General Summary of Division of Medical Oncology and Surgical Oncology

The major obstacles of cancer treatment are metastasis and drug resistance.

The goal of our translational research is the establishment of novel molecular targeted therapeutics for overcoming metastasis and drug resistance of malignant solid tumors, such as lung cancer, pleural mesothelioma, gastric cancer and pancreatic cancer. Our main achievements are as follows.

A) Discovery of novel resistance mechanism to gefitinib in lung cancer harboring EGFR activating mutation.

Lung cancer with epidermal growth factor receptor (EGFR)-activating mutations responds favorably to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib. However, 25% to 30% of patients with EGFR-activating mutations show intrinsic resistance, and the responders invariably acquire resistance to gefitinib. We demonstrated that hepatocyte growth factor (HGF), a ligand of MET oncoprotein, induces gefitinib resistance of lung adenocarcinoma cells with EGFR-activating mutations by restoring the phosphatidylinositol 3-kinase/Akt signaling pathway via phosphorylation of MET, but not EGFR or ErbB3. These findings suggest that inhibition of HGF-MET signaling may be a considerable strategy for more successful treatment with gefitinib.

B) Development of novel molecular targeted therapy for lung cancer metastasis.

Bone metastases occur in more than one-third of patients with advanced lung cancer and are difficult to treat. We previously established osteolytic bone metastasis model of human small cell lung cancer in natural killer cell-depleted SCID mice. Using this metastasis model, we showed that combined use of anti-parathyroid hormone-related protein (PTHrP) neutralizing antibody insensify the therapeutic effect of a third-generation bisphosphonate, zoledronate. In addition, follistatin (FST), an inhibitor of activin, could inhibit the production of multiple-organ metastasis, predominantly by inhibiting the angiogenesis.

C) Development of novel molecular targeted therapy for malignant mesothelioma.

Malignant pleural mesothelioma (MPM) is an aggressive malignancy, which has a poor prognosis with a median survival of less than 1 year. We recently established clinically relevant orthotopic implantation model of MPM. Using this model, we demonstrated that combined use of the antihuman VEGF neutralizing antibody, bevacizumab, enhanced therapeutic effect of pemetrexed. Moreover, vandetanib, a triple inhibitor of EGFR, VEGFR, and RET, showed dramatic therapeutic activity against MPM expressing RET oncogenic rearrangement and VEGF. Furthermore, we found that Lysophosphatidic acid (LPA), one of the simplest natural phospholipids, was a critical factor on

proliferation though its' receptor LPA_1, and on motility though LPA_2, suggesting novel therapeutic targets against MPM.

D) Development of novel molecular targeted therapy for malignant ascites of gastric cancer.

Peritoneal carcinomatosis is a frequent cause of death in patients with advanced gastric carcinoma. We demonstrated that the CXCR4/CXC12 axis facilitated the development of peritoneal carcinomatosis from gastric carcinoma. These findings suggest that CXCR4 may be a potential therapeutic target for peritoneal carcinomatosis of gastric carcinoma.

E) Early detection and molecular targeted therapy for pancreatic cancer.

Pancreatic cancer is the most chemo-refractory neoplasm, so early detection is essential for improvement the prognosis. By the highly sensitive methylation-specific polymerase chain reaction (MSP) and quantitative MSP (Q-MSP) assay using the pure pancreatic juice (PPJ), we found that promoter methylation of TFPI-2 in the PPJ could be a useful marker in the diagnosis of pancreatic cancer using an endoscopically feasible approach.