Department of Molecular and Cellular Biology

Graduate Seminar MCB*6500

Friday, May 24th, 2024 @ 12:00 p.m.

presented by:

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(Advisor: Dr. Siavash Vahidi)

"Investigating LonP1 Protease Inhibition to Target Acute Myeloid Leukemia "

Acute myeloid leukemia (AML) is a blood cancer with an exceptionally poor prognosis for patients. As of 2016, the estimated 2-year survival remained at a mere 32%, highlighting the need for novel therapeutics. Like many cancer types, AML cells upregulate select proteases and chaperones to combat increased levels of cytotoxic protein aggregation in the harsh tumor microenvironment. The inhibition of the Lon protease (LonP1) has been shown to induce selective cell death in a subset of AML cells. Therefore, LonP1 represents an emerging therapeutic target for the treatment of AML. LonP1 is a multidomain ATP-dependent protease with an inherently dynamic structure. To date, the few LonP1 inhibitors that have been identified suffer from poor target specificity and are largely uncharacterized. Here, I propose an in-depth investigation of putative LonP1 small-molecule inhibitors, CDDO-me and Omaveloxolone, to understand the link between the mechanism of action of these small molecules and the inherent conformational dynamics of LonP1. I will use biochemical assays to probe the impact of these inhibitors on the peptidase, proteolytic, and ATPase function of LonP1. By employing multiple structural biology techniques such as hydrogen-deuterium exchange mass spectrometry and cryo-EM, I will determine the binding site(s) and the mechanism by which these compounds abolish LonP1 enzymatic activity. My research will shed light on the mechanism of action of small molecule inhibitors targeting LonP1 and guide the development of more potent and specific LonP1 inhibitors for the treatment of AML.