1. **No.**

   FP01801018

2. **Title**

   Development of mouse small cell lung cancer models, and studies on the effect of smoking on mouse small cell carcinogenesis

3. **Period**

   2016-2018

4. **Summary**

   Considering importance of a molecular pathway consisting of p53/Rb double-mutations and inactivation of Notch signaling accompanying with Ascl1 expression in small cell lung cancer (SCLC) carcinogenesis, we established lung-specific, doxycycline-inducible p53(-/-); CCSPrtTA; Tet OCre; floxed Rb mice, p53(-/-); CCSPrtTA; TetOCre; floxed Notch1 mice, and p53(-/-); CCSPrtTA; TetOCre; floxed Rb1; floxed Notch1 mice. After treatment with doxycycline for 6-12 weeks, pulmonary neuroendocrine neoplasms (PNEN) occurred in the airway and alveolar epithelia of the p53(-/-); CCSPrtTA; TetOCre; floxed Rb1; floxed Notch1mice. Immunohistochmical studies revealed that the PNENs were positive for INSM1 and CGRP, and that Ki-67 labelling index was about 20%. Moreover, addition of a mutant oncogene mice in the PNEN GEMM mice made in situ SCLC in the lobar bronchus of the mice. NNK, tobacco-related nitrosamine, did not affect incidence or histology of the PNEN induced. For future development of *in vitro* 3D SCLC carcinogenesis model, we succeeded to make alveolus-like organoids *in vitro* from isolated lung tip epithelia of embryonic mouse lungs.