1. No.
   2019T014

2. Title
   Detection of driver mutations of early lung cancer in non-neoplastic lung tissues.

3. Period
   2019-2023

4. Summary
   Recently, attention has focused on the so-called *p53* signature in the fallopian tube epithelium as a developmental matrix for ovarian cancer, and age-related NOTCH1 gene abnormalities in esophageal epithelium. Therefore, we have investigated the methodology to determine whether the driver mutations in the earliest stages of lung cancer identified in this specific group study are already present in histologically non-tumorous lung tissue. First, we established an immunohistochemistry (immunostaining) technique for formalin-fixed, paraffin-embedded tissue specimens using the electric field non-contact agitation method. The method was verified for the possibility of its clinical application. In the FY2022 and FY2023, the RNAscope® was applied to TEVs (tumor-derived extracellular vesicles), which are microstructures outside the observation limit of optical microscopy and can only be observed with electron microscopy, and ERBB2 mRNA, which is contained in large amounts as the content of these microstructures. We planned to visualize TEVs indirectly on tissue sections by performing *in situ hybridization* using the RNAscope® for TEVs (Tumor-derived extracellular vesicles) containing ERBB2 mRNA as their contents. In summary, the introduction of new technologies such as the electric field non-contact agitation method and the RNAscope® may allow us to visualize whether the earliest driver mutations of lung adenocarcinoma are already present in lung tissue that is not histologically determined to be tumor, or clonal evolution in early-stage lung adenocarcinoma lesions. Therefore, we will further investigate primary mutations such as *EGFR, MET,* and *ERBB2,* which are the results of another project of this special study.