Project Title:

Circulating DNA derived tumor content for early detection of lung cancer

PI: Professor ZHENG Zongli of CityUHK

Co-Is: Professor Michael YANG Mengsu of CityUHK and Professor JI Mingfang of Zhongshan City People's Hospital

Project Abstract/Proposal Summary:

Lung cancer accounted for 11.4% of newly diagnosed cancer cases and 18.0% of cancer-related deaths in 2020, with about 2.2 million new cases and 1.8 million deaths. Although new treatments, such as targeted therapies and immune checkpoint blockade therapies, have greatly improved patient outcome but they are effective in only a subset of non-selected NSCLC patients and the five-year survival rate of all lung cancer patients remains only about 20%. In contrast, for patients with stage I tumor, the five-year survival rate is about 80%. These data suggest that detecting lung cancer at an early stage via screening would be an effective way to improve survival for lung cancer patients. Low-dose computed tomography (CT) is one way for screening and detecting early-stage lung cancer, with an estimated reduction in the mortality of lung cancer by 24% to 33%. However, in the setting of population-based screening, the exposure to radiation among the large number of subjects in the screening population and the false positive-associated overdiagnosis and overtreatment are concerning. Circulating cell-free DNA (ccfDNA) shed from solid tumors may provide an opportunity to detect cancer non-invasively and safely. A number of circulating cell-free DNA features have been studied for cancer detection, including somatic copy number alteration (SCNA) in peripheral blood. SCNA analysis in circulation allows for estimating the tumor-derived DNA fraction in the total circulating cell-free DNA (ccfDNA), which has been linked to tumor burden and cancer prognosis. Previous studies have suggested the utility of SCNA in the early detection of lung cancer (lung cancer), primarily using samples collected from hospital patients, who typically present a high tumor burden. However, with respect to pre-clinical lung cancer cases who would benefit most from early detection, the tumor burden is generally lower. Due to the challenges in study design (requires prospective longitudinal follow up of a large number of individuals to accumulate just a handful of incident cases) and the methodological challenges associated with measuring low-level SCNA, few studies are available to evaluate the potential of SCNA as a tool for early diagnosis in a pre-clinical setting. We hypothesize that the SCNA profile in ccfDNA changes across the natural progression of lung cancer, from years preceding

diagnosis through to advanced disease stages, as well as after surgery treatment. Specifically, we aim to **i**) compare the distribution of tumor content and genome-wide copy number profile in lung cancer before and after surgery treatment; **ii**) compare the prognosis of lung cancer by tumor content status (high vs low) after adjusting for potential confounders including tumor stage; and **iii**) by density sampling within a nested case-control design, to evaluate the screening performance (sensitivity, specificity and AUC) of using circulating tumor content for early detection of lung cancer.