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TARGETING HIPPO-MUTANT TUMORS THROUGH TANKYRASE INHIBITORS AND STATINS

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Abstract: The Hippo pathway is a signaling pathway that regulates cell number and organ size from early development to adulthood. This tumor suppressor pathway is composed of the tumor suppressor gene, NF2 and the kinases MST1/2 and LATS1/2 that control the activities of two oncogenes YAP and TAZ. YAP and TAZ act as co-activators of TEAD1-4 transcription factors when localized in the nucleus and consequently regulate the expression of genes involved in cell proliferation and motility. In the laboratory in which I am working during the summer, the tankyrase inhibitor, XAV939, has been identified as a small molecule inhibitor that antagonizes activated TEAD/YAP transcription and interferes specifically with proliferation of tumor cells with Hippo pathway deregulation. Furthermore, XAV939 causes stabilization of angiomotin, which binds to YAP in the cytosol. Simvastatin has been reported to inactive TEAD/YAP-dependent transcription via a different mechanism that involves YAP/TAZ phosphorylation but has not been used on mesothelioma tumors. My summer project is to target Hippo deregulated human mesothelioma cell lines H-2052 (NF2 and LATS2 mutant) and H-2373 (NF2 mutant) using XAV939 and Simvastatin and assessing the potential cooperation between the two drugs. Successful outcome will serve as a new therapeutic approach with less toxicity for tumors in which the Hippo pathway is deregulated.

Keywords: XAV 939 tankyrase inhibitor, Simvastatin, cancer therapeutics.