Enabling Structure-Based Drug Discovery For NUAK Kinases

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Novel (nua) kinase (NUAK1 and NUAK2) are serine/threonine kinases belonging to the AMPK family. Despite the rich history of structural biology around other AMPK kinases (AMPK, MARK, BRSK, MELK, etc.) there are no publicly available structures for NUAKs. NUAKs are implicated in the progression of neurodegenerative tauopathies and multiple cancers making them attractive targets for drug discovery. Development of robust structure-based drug discovery systems for NUAK kinases necessitated extensive protein characterization efforts. These included limited proteolysis, HDX-mass spectrometry, phosphorylation mapping, tool compound screening, and purification development to obtain homogenous and thermostabilized NUAK1 and NUAK2. Here we report the kinase domain crystal structures of phosphorylated human NUAK1 and dephosphorylated human NUAK2, both in complex with an orthosteric small molecule inhibitor. Structural comparisons between the NUAKs and the other AMPK family kinases are explored.