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Disrupting HIV Nucleocapsid Protein with Mercaptobenzamides

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Simple mercaptobenzamide derivatives inactivate the nucleocapsid protein, NCp7, of HIV-1 via a unique mechanism of intracellular acetylation. The protein NCp7 is a small protein that contains 55 amino acids and consists of two zinc-finger motifs that bind to oligonucleotides. There are a number of regulatory roles for NCp7 in the HIV lifecycle, but the principle functions are to bind viral RNA, protect it from degradation, and facilitate packaging of genomic RNA into a new viral particle. The zinc-fingers of NCp7 are highly conserved among HIV viral strains, and mutations of the zinc-finger motif render the virus non-infectious. Therefore, disruption of NCp7 is an effective strategy to prevent HIV maturation and represents a unique strategy for drug development. Treatment of HIV-infected white blood cells with specific mercaptobenzamide derivatives results in crosslinking of NCp7, mis-processing of the gag polyprotein, and production of non-infectious virus particles. These observations are consistent with a mechanism of action where the mercaptobenzamide promotes ejection of zinc from NCp7. Another facet of this mechanism is that the molecule reacts intracellularly with acetyl CoA to form an acetyl thioester intermediate. This S-acyl intermediate reacts directly with NCp7 to transfer an acetyl group to the protein, leading to zinc ejection, inactivation of NCp7, and regeneration of the original mercaptobenzamide molecule which can re-enter the acetyl CoA acylation pathway. In addition to presenting the mechanism of action, recent results on antiviral activity, formulation, and translation of prodrug derivatives to an orally bioavailable drug will be presented.

Date: Wed, April 18, 2018
Time: 4:30-5:30 pm
Location: 208 Clark Hall

Students, meet the speaker over coffee and cookies in the Bennett Conference room at 3:30 pm