Progress report 2022

Department of Immunotherapeutics

Project Professor: Kazuhiro Kakimi, M.D., Ph.D.
Project Assistant Professor: Koji Nagaoka, Ph.D.
Project Assistant Professor: Yukari Kobayashi
Research Assistant: Yaeko Furuhashi
Mikiko Shibuya
Yuki Konakai

Homepage http://immunoth.umin.jp/

■ Introduction and Organization

Since immune checkpoint blockade therapies were approved for the treatment of many cancer types, remarkable clinical responses have been achieved in a certain proportion of patients. Nonetheless, many patients are unresponsive, and there remain several tumor types that are refractory to immunotherapy. Multiple immunosuppressive mechanisms operate in the tumor microenvironment (TME), and any anti-tumor immune cells that might be present are often impaired in the TME.

Thus, effective immunotherapy requires a combination of potent stimulation of anti-tumor immune responses and, additionally, manipulation of the immunosuppressive environment to prevent tumor escape. Therefore, elucidating the mechanisms of responsiveness or refractoriness and the molecular determinants thereof is required to improve cancer immunotherapy.

The study objective of our department is to demonstrate the feasibility of an immunological data-guided personalized adaptive approach to immunotherapy, whereby immunomodulatory strategies are tailored to the patient's specific TME.

■ Research activities Research activities

In the AMED Innovative Cancer Therapy Practical Research Project, "Development of TCR-T cell therapy specific for neoantigen and analysis of tumor immune response using whole genome information," genomic analysis of sarcoma, lung cancer, and gastric cancer was conducted. In addition to analyzing the immune genome response in tumors, a method for analyzing neoantigens based on whole genome data was developed, and TCR gene cloning and introduction methods for neoantigen-specific T cells were established. These efforts led to the development of a neoantigen-specific TCR-T cell therapy that integrates these methods.

■ List of Publications

1. Izawa M, Tanaka N, Murakami T, Anno T, Teranishi Y, Takamatsu K, Mikami S, Kakimi K, Imamura T, Matsumoto K, Oya M. Single-Cell Phenotyping of CD73 Expression Reveals the Diversity of the Tumor Immune Microenvironment and Reflects the Prognosis of Bladder Cancer. Lab Invest. 2023 Jan 10;103(4):100040. doi:10.1016/j.labinv.2022.100040. Epub ahead of print. PMID: 36870289.
2. Chen P, Yang W, Nagaoka K, Huang GL, Miyazaki T, Hong T, Li S, Igarashi K, Takeda K, Kakimi K, Kataoka K, Cabral H. An IL-12-Based Nanocytokine Safely Potentiates Anticancer Immunity through Spatio-

temporal Control of Inflammation to Eradicate Advanced Cold Tumors. Adv Sci (Weinh). 2023 Feb 5:e2205139. doi:10.1002/advs.202205139. Epub ahead of print. PMID: 36739605.

3. Ishii T, Mimura I, Nagaoka K, Naito A, Sugasawa T, Kuroda R, Yamada D, Kanki Y, Kume H, Ushiku T, Kakimi K, Tanaka T, Nangaku M. Effect of M2-like macrophages of the injured-kidney cortex on kidney cancer progression. Cell Death Discov. 2022 Dec 5;8(1):480. doi: 10.1038/s41420-022-01255-3. PMID: 36470862; PMCID: PMC9722672.

4. Sun C, Nagaoka K, Kobayashi Y, Maejima K, Nakagawa H, Nakajima J, Kakimi K. Immunotherapies targeting neoantigens are effective in PD-1 blockade-resistant tumors. Int J Cancer. 2022 Nov 30. doi: 10.1002/ijc.34382. Epub ahead of print. PMID: 36451303.

5. Teshima T, Kobayashi Y, Kawai T, Kushihara Y, Nagaoka K, Miyakawa J, Akiyama Y, Yamada Y, Sato Y, Yamada D, Tanaka N, Tsunoda T, Kume H, Kakimi K. Principal component analysis of early immune cell dynamics during pembrolizumab treatment of advanced urothelial carcinoma. Oncol Lett. 2022 Jun 16;24(2):265. doi: 10.3892/ol.2022.13384. PMID: 35765279; PMCID: PMC9219027.

6. Miyamoto A, Honjo T, Masui M, Kinoshita R, Kumon H, Kakimi K, Futami J. Engineering Cancer/Testis Antigens With Reversible S-Cationization to Evaluate Antigen Spreading. Front Oncol. 2022 May 4;12:869393. doi: 10.3389/fonc.2022.869393. PMID: 35600379; PMCID: PMC9115381.

7. Saito N, Sato Y, Abe H, Wada I, Kobayashi Y, Nagaoka K, Kushihara Y, Ushiku T, Seto Y, Kakimi K. Selection of RNA-based evaluation methods for tumor microenvironment by comparing with histochemical and flow cytometric analyses in gastric cancer. Sci Rep. 2022 May 20;12(1):8576. doi:10.1038/s41598-022-12610-w. PMID: 35595859.

8. Sato S, Matsushita H, Shintani D, Kobayashi Y, Fujieda N, Yabuno A, Nishikawa T, Fujiwara K, Kakimi K, Hasegawa K. Association between effector-type regulatory T cells and immune checkpoint expression on CD8+ T cells in malignant ascites from epithelial ovarian cancer. BMC Cancer. 2022 Apr 21;22(1):437. doi: 10.1186/s12885-022-09534-z. PMID: 35449092; PMCID: PMC9026673.