implicated in human pancreatic, breast, lung, and prostate cancer. Further, emerging evidence suggests that different PKD isoforms may be associated with specific cancers. For example, PKD1 and PKD2 are up-regulated in pancreatic cancer, PKD3 is more closely associated with prostate cancer, and PKD2 signaling has been linked with glioblastoma.



Over the past 5 years, our lab has focused on the design and synthesis of small molecule pan-PKD inhibitors.[1] Specifically, we have developed efficient synthetic routes to 5 distinct inhibitory chemotypes, and several of these have been tested in cancer xenograft animal models. We are currently pursuing the design and synthesis of PKD subtype-selective inhibitors.

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[1] Tandon, M.; Johnson, J.; Li, Z.; Xu, S.; Wipf, P.; Wang, Q. J., "New pyrazolopyrimidine inhibitors of protein kinase D as potent anticancer agents for prostate cancer cells." *PLoS One* **2013**, 8, e75601.