

Department of Chemistry & Biochemistry

SEMINAR

**“Engineering kinases to phosphorylate nucleoside analogs
for antiviral and cancer therapy”**

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Abstract: Nucleoside analogs (NAs) represent an important category of prodrugs for the treatment of viral infections and cancer, yet their biological potency is compromised by inefficient activation through cellular 2'-deoxyribonucleoside kinases. The problem can be address by coadministration of novel NA kinases, engineered to effectively and selectively phosphorylate the prodrugs. In two separate experiments, we applied directed evolution and computational enzyme design by Rosetta Design software to generate orthogonal NA kinases. Both strategies yielded kinase variants with improved activity and overall 10,000-fold change in substrate specificity. Intriguingly, the two approaches found distinct solutions, highlighting some of their advantages and limitations to enzyme engineering. Together, the two experiments identified a small number of key active site residues which define the enzyme's binding specificity for the sugar moiety of the nucleoside substrate, guiding future engineering of selective kinase:NA pairs and providing valuable insight into the structure–function relationship in these kinases.

Date: Friday February 11th, 2011

Time: 11:00 am

Location: Wertheim - WC130

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