

## Department of Surgery

### Division of Thoracic Surgery and of Breast and Endocrine Surgery

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#### Thoracic Surgery

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### General Summary

The Divisions of Thoracic Surgery and of Breast and Endocrine Surgery were established in June 2005. Since then, we have provided comprehensive diagnostic and therapeutic services for patients with surgical diseases of the chest, breast, and endocrine system. We are leaders in our fields of surgery, with a focus on minimally invasive surgery.

### Research Activities

#### *Thoracic Surgery*

Thoracic surgeons of The Jikei University connect biomedical breakthroughs to practical applications to improve lives. Clinical research is an important part of our program and can provide novel treatments before they are widely available. Our research topics include (1) pulmonary function after lung resection, (2) surgery for lung cancer with oligometastatic disease, and (3) the effect of pleural abrasion and coverage with a polyglycolic acid sheet for pneumothorax. We are also involved in multiple basic research studies to understand, diagnose, and develop new treatments for pulmonary disorders and lung cancer.

Lung transplantation has become a well-established therapy for patients with severe or terminal pulmonary diseases that cannot be cured completely by medical treatments. Bronchiolitis obliterans and bronchiolitis obliterans-related syndrome are recognized as severe complications of lung transplantation. We have hypothesized that carbon monoxide can improve bronchiolitis obliterans through the inhibition of T-cell infiltration and the downregulation of inflammatory cytokine expressions in the transplanted grafts. To assess this hypothesis, we will examine the effect of carbon monoxide with an artificial gas carrier in a mouse model of orthotopic tracheal transplant.

We are also starting our basic research in oncology. Tumors exhibit multiple somatic mutations. Neoantigens derived from such tumor-specific mutations are potential targets for antitumor immune responses. The role of neoantigens in naturally occurring and therapeutically induced immune responses to cancer. We are planning to investigate mutation burden, neoantigen load, and the depletion of expected antigenic mutations in cases of lung cancer surgically removed by our division. Our aim is to find the new neoantigens derived from tumor-specific mutations that can be targets for antitumor immune

responses.

### *Breast and Endocrine*

#### 1. Clinical study

1) Immediate breast reconstruction is rarely performed after neoadjuvant chemotherapy. The purpose of our clinical study is to evaluate the short- and long-term outcomes of this procedure after neoadjuvant chemotherapy in patients with breast cancer.

2) We have participated in a multicenter clinical trial to evaluate the oncological safety of patients with metastases to 1 or 2 sentinel nodes after omission of axillary lymph node dissection.

3) Aromatase inhibitors have been established as the gold-standard therapy for postmenopausal patients. We plan to participate in a multicenter clinical trial to evaluate the efficacy of denosumab for the treatment of aromatase inhibitor-associated bone loss in Japan.

4) Cryoablation with extremely cold temperatures to destroy tumor tissues has been recognized as a highly efficient cancer therapy and is used to treat several types of cancer, including those of the breast, skin, prostate, and bone. The efficacy and side effects have been evaluated in patients with early-stage breast cancer.

#### 5) Therapeutic strategy for oligometastatic breast cancer

For 30 years we have analyzed patients with metastatic breast cancer. The analysis indicates that oligometastatic breast cancer is a distinct subgroup with a long-term prognosis superior to that of other metastatic breast cancers. We are performing prospective studies to characterize oligometastatic breast cancer and to evaluate the efficacy of a multidisciplinary strategy, including medication, radiotherapy, and resection, to improve prognosis.

6) Because of recent progress in the diagnosis and treatment of breast cancer and with the development of fertility preservation, oncofertility has become more important. With close cooperation among healthcare providers, we analyzed how we provide information of fertility preservation to young patients with breast cancer.

7) Lenvatinib, a tyrosine kinase inhibitor, prolongs the progression-free survival of patients with thyroid cancer. We have participated in a multicenter clinical trial to evaluate the antitumor effects and side effects of lenvatinib for patients with thyroid carcinomas, including papillary carcinoma, medullary carcinoma, and undifferentiated carcinoma.

#### 2. Basic research

1) In breast cancer, cells with high expression of CD44 and with no or very low levels of CD24 are identified as cancer stem cells. Several previous studies have shown that CD44+/CD24-/low tumor cells in primary breast cancer are prognostic factors for relapse and survival. How CD44+/CD24-/low tumor cells in metastatic sites affect outcome has been unclear. We have analyzed the presence of CD44+/CD24-/low tumor cells among metastatic tumor cells to identify any biological characteristics that reflect long-term survival.

#### 2) Dual specificity tyrosine phosphorylation regulated kinase 2

Accumulating evidence suggests that dual-specificity tyrosine-regulated kinase 2 (DYRK2) functions as a tumor suppressor by regulating cell survival, differentiation, proliferation, and apoptosis. However, little is known about the mechanisms of transcrip-

tional regulation by DYRK2 in cancer progression. We found that reduced DYRK2 expression increases cyclin-dependent kinase 14 (CDK14) expression, which promotes cancer cell proliferation and invasion in vivo. Expression of CDK14 and of DYRK2 are inversely correlated in human breast cancer tissues.

### 3) The detection of antigens of thyroid carcinoma in sera

A monoclonal antibody, designated JT-95, was made against a thyroid papillary carcinoma obtained by the Department of Breast and Endocrine Surgery. We are attempting, in collaboration with the Molecular Cell Biology Division of The Jikei University, to measure the antigen recognized by JT-95 in the serum of patients with papillary carcinoma. The quantity of the JT-95 antigen is higher in patients with papillary carcinoma, especially those with metastasis to lung or bone, than in patients with breast carcinoma. We are now trying to improve chromatography for JT-95 to more easily detect thyroid carcinoma antigens.

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