1. **No.**

   FP01801016

2. **Title**

   Inhibition of Functions of Various Receptors by Stiffening of Cell Membrane and Lung Cancer Treatment

3. **Period**

   2016-2018

4. **Summary**

   Based on our results that green tea catechin, (-)-epigallocatechin gallate (EGCG), is stiffening cancer cells, we hypothesize that increase of stiffness is a new strategy for lung cancer treatment. We have found that higher level of AXL receptor tyrosine kinase is well correlated with high motility and metastatic ability in lung cancer cell lines. Inhibition of AXL with R428 or siAXL increased cell stiffness and inhibited motility. EGCG inhibited Gas6-dependent and -independent phosphorylation of AXL. In this experiment, we succeeded measurement of stiffness of cancer stem cells (CSCs), showing that CSCs have much lower stiffness that parental cells. Treatment with EGCG or siAXL similarly inhibited sphere formation in 3D culture. EGCG increased stiffness of CSCs, along with reduction of % of ALDH positive cells and Slug gene expression. AXL-low clone showed low tumorigenicity in a mouse xenograft model. Thus, AXL stimulates cell softening, metastasis and stemness, and AXL is a new molecular target for lung cancer treatment. Stiffening of membrane in cancer cells with EGCG inhibited expression of an immune check point molecule, PD-L1, induced by EGF and INF-γ, resulting in stimulation of anti-tumor immunity and inhibition of lung carcinogenesis. All data indicate that stiffening of cancer cells is the effective strategy to improve lung cancer treatment.