METHOD AND KIT FOR DIAGNOSIS AND MONITORING NON-SMALL CELL LUNG CANCER

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Experience:

Dr. Tsai received her medical degree at National Taiwan University (NTU) and completed Internal Medicine residency and Pulmonology fellowship at NTU Hospital. Subsequently, Dr. Tsai received her PhD and postdoctoral training in a cancer epigenetics laboratory at Johns Hopkins University School of Medicine. Following her research training, Dr. Tsai joined the faculty of Graduate Institute of Toxicology at NTU College of Medicine. She also resumed her clinical practice as attending physician in the Department of Internal Medicine at NTUH. The patient-care experiences and medical knowledge learned over the years laid a strong foundation for Dr. Tsai to conduct biomedical research with high clinical relevance and implications. Dr. Tsai's past and current research achievements include molecular and cellular mechanisms of two DNMT1 inhibitors, 5-aza-2'-deoxycytidine and 5-azacitidine (*Cancer Cell 2012*), interactions of DNA methyltransferases in maintaining cancer-specific DNA methylation across major genome features (*Genome Research 2017*), as well as potentiating effects of epigenetic therapy for γδ T-based cellular immunotherapy in lung cancer (*Nature Communications, 2021*), among others. Dr. Tsai has received several prestigious institutional and national research awards in the field of cancer epigenetics. She also holds two provisional patents on novel diagnostic and therapeutic strategies in cancer. Dr. Tsai is now the deputy director of NTUH Center for Frontier Medicine and help facilitate clinical development of cellular immunotherapy in cancer.

Market Needs:

Lung cancer is the leading cause of cancer-related mortality and remains a global health threat. Early detection of lung cancer is clinically challenging even with the wide use of low-dose computed tomography (CT) screening programs in many countries, due to its high false positive rate. On the other hand, patients with late-stage diseases often undergo various therapies, but few diagnostic modalities can easily track the dynamics of disease control. In clinical practice, imaging-based methods were used for early detection of lung cancer or evaluation of treatment responses in late-stage diseases. However, these methods were neither specific enough for early stage nor sensitive enough for late-stage diseases. Tumor biopsy, while accurate, is invasive and hardly repeatable throughout the course. Hence, there is great need for a reliable non-invasive tool for both early-detection and disease monitoring in lung cancer.

Our Technology:

To overcome the shortcomings of current technology, we sought to develop technology focusing on circulating free DNA (cfDNA). cfDNA can originate from apoptotic or necrotic tumor cells which can reflect both disease burden and also molecular characteristics. To differentiate the origin of cfDNA from cancer cells or normal cells, sequencing for tumor specific mutations or genomic alterations was required traditionally which can be financially impractical. On the other hand, cfDNA in cancer cells bears aberrant DNA methylation, which is a hall mark of carcinogenesis and can be assessed in simpler ways. Prior studies of methylation markers for lung cancer diagnosis were either limited to specific known sites or with limited sensitivity and specificity.

We developed the four-gene based panel from in-house surgically removed lung cancer /adjacent normal tissues using high-throughput genome-wide DNA methylation array. These probes were both highly methylated in our cohort and also in the validation cohort of TCGA lung cancer patients. The four-gene panel showed low methylation profile in control subjects' peripheral blood mononuclear cells from Taiwan Biobank sample. We then utilized multiplex methylation specific droplet digital polymerase chain reaction (ddPCR) to test both tumor cells and cfDNAs using specifically designed methylation primers for the four probes. By utilizing a methylation score developed from the four-gene ddPCR panels, we were able to achieve good sensitivity and specificity for lung

cancer diagnosis in a clinical cohort of lung cancer patients and healthy controls. The methylation scores were longitudinally tested in the cohort of lung cancer patients, and the scores were correlated with disease progression.

Strength:

Our design of testing cfDNA has the strengths of:

1. Our assay with excellent sensitivity and specificity.
2. In-house designed methylation probes using ddPCR is highly sensitive and cost-effective for testing cfDNA methylation.
3. The methylation score had been tested for not only lung cancer diagnosis but also for disease follow up and monitoring.
4. The performance of the methylation scores were not limited to any molecular characteristic of lung cancer.

Competing Products:

Epi ProLung® is currently the only commercialized product for lung cancer diagnosis using 2-gene panel in a PCR based assay. This assay used different genes and had lower diagnostic power as compared with our assay. There is also lack of data regarding disease monitoring for the product. Other locus specific panels for lung cancer diagnosis had been reported but had not been used in clinical practice.

Intellectual Properties:

US provisional patent: Tsai HC, Yu CJ, Lu HH, Lin SY, Huang YJ (2021) METHOD AND KIT FOR MONITORING NON-SMALL CELL LUNG CANCER, Patent Number: 63/154837

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