Comparison of autophagy inducing effect in various tyrosine kinase inhibitors in cancer cells by quantitative autophagy flux monitoring system

We reported that tyrosine kinase inhibitors (TKIs) including gefitinib (GEF) and imatinib (IMA) induce autophagy in many types of cancer cells. We also reported that GEF induces autophagy in EGFR knock-out A549 cells. This indicated GEF-induced autophagy is independent of EGFR inhibition. Therefore, other target(s) might be involved in TKI-induced autophagy. We here compared autophagy inducing ability of various TKIs by establishment of the quantitative autophagy flux assay system.

We transfected GFP-LC3-mCherry-LC3  
triangle G plasmid (a kind gift from Prof. Mizushima and modified) to A549, PC-9 and CAL27 cell lines and generated stable expression clones. Monitoring the fluorescent ratios of GFP/mCherry by IncuCyte Cell Imaging System enabled us to evaluate the autophagy flux condition during exposure to TKIs: GEF, osimertinib (OSI) and lapatinib (LAP) for EGFR-TKI, lenvatinib (LEN) and sorafenib (SOR) for VEGFR-TKI, IMA and dasatinib (DAS) for ABL- and KIT-TKI, and tivantinib (TIV) for HGFR-TKI.

Among eight TKIs, DAS, GEF and SOR exhibited the prominent autophagy inducing effect in A549 and PC-9 cells. In CAL27 cells, IMA, SOR and LEN exhibited autophagy induction, but less strong, probably because of upregulation of endogeous autophagy. We also reported that macrolide antibiotics including AZM have an effect of blocking autophagy. Combined treatment of either DAS, GEF or SOR with AZM all resulted in pronounced cytotoxicity in A549 cells. Thus, autophagy induction by TKIs appears to function as cytoprotective. Blocking autophagy appears to enhance the therapeutic effect of TKIs in various cancers.

Comparison of amino acid profile between non-tumor and tumor regions in the patients with lung cancer

We are planning to increase the number of cases and add examinations of muscle mass and muscle strength.

Discussion
From this examination, it is suggested that measuring urinary titin may become a nutritional indicator prior to surgery for patients with cancers of the patients, this study purposed to compare the AA profile between the non-tumor and tumor regions within the same patients suffered from lung cancer.

Methods
Non-tumor and tumor regions in lung tissue were harvested from the 14 patients with small cell cancer who underwent lung resection under obtaining informed consent. The AAs profiling in both the