**Title: Point-of-Care Screening and diagnosis of liver cancer in Chinese population**

**Specific Aims**

Liver cancer is the second leading cause of cancer death in China and urban areas and the third leading cause in rural areas. In 2009, approximately 380,000 new liver cases and 350,000 liver cancer deaths occurred all over the China as a results of the high prevalence of chronic viral hepatitis. The crude incidence and crude mortality of liver cancer was 28.71/100,000 and 26.04/100,000, respectively. Analysis on the basis of geographic location showed that the incidence rate was higher in rural areas than in urban areas. The crude and age-standardized incidence rates were 35.78/100 000 and 34.34/100 000 for rural areas. There are increasingly growth in cancer incidence in China due to rapid industrialization and population growth, environment deterioration and aging. We also observe that the cancer mortality in China and low-and middle-income countries is on the rise due to limited resources for cancer screening, early detection and treatment. To address the great challenges in cancer detection and preventions in China and the developing countries, overall objective of this application is to use mobile health (mHealth), lab-on-a-chip (LOC ), biosensors, portable ultrasound imaging, and nanopore-sequencing technologies to develop low cost, convenient, user-friendly devices or assays, and hand held scanners for screen and early detection of liver hepatocellular carcinoma in Chinese population, validate their analytical and clinical performance, and bring cancer detection, diagnostics, monitoring and treatment to the patient . To accomplish this goal, we tentatively plan to address four interrelated specific aims:

**Aims: the UH2 phase**

Aim1: Adapt the ultrasound technologies which can plug into smartphones and tablets to develop a new generation of high-performance, low-cost, non-invasive and portable ultrasound scanner (the MobiUS SP1 smartphone system) for early detection and screen of hepatocellular carcinoma (HCC) at the point of care in Chinese population. To explore the transition of the image from the scanner to the hospital or data collection and analyze center via secure Wi-Fi. To assess the performance of the proposed portable ultrasound scanner, we also use the contrast enhanced ultrasound (CEUS) scanner to detect hepatocellular carcinoma and compare the accuracy of two types of scanners for detection of hepatocellular carcinoma in Chinese population.

Aim 2: MiRNAs are circulated to the serum in the early stage of HCC. Our study has demonstrated that miRNA expression profiles in HCC and normal individuals are significantly different. We identified a miRNA panel with 7 miRNA from 723 miRNA which provided a high diagnostic accuracy of HCC (AUC=0.864 and 0.888 for training and validation dataset, respectively). Thus, the discovered miRNA panel can be used as potential biomarkers for detection of HCC. In this application, we use lab-on-a-chip (LOC ) techniques to develop a low cost, portable and programmable miRNA-based nano-bio-chip diagnostic kit for early detection of HCC in Chinese population and further move the biomarkers from discovery through validation and on clinical implementation in Chinese population.

Based on the experience and clinical results of UH2 phase, we design validation study and develop plan for regulatory approval and production and maintenance of the developed portable ultrasound scanner and nano-bio-chip diagnostic kit .

**Aims: the UH3 phase**

Aim 1: Validate smartphone ultrasound scanner for early detection of HCC by adding additional five clinical sites, including two sites in the rural areas. In addition to the MobiUS SP1 smartphone system, in this phase we also evaluate the performance of the MobiUS TC2 system and assess the impact of several parameters of the systems and surveillance interval on the accuracy of early detection of HCC. To explore the transition of the image from the scanner to a central facility via secure Wi-Fi or internet, and develop intelligent and computerized ultrasound scanner for detection of HCC with minimal training to perform ultrasound scans combing growing computational power, new communication technologies and improved imaging techniques. In the large-scale clinical setting, we will evaluate the performance of the new generation of intelligent smartphone ultrasound scanner for early detection of HCC with conventional ultrasound techniques.

Aim 2: Move programmable miRNA-based nano-bio-chip diagnostic assay from discovery to validation and clinical implementation by expanding clinical sites to seven, including two sites in the rural areas. Further expand miRNA-based nano-bio-chip diagnostic kit by incorporating age, gender, ethnic, geographic information and additional miRNAs which are specific to sub Chinese population into the diagnosis. Due to influence by population substructure and environmental risk factors, the informative miRNAs for detection of HCC may vary from site to site. To adapt miRNA detectors of HCC to the specific subpopulation and clinical sites, we explore nanopore sensors for nucleic acid analysis techniques to develop a new generation of low-cost and portable sequencing machine to generate miRNA-seq signatures which may vary from site to site for early detection of liver hepatocellular carcinoma in Chinese population.

To maximally employ information from ultrasound and miRNA scanners, we will explore machine learning and high dimensional data reduction techniques to develop intelligent and smart diagnosis system of HCC that integrate ultrasound image and miRNA information.

In addition to developing plan for regulatory approval and production and maintenance of the developed portable ultrasound scanner and nano-bio-chip diagnostic kit, we also develop education plan for health care delivery users via local and nation-wide workshops or exhibit shows to teach how to use hardware and software and consult with patients.