

MPIs: Devanand Sarkar, PhD; Huiping Zhou, PhD; Xiang-Yang (Shawn) Wang, PhD; and Paul B. Fisher PhD

Academic Rank: Sarkar (Professor), Zhao (Professor), Wang (Professor) and Fisher (Professor)

Title: Exploiting Therapeutic Vulnerabilities in Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC), the primary malignancy of hepatocytes, is a diagnosis with bleak outcome. With the alarming rise in global obesity incidence, obesity-induced non-alcoholic steatohepatitis (NASH) is becoming a leading cause of HCC. HCC is usually diagnosed at an advanced stage when the tumor is unresectable. In such instances, systemic therapy with tyrosine kinase inhibitors (TKIs, such as sorafenib) is the main treatment option, even though it benefits only 30% of patients, provides only a modest (~3 months) increase in overall survival and causes drug resistance within 6 months. Immune checkpoint inhibitors (ICIs, i.e., anti-PD-1 antibodies) have been approved for HCC treatment by FDA, although only 19% of HCC patients responded. Additionally, recent studies document that immunotherapy may be less effective in patients with NASH-induced HCC (NASH-HCC) than in HCC patients with viral hepatitis. Thus, there is an unmet need to develop novel and effective modalities of treatment for advanced HCC. The P01 proposal Exploiting therapeutic vulnerabilities in hepatocellular carcinoma (ELEVATE), which involves four projects, an administrative and biostatistics core (Core 1), and a mouse model and pathological analysis core (Core 2), aims at interrogating molecular changes in HCC and exploiting them to develop combinatorial treatment approaches especially targeted to NASH-HCC. The overall objectives include interrogation of molecular mechanisms regulating NASH-HCC and development of novel combinatorial treatment approaches based on the identified molecular abnormalities, evaluation of approaches that improve efficacy of approved immunotherapy using an authentic NASH-HCC mouse model, and development and evaluation of novel approaches that engage the immune system to counteract HCC (inflammatory and NASH-HCC). To achieve this objective this P01 comprises experts, with an established history of highly integrated interaction, in HCC biology and mouse modeling, liver physiology and pathology, medicinal chemistry, cancer immunotherapy, pathological diagnosis, nanoparticle delivery and bioinformatics and biostatistics. Successful completion of the proposed studies will significantly advance our understanding of the molecular mechanism of HCC pathogenesis and novel therapeutics, and generate translationally relevant data from pre-clinical models having the potential to radically transform management of HCC patients facilitating prolonged survival. Thus, this innovative P01 grant has high mechanistic and translational significance. ELEVATE brings together expertise of a highly integrated team providing synergistic outcome which may not be delivered by each project alone.