

## 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  
active, recruiting  
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  
active, recruiting  
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

### $\gamma\delta$ T cell therapy for advanced cancer

3. UMIN registration number : UMIN000006128  
active, recruiting  
IRB number : P2011018-11Z  
Adoptive immunotherapy using zoledronate-expanded autologous  $\gamma\delta$  T cells for patients with non-small cell lung cancer refractory to standard treatment.
4. UMIN registration number : UMIN000001419  
active, recruiting  
IRB number : 2120-(1)  
The efficacy and safety of autologous  $\gamma\delta$  T cell transfer therapy for esophageal cancer
5. UMIN registration number : UMIN000004130  
active, not recruiting  
IRB number : P201019-11Z  
Intraperitoneal autologous  $\gamma\delta$  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  $\gamma\delta$  T cell transfer therapy for esophageal cancer.
7. UMIN registration number : UMIN000011184  
active, recruiting  
IRB number : P2012053-11Z  
Hepatic arterial infusion of autologous gamma/delta T cell for advanced hepatocellular carcinoma

### 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

- Hirano K, Hosoi A, Matsushita H, Iino T, Ueha S, Matsushima K, Seto Y, Kakimi K. The nitric oxide radical scavenger carboxy-PTIO reduces the immunosuppressive activity of myeloid-derived suppressor cells and potentiates the antitumor activity of adoptive cytotoxic T lymphocyte immunotherapy. *Oncoimmunology*. 2015 Apr 1;4(8):e1019195.
- Ueha S, Yokochi S, Ishiwata Y, Ogiwara H, Chand K, Nakajima T, Hachiga K, Shichino S, Terashima Y, Toda E, Shand FH, Kakimi K, Ito S, Matsushima K. Robust Antitumor Effects of Combined Anti-CD4-Depleting Antibody and Anti-PD-1/PD-L1 Immune Checkpoint Antibody Treatment in Mice. *Cancer Immunol Res*. 2015 Jun;3(6):631-40.
- Kurose K, Ohue Y, Wada H, Iida S, Ishida T, Kojima T, Doi T, Suzuki S, Isobe M, Funakoshi T, Kakimi K, Nishikawa H, Uono H, Oka M, Ueda R, Nakayama E. Phase Ia Study of FoxP3+ CD4 Treg Depletion by Infusion of a Humanized Anti-CCR4 Antibody, KW-0761, in Cancer Patients. *Clin Cancer Res*. 2015 Oct 1;21(19):4327-36.
- Futami J, Nonomura H, Kido M, Niidoi N, Fujieda N, Hosoi A, Fujita K, Mandai K, Atago Y, Kinoshita R, Honjo T, Matsushita H, Uenaka A, Nakayama E, Kakimi K. Sensitive Multiplexed Quantitative Analysis of Autoantibodies to Cancer Antigens with Chemically S-Cationized Full-Length and Water-Soluble Denatured Proteins. *Bioconjug Chem*. 2015 Oct 21;26(10):2076-84.
- Guidance Development Review Committee; Working Group for Clinical Studies of Cancer Immunotherapy; Working Group for Effector Cell Therapy; Working Group for CMC/Non-clinical Studies; Working Group for Cancer Vaccines and Adjuvants; Working Group for Anti-immune Checkpoint Therapy and Comprehensive Cancer Immunotherapy; Biostatistics Subcommittee. 2015 Guidance on cancer immunotherapy development in early-phase clinical studies. *Cancer Sci*. 2015 Dec;106(12):1761-71.
- Karasaki T, Nagayama K, Kawashima M, Hiyama N, Murayama T, Kuwano H, Nitadori JI, Anraku M, Sato M, Miyai M, Hosoi A, Matsushita H, Kikugawa S, Matoba R, Ohara O, Kakimi K, Nakajima J. Identification of Individual Cancer-Specific Somatic Mutations for Neoantigen-Based Immunotherapy of Lung Cancer. *J Thorac Oncol*. 2015 Dec 29;11(3):324-333.

### ■ International conference presentation

- 2015/7/10, ICCIM2015 (International Conference of Cancer Immunotherapy and Macrophages 2015), Tokyo, Japan, (Symposium • Invited) Kazuhiro Kakimi, CTL-therapy induced Tumor immunosuppressive Environment
- 2016/3/4, International medical interface symposium (2016IBMI), Taipei City, Taiwan, (Symposium • Invited), Kazuhiro Kakimi, Toward personalized cancer immunotherapy