Progress report 2015

Department of Immunotherapeutics

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■ Introduction and Organization

The aim of our Department is to execute basic and clinical research on cancer immunology and immunotherapy and to establish its role in the treatment of cancer. Cancer immunotherapy requires the expansion of functional T cells and/or dendritic cells (DC) that are responsible for the anti-tumor immune response in vivo. The GMP-level Cell Processing Center (CPC) was installed in the Department. Peripheral blood mononuclear cells (PBMC) are isolated from the patients and processed in the CPC to ensure that they maintain optimal functionality, or for triggering new functions in vitro prior to clinical application. Autologous cells derived from cancer patients are processed for therapeutic use in our CPC in accordance with all current regulations and ethical obligations.

To perform reliable high quality translational research, we designed our Department’s facilities literally from the bench to the bedside. The Department consists of three divisions, (1) laboratory for basic and pre-clinical research (2); Cell Processing Center and (3) outpatient clinic. Because these three divisions are situated side-by-side on the same floor, close cooperation between the members of each group can be more easily and better organized. As soon as blood is drawn from the patient at the outpatient clinic, it is directly transferred to the CPC through the pass-box between the two. The cells processed and cultured in the CPC are scrutinized in the laboratory next door to the clinic and CPC regarding their quality and function. Those cultured cells which are approved following this examination are transferred back to the clinic and administered to the patient. The patients are followed-up at regular intervals by the research staff at the laboratory to monitor their immune responses to evaluate the impact of the immunotherapy.

All protocols for cancer immunotherapy performed in our Department are submitted to the institutional review board (IRB). Once approved, the protocols are registered in the UMIN clinical research registration system to provide open access to any interested parties. Because the cells used for treatment are derived from each individual patient; it is really difficult to guarantee consistent quality. However, we do everything possible to provide the cultured cells with the best conditions, by means of well-trained specialist staff following standard operating procedures. All these efforts allow us to reliably perform cancer immunotherapy clinical trials in cooperation with many clinical departments of the University of Tokyo Hospital.

■ Clinical activities

We provide outpatient services for cancer patients. All interventions performed in the department are defined by the protocols of the particular clinical trial approved by the IRB. The following clinical trials are underway in our department:

Dendritic cell therapy

1. UMIN registration number: UMIN000002837
   IRB number: 2759
   Safety, efficacy and immunogenicity of autologous tumor lysate-pulsed dendritic cell therapy after resection of stage2A (T2N0,T3N0) esophageal cancer

2. UMIN registration number: UMIN000006646
   IRB number: P2011025-11Z
   Safety, efficacy and immunogenicity of concomitant interferon alpha and autologous tumor lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma
γδ T cell therapy for advanced cancer

3. UMIN registration number: UMIN000006128
   active, recruiting
   IRB number: P2011018-11Z

4. UMIN registration number: UMIN000001419
   active, recruiting
   IRB number: 2120-(1)
   The efficacy and safety of autologous γδ T cell transfer therapy for esophageal cancer

5. UMIN registration number: UMIN000001184
   active, recruiting
   IRB number: P2012053-11Z
   Intraperitoneal autologous γδ T cell therapy for refractory gastric cancer with ascites

6. UMIN registration number: UMIN000008097
   active, recruiting
   IRB number: P201019-11Z
   Combination of chemotherapy with docetaxel / cisplatin / fluorouracil (DCF) and autologous γδ T cell transfer therapy for esophageal cancer.

Immunomodulator (anti-CCR4 mAb)

8. UMIN registration number: UMIN000010050
   Open public recruiting
   IRB number: 2013040-11DX
   <Phase Ia>
   To assess the safety and pharmacokinetics of weekly repeated doses of Mogamulizumab.
   <Phase Ib>
   To assess the safety and effect of Treg depletion of weekly repeated doses of Mogamulizumab.

Research activities

All of our research activities are directed at understanding the dynamics of the immune response in vivo at the molecular, cellular and organismal levels and to develop more effective immunotherapy against cancer. To this end, we perform both clinical immunology in humans and basic preclinical immunology using animal models. We especially focus on the spatiotemporal analysis of anti-tumor immunity in both humans and experimental animals. During the course of each trial, many samples from the clinic are delivered to the research laboratory to monitor immune responses in patients. Tumor-specific immunity is evaluated using standardized immunological assays, such as ELISA, ELISPOT and flow cytometry.

To develop novel immunological interventions, tumor-bearing mice are used to confirm principles believed to be the basis for the new immunotherapy. Using many different TCR-transgenic and human MHC class I-bearing mice we can provide clear answers regarding the antigen-specific immune response. As described above, we pursue a research strategy of going back and forth from the bench to the bedside and from basic to clinical immunology in order to maximize benefit to patients via the rapid application of new knowledge to clinical practice.

There are currently three major approaches to T cell-based cancer immunotherapy, namely, active vaccination, adoptive cell transfer therapy and immune checkpoint blockade. Recently, this latter approach has demonstrated remarkable clinical benefits, putting cancer immunotherapy under the spotlight. Better understanding of the dynamics of anti-tumor immune responses (the “Cancer-Immunity Cycle”) is crucial for the further development of this form of treatment. Tumors employ multiple strategies to escape from anti-tumor immunity, some of which result from the selection of cancer cells with immunosuppressive activity by the process of cancer immunoediting. Apart from this selective process, anti-tumor immune responses can also be inhibited in multiple different ways which vary from patient to patient. This implies that cancer immunotherapy must be personalized to (1) identify the rate-limiting steps in any given patient, (2) identify and combine strategies to overcome these hurdles, and (3) proceed with the next round of the “Cancer-Immunity Cycle”.

Cancer cells have genetic alterations which can provide the immune system with targets by which to recognize and eradicate the tumor. Mutated proteins expressed exclusively in cancer cells and recognizable by the immune system are known as neoantigens. The development of next-generation sequencing technology has made it possible to determine the genetic landscape of human cancer and facilitated the utilization of genomic information to identify such
candidate neoantigens in individual cancers. Until recently, a major aim of cancer immunotherapy was to identify shared tumor antigens. However, identification of neoantigens and preparation of personalized cancer vaccines in individual patients will become the mainstream of cancer immunotherapy in future because anti-tumor immunity that can control tumor growth focuses on neoantigens.

Therefore, future immunotherapy needs to be personalized in terms of the identification of immunosuppressive mechanisms as well as target antigens and integrated with immune regulatory strategies. For that purpose, intense collaboration between academia, business and regulatory authorities will be crucial.

### List of Publications


### International conference presentation

1. 2015/7/10, ICCIM2015 (International Conference of Cancer Immunotherapy and Macrophages 2015), Tokyo, Japan, (Symposium ・Invited) Kazuhiro Kakimi, CTL-therapy induced Tumor immunosuppressive Environment

2. 2016/3/4, International medical interface symposium (2016IBMI), Taipei City, Taiwan, (Symposium ・Invited), Kazuhiro Kakimi, Toward personalized cancer immunotherapy