



## CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:  
RP150587

Project Title:  
The Texas Hepatocellular Carcinoma Consortium (THCCC)

Award Mechanism:  
Multi-Investigator Research Awards (Version 2)

Principal Investigator:  
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Entity:  
Baylor College of Medicine

### Lay Summary:

Our goal is to reduce the death and suffering related to liver cancer in Texas and the world by conducting cutting edge collaborative research in our proposed Texas Hepatocellular Carcinoma Consortium (THCCC).

Hepatocellular cancer (HCC) is the most common (>95%) of liver cancers. HCC is also the fastest rising cause of cancer-related deaths in the U.S. HCC is particularly important for Texas residents. Texas has the second highest death rate from HCC in the nation. The 5-year HCC survival remains low (10-15%) and most patients get diagnosed at late stages. Texas residents notably Hispanics and African Americans are greatly affected with established HCC risk factors including hepatitis C virus, hepatitis B virus and alcoholic liver disease. Furthermore, emerging HCC risk factors, specifically the metabolic syndrome and non-alcoholic fatty liver disease (NAFLD), are exceptionally common in Texans.

Effective prevention and early detection measures are urgently needed to reverse the epidemic of HCC but has been hampered by several factors.

- Most cases of HCC (90%) arise in the background of cirrhosis (a damaged and scarred liver). Cirrhosis is a common problem that affects at least one million adults in the U.S. However, only 2-5% of persons with cirrhosis develop HCC every year. Thus, there is a pressing need to better identify which cirrhosis patients progress to HCC so they get targeted for prevention and surveillance.
- The US in general and Texas in particular are in the midst of an epidemic of metabolic syndrome (obesity, diabetes, hypertension, high triglycerides, and low HDL cholesterol). Although linked to increased risk of liver disease including HCC, the effect of metabolic syndrome on HCC risk among patients with cirrhosis is not known.
- Metabolic syndrome is a strong risk factor for non-alcoholic fatty liver disease (NAFLD (fatty liver)), which has been linked to the development of cirrhosis and possibly HCC but high quality studies on the effect of NAFLD on association are non-existent.
- Circadian rhythm disruption (resulting from sleep disturbances) has been associated with the development of metabolic syndrome and NAFLD in our preliminary animal data. However, the relevance of these findings to humans is unknown.

- Early detection of HCC in patients with cirrhosis remains suboptimal, and the implementation of HCC surveillance (by ultrasound) in practice is very low.

We have assembled an outstanding group of investigators with complementary expertise in molecular biology, HCC biomarkers, epidemiology and biostatistics. Between them, they published > 200 papers on various aspects of HCC.

Our proposed Projects address these knowledge gaps.

Project 1. Risk Factors of Hepatocellular Carcinoma in Non-alcoholic Fatty Liver Disease. We will use Texas VA datasets to assemble the largest NAFLD-to-HCC study to date (including over 45,000 NAFLD patients in Texas) to determine the number of patients to develop HCC and to identify factors that increase patients' risk for HCC.

Project 2: Metabolic Syndrome and Risk Prediction of Hepatocellular Carcinoma. This project will develop risk stratification algorithms based on demographic, clinical, molecular and epidemiological risk factors to identify cirrhosis patients who might benefit from prevention or intensive surveillance. We will evaluate molecular and genotypic aspects of the metabolic syndrome as well as established risk factors.

Project 3: Circadian Disruption and Bile Acids as HCC Risk Factors. This project will identify pathways for chemoprevention related to the role of circadian rhythm and bile acids in NAFLD, metabolic syndrome, and HCC.

Project 4: Novel Biomarkers for Hepatocellular Carcinoma. This project will identify and validate novel blood markers (tests) for early HCC detection. We will also validate promising existing markers, and discover novel biomarkers for HCC detection.

Project 5: A comparative effectiveness randomized controlled trial of strategies to increase HCC surveillance. We propose the first multi-center outreach intervention aimed at improving surveillance process completion among at-risk patients with cirrhosis.

A main source of synergy and efficiency in the THCCC is the assembly of largest prospective cohort study of cirrhosis) in the U.S. to address immediate questions regarding risk stratification (Projects 1-3), surveillance uptake (Project 5), and early detection (Project 4) and provide platform for addressing future questions regarding HCC prognosis and treatment.

Our Projects and Cores have a hypothesis driven focus on producing specific and timely results that impact clinical practice. Concurrently, the THCCC maintains a forward outlook by building an infrastructure of patient cohorts with relevant samples for testing new hypotheses, and establishing a trans-Texas multidisciplinary HCC research group.