Identification and Analysis of Metabolic Inhibitors in Ctnnb1-Driven Hepatocellular Carcinoma (HCC)

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Liver cancer is the third leading cause of cancer deaths worldwide, resulting in over 800,000 deaths each year. About 90% of all primary liver cancers are characterized as hepatocellular carcinomas (HCC). Two of the biggest challenges in HCC are its many unknown drivers and lack of effective therapeutics. In addition, the incidence of HCC is growing due to the ongoing rise in metabolic disorders, as lipid metabolism dysregulation is a key part of HCC development. One of the most commonly mutated genes in HCC is CTNNB1, which encodes B-catenin. By using a line of transgenic zebrafish that expresses hepatocyte-specific activated B-catenin, resulting in significant liver enlargement and recapitulating human HCC, I aim to identify and analyze compounds which have anti-tumor effects in order to better understand the mechanisms of HCC. In this project, from a screen of 240 metabolic/protease-related compounds, I performed extensive testing on the top fifteen compounds that had the potential to ameliorate the liver enlargement. I identified a novel compound: FAAH-IN-2, which resulted in a significant transgenic liver size reduction. This points towards the previously unknown involvement of FAAH in HCC. In addition, I performed further analysis in order to elucidate the potential mechanism through which FAAH inhibition combats HCC. My project successfully identified a key compound that combats HCC in transgenic zebrafish. Further study of FAAH inhibition and the novel compound FAAH-IN-2 could uncover new insights into their roles in lipid metabolism dysregulation, leading to more effective treatments and a better understanding of HCC.

Awards Won:

Fourth Award of $500