ACHA 2026 Research Grant Award

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Title: ***Genomic and Transcriptomic Characterization of Hepatocellular Carcinoma in Fontan-Associated Liver Disease***

Individuals born with single ventricle anatomy who have undergone the Fontan operation are at risk for liver disease—aka Fontan-associated liver disease (FALD)—which is characterized by liver congestion, scarring, and even cirrhosis. Alarmingly, individuals with Fontan circulation (FC) are increasingly being diagnosed with liver cancer or hepatocellular carcinoma (HCC) and dying at higher rates than people without FC. It is not known exactly why this is happening or what we can do about it. We believe a crucial initial step is understanding the molecular mechanisms of HCC in FALD, which remain essentially unknown.

Molecular profiling of non-FALD HCC has identified key genetic, epigenetic, and transcriptomic drivers of liver cancer development and progression. These scientific discoveries have enabled doctors to define mechanisms of disease, understand prognosis, and develop screening protocols and treatments—all of which are currently lacking for individuals with FC.

Our proposal is to start with 23 HCC tumor samples from three high volume adult congenital heart disease centers (University of Pennsylvania/CHOP, UCLA, and Vanderbilt) to investigate the genetics of FALD-HCC. We would leverage historic tumor tissue samples to 1) perform targeted DNA sequencing of genes known to be involved in solid tumor development and 2) perform bulk RNA sequencing to identify genetic drivers and crucial signaling pathways involved in FALD-HCC.

The ultimate goal of this proposal is to build a multicenter biorepository linked to a clinical database of 58 FALD-HCC cases across North America through the Alliance for Adult Research in Congenital Cardiology (AARCC) Network, which has already produced two manuscripts on FALD-HCC. This would be the first integrated clinical-tumor registry dedicated to FALD-HCC and begin the efforts toward prevention and cure of this devastating complication of single ventricle palliation.