1. **No.**

   FP01902044

2. **Title**

   Oxidative Stress by Cigarette Smoke and Breakdown of Proteasomal Recovery

3. **Period**

   2018-2020

4. **Summary**

   The proteasome is an intracellular protease responsible for most intracellular protein degradation. In particular, the proteasome degrades most oxidized, aggregated, and misfolded proteins. Since the proteasome plays an essential role in cellular homeostasis, an age-associated decline in proteasome function is assumed to contribute to the development of age-related pathologies and to the aging process itself. First year, we performed clinicopathological evaluation of proteasome expression in non–small cell lung carcinomas. Second year, we analyzed cellular responses of alveolar epithelial cells and lung fibroblast cells to cigarette smoke, focusing on proteasome function. Last year, we demonstrated whether decreased proteasomal activity and oxidative stress by cigarette smoke induces neuronal death. Our results suggest that the age-related decline in proteasomal activity plays a vital role in the pathogenesis of age-related disorders, such as carcinomas, chronic obstructive pulmonary disease, and progressive neurodegenerative disorders. Future studies are needed to address the molecular mechanisms underlying proteasomal impairment with age, and to identify specific substrate proteins whose altered expression contributes to the development of age-related disorders. Such studies may provide a new approach to the prevention and treatment of age-related disorders.