

## **Project Proposal – Upper GI Cancer**

### **Background**

Esophageal cancer is the eighth most common malignancy and the sixth most common cause of cancer death in the worldwide, with an estimated 455,784 new cases and 400,156 deaths in 2012. Esophageal squamous cell carcinoma (ESCC) is the most common histological type of esophageal cancer worldwide. The 5-year survival of late stage patients is less than 15%, however, tumors detected at an early stage prior to lymph node spread and when the disease is confined to the mucosa or submucosa have a survival in excess of 80%. Endoscopic screening is not feasible on the population scale because of the invasiveness and the potential for sample error with random endoscopic biopsy limits its' effective. Therefore, the discovery of new molecular markers for the early diagnosis of esophageal cancer would be critical for improving a patient's prognosis.

### **Objective:**

To discover and validate the biomarkers in cancer screening and early diagnosis among high risk populations in rural area in China, focusing on the upper gastrointestinal cancers (esophageal cancer and stomach cancer).

### **Resources available**

A Population based prospective cohort has been initiated and built in esophageal cancer high risk areas in rural China from year 2005 to 2009. 3000 local residents have been examined by endoscopic screening. Risk factor information has been surveyed by questionnaires; we also offered the basic health examination and collected the blood sample at the baseline.

A new cancer screening program in rural China will be initiated next year. 20,000 subjects from high risk rural areas will be recruited and screened for Upper GI cancer with endoscopy. Biopsy and blood sample (anticoagulant and non-anticoagulant blood from each subject) will also be collected at the baseline.

### **Progression**

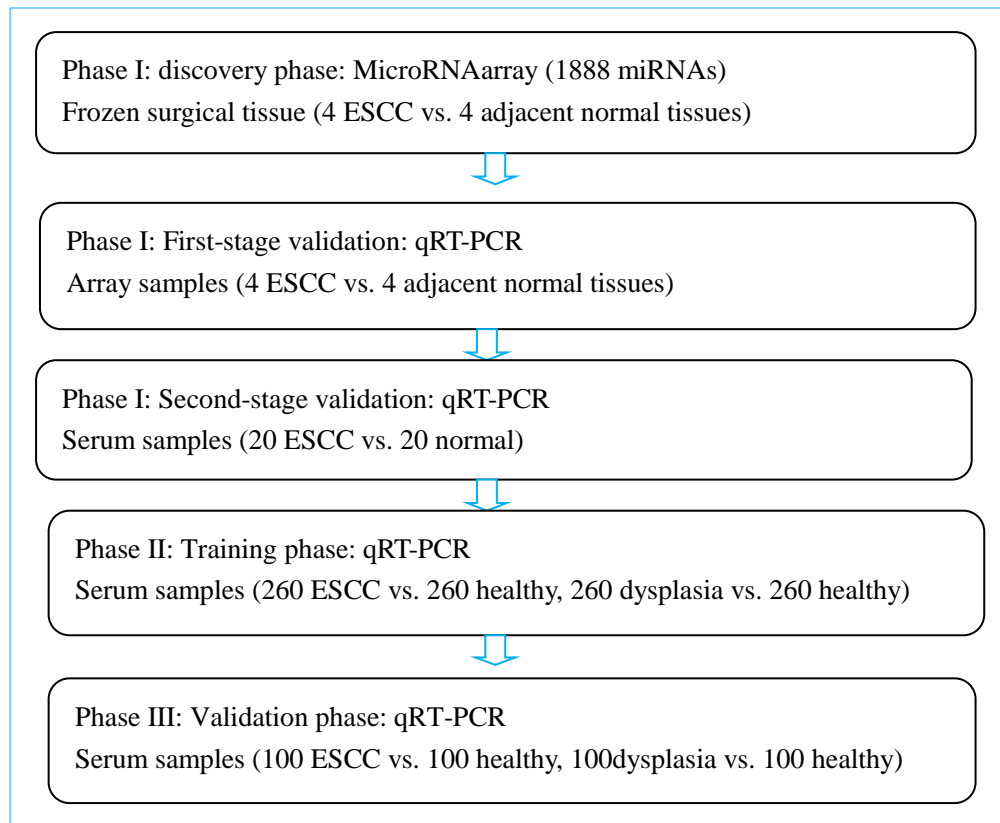
Based on the population cohort, the discovery of new molecular markers for the early diagnosis of esophageal cancer would be critical for improving a patient's prognosis. A multi-stage, nested case-control study from two large cohorts to identify and validate the differential serum microRNAs (miRNAs) in ESCC, esophageal dysplasia and healthy controls. This study was divided into three stepwise phases: phase I, marker discovery; phase II, marker selection and training; and phase III, marker validation (Figure 1). The project has obtained the National Natural Science Foundation of China No. 81473056.

#### **Phase I: marker discovery**

In this phase, pre-operative plasma, primary cancerous biopsies and their adjacent non-cancerous esophageal tissues from four patients with ESCC were collected. Serum from four age-matched healthy subjects was collected as the control. MiRNA profiles were generated from the following samples: (1) ESCC plasma, (2) normal plasma, (3) ESCC tissues, and (4) adjacent normal tissues. Differential miRNAs were identified by array analysis. By comparing miRNA profiles from ESCC tissues versus adjacent normal tissues and ESCC plasma versus normal plasma, two differential miRNA expression patterns were established and then compared. The

upregulated miRNAs or downregulated miRNAs having functional or biomarker-related indications were selected for further analysis.

So far among 1888 miRNAs analyzed, 17 showed >2-fold upregulated and 21 showed <0.5-fold downregulated changes in ESCC tissue. Fourteen dysregulated miRNAs (miR-1246, miR-130b-3p, miR-15b-5p, miR-185-5p, miR-21-5p, miR-101-3p, miR-140-3p, miR-143-3p, miR-145-5p, miR-195-5p, miR-29c-3p, miR-30a-5p, miR-378i, miR-99a-5p) demonstrating remarkable expression changes in ESCC tissue and having functional reports were selected as the candidates for the first stage validation using quantitative reverse transcription-polymerase chain reaction (qRT-PCR).



### Future plan:

1. Finish the phase II and phase III validation in Chinese ESCC patients.
2. Compare the diagnostic value of miRNAs with Carcinoembryonic antigen (CEA), Carbohydrate antigen (CA) 19-9 and squamous cell carcinoma antigen (SCCA).
3. Validate the miRNAs profile in US patients. Compare the results in two populations.

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