ORGANIC SEMINAR

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"Structure-Activity Relationship Studies of Chimeric Inhibitors of HIV-1 Protease and Histone Deactylase-3"

There are an estimated 41 million people currently living with HIV. Despite extensive progress in treatment development, there remains no cure. One of the biggest obstacles towards a cure is the presence of latent HIV reservoirs which have been unsuccessfully targeted in recent endeavors. To that end, our lab, in collaboration with the Chmielewski group, has developed a first-in-class compound targeting these reservoirs. Our method focuses on a "Shock-and-kill" approach wherein latent cells are reactivated (the "shock") and viral maturation is blocked thus allowing these cells to be destroyed by the innate immune system (the "kill"). To achieve this, we developed a dual inhibitor of histone deacetylase (HDAC) to reverse latency and HIV-1 protease to block viral maturation in a spatiotemporally linked manner. Our current generation of compounds exhibit sub-micromolar IC50 values in assays for both enzymes and were shown to inhibit up to 99% of cell-to-cell transmission events in cellular assays. However, the potency of these compounds were found to be approximately 20 times worse in the cellular assays compared to the enzymatic assays.

In this talk, I will discuss a small study on the structure-activity relationships of one of our lead compounds with the aim of improving HIV-1 protease inhibition while also increasing cellular penetration. More specifically, I will discuss the design and syntheses of this series of compounds and what has been observed thus far. Additionally, I will talk briefly about the future of this project and potential new avenues for our designs.