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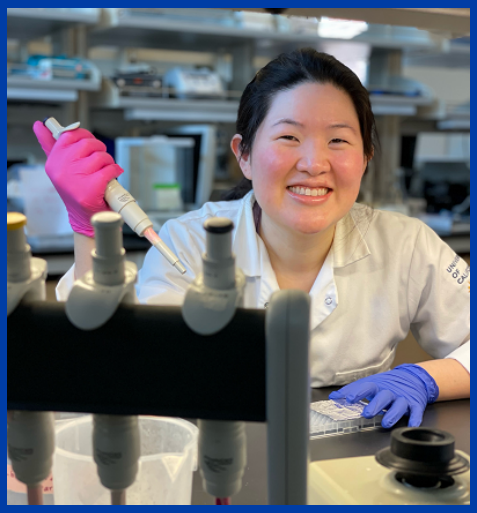
DIVISION OF BIOMEDICAL SCIENCES

PH.D. DISSERTATION DEFENSE OF



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Targeting ML-IAP for the Design of Cancer Therapeutics

Metastatic melanoma is the leading cause of skin cancer-related death in which most overexpress an oncogene called melanoma inhibitor of apoptosis protein (ML-IAP), a member of inhibitor of apoptosis (IAP) proteins, that include also oncogenic proteins XIAP, cIAP1, and cIAP2. These proteins render cancer cells resistant to apoptosis induced by anti-cancer therapies. ML-IAP is overexpressed in melanoma and several other solid tumors, but it is not present in normal adult tissues, making it potentially an ideal target for novel apoptosis-based therapies. However, studies to validate its potential as a therapeutic target have been hampered by the lack of potent and selective pharmacological inhibitors.

To this end, we first characterized IAP antagonists that have been recently designed to mimic the interactions between an endogenous IAP antagonist, namely the second mitochondria-derived activator of caspases protein (SMAC) and IAPs. SMAC's pro-apoptotic activity is based on a conserved IAP-binding motif of sequence Alanine-Valine-Proline-Isoleucine/Phenylalanine (AVPI/F). We employed a highly innovative structure-driven approach to target covalently a nucleophilic Lysine (Lys) residue present in the AVPI/F binding site of both ML-IAP and XIAP, but not in cIAP1 or cIAP2. Our derived agent, 14215 is a first-in-class potent and selective Lys-covalent ML-IAP inhibitor, which is as effective as pan-IAP inhibitors in restoring apoptosis in apoptosis resistant melanoma cell lines. In summary, we derived an innovative and unprecedented pharmacological tool targeting ML-IAP covalently that can be used to further characterize the role of this oncogene in cancer resistance and could provide a valuable steppingstone for the development of novel apoptosis-based therapeutics.

Wednesday, June 9, 2021
12:00 pm (PST)

Zoom Meeting ID: 97383079262 Password: 008377
https://ucr.zoom.us/j/97383079262?pwd=ci95WlNyb2hxeUZSMWRqZnpTL0tqZz09