Abstract: Fibrolamellar hepatocellular carcinoma (FLC) is a rare liver tumor affecting adolescents and young adults. Patients with FLC have a poor 5-year survival and are in urgent need of new therapeutic options. We have developed several patient derived xenograft (PDX) models that retain expression of the driver, histology, transcriptome and proteome of the original human tumor. Here, we propose to perform unbiased chemical screens to identify compounds that induce tumor cell death and tumor regressions in PDXs of FLC. Using a novel high-throughput screening platform called high-throughput dynamic BH3 profiling, we will identify whether a 24-hour ex vivo chemical treatment sensitizes freshly isolated tumor cells from FLC PDX models to mitochondrial mediated apoptosis. To facilitate subsequent in vivo testing and eventual clinical translation, our initial chemical library will be composed of bioactive molecules, of which many were previously used in pre-clinical models or human clinical trials. We will validate hits and prioritize compounds for in vivo testing that have good pharmacokinetic properties and do not increase apoptotic sensitivity in healthy cells. Our top hits will be evaluated in vivo in PDX bearing mice as single agents or in combination to identify treatments that induce tumor regression. Since we have demonstrated that the tumor’s transcriptome and the proteome are consistent across patients, we expect that identified therapy should be broadly applicable. As this is a rare disease with an unmet need for systemic therapy, our study has high potential for clinical translation, and may offer the first relief for these young patients.