Abstract of Presentation

Note: This paper should be typed in "Times New Roman" of 12pt.

Presentation Title(Should be no more than 20 words):

Discovery and clinical application of a novel oncogene, *EML4-ALK*, in lung cancer

Abstract :

Lung cancer remains the leading cause of cancer deaths worldwide. Conventional chemotherapeutic regimens improve only marginally the outcome of individuals with non-small-cell lung cancer (NSCLC), resulting in a median survival time of <1 year. In order to discover novel transforming genes in lung cancer, we have developed a sensitive retroviral expression library system for full-length cDNAs, and applied this technology to an NSCLC specimen without *EGFR* mutations. A focus formation assay with the library led to the discovery of a novel fusion gene between the echinoderm microtubule–associated protein-like 4 (EML4) and the anaplastic lymphoma kinase (ALK) genes, both of which are closely mapped to the same short arm of chromosome 2 (*Nature* 448:561). Fusion to EML4 induces a constitutive dimerization of the ALK kinase domain, and thereby its marked activation.

Transgenic mice expressing *EML4-ALK* in lung epithelial cells generate hundreds of adenocarcinoma nodules only at a few weeks after birth, demonstrating the pivotal role of this fusion kinase in NSCLC (*PNAS* 105:19893). Further, oral administration of a specific inhibitor to ALK successfully cleared such nodules from the mice. Knowing the high efficacy of such compounds for *EML4-ALK*–positive NSCLC, we have tried to develop a multiplex RT-PCR system for *EML4-ALK* messages and a sensitive immunohistochemical detection system for the encoded protein. By utilizing such technologies, we have constructed a nation–wide diagnostic network for *EML4-ALK*–positive NSCLC in Japan, and have unexpectedly discovered another fusion of ALK, KIF5B-ALK, in a subset of NSCLC (*Clin Cancer Res* 15:3143).

Several pharmaceutical companies are currently known to develop ALK–specific inhibitors to treat *EML4-ALK*–positive individuals, and, among them, Pfizer Inc. has recently published the outcome of a Phase I clinical trial with an ALK inhibitor, demonstrating a significant reduction of tumor burden among 53% of the patients (http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=30947).

These data demonstrate that a subset of lung cancer express previously unidentified fusion kinases that are promising candidates for a therapeutic target as well as for a diagnostic molecular marker for this intractable disorder.