UCMERCED | CHEMISTRY & BIOCHEMISTRY

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# CHEMISTRY & BIOCHEMISTRY SEMINAR SERIES:

## Using Temperature Perturbation to Reveal Unique Conformations of Cdk2 and Study the Structural Dynamics of Gatekeeper Mutants


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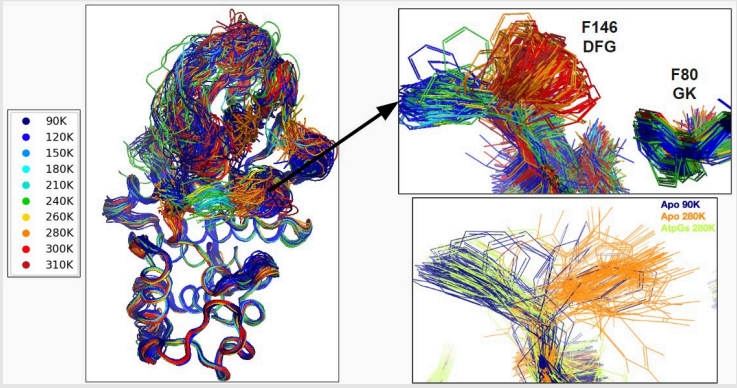



## Abstract:

Cyclin-dependent kinase 2 (Cdk2) is one of the key proteins which controls cell cycle progression and has long been a target for cancer drug development. Historically, development of selective Cdk inhibitors has been difficult due to the high structural similarity between different Cdks. In the case of Cdk2 specifically, its high sequence and structural homology with Cdk1 has led to inhibitors with poor selectivity, which can lead to toxicity and off-target effects. Furthermore, while inhibitors targeting other Cdks have proven to be effective cancer therapeutics, mutations in conserved regulatory regions of the target kinase can lead to the emergence of drug resistant cancers. For example, so-called “gatekeeper” mutations alter residues that control access to the nucleotide binding pocket commonly targeted by kinase inhibitors, leading to loss of inhibitor efficacy. Our goal is to characterize the conformational landscapes of wild type Cdk2 and two gatekeeper mutants (F80L and F80G) in order to overcome these challenges associated with Cdk2 inhibition. We aim to identify unique conformations of wild type Cdk2 that are not well represented at equilibrium, but might present structural features that can be selectively targeted in Cdk2 over other related Cdks. Additionally, we seek to understand how gatekeeper mutations change the conformational landscape of Cdk2 and impact the affinity of different types of inhibitors. This information has the potential to help facilitate the development of Cdk2 inhibitors that avoid loss of affinity due to mutations in this conserved kinase region.


## About the Speaker:

Alexander is a third year PhD candidate in the department of Chemistry and Biochemistry at UC Merced. He received his Bachelors of Science in Biochemistry from UC San Diego where he worked in the Paesani Research Group on a data-driven, many-body computational model for predicting the hydration structure of group 1 ions. He also previously conducted research on G-protein Coupled Receptors at The Bridge Institute at USC, working under Raymond Stevens. While there he studied the allosteric effects linking sodium and other cation binding to GPCR signal transduction.