Social Cooperation Research Program

Division of Clinical Precision Research Platform

臨床精密研究基盤社会連携研究部門

Project Professor	Satoshi Takahashi, M.D., D.M.Sc.	特任教授　博士（医学）	高　橋　　聡
Project Assistant Professor	Kimihito Kawabata, M.D., D.M.Sc.	特任助教　博士（医学）	川　畑　公　人

Our research objectives are to conduct precision research for the development of precision medicine, to combine comprehensive multi-omics analysis including clinical epigenomics and single-cell sequencing with drug sensitivity screening (DSS) in hematopoietic diseases and colorectal cancer, to study each method for these integrated data analysis, and to understand diseases and create new treatments. Missions for this include conducting optimizing methods for processing small amounts of clinical specimens, promoting miniaturization and automation of drug sensitivity test, and model establishment, and conducting research that leads to clinical applications. We have a joint research agreement with Daiichi Sankyo RD Novare Co., Ltd. in 2021 and are pursuing our research activity.

In 2022, we continued to focus on the development of experimental flow for DSS using primary tumor specimens derived from patients with hematologic malignancies. In order to build a novel platform for precision medicine projects combining DSS and comprehensive multi-omics analysis, we aimed to optimize tissue culture methods for leukemia cells obtained from patients with acute myeloid leukemia. Using clinical specimens provided by the Department of Hematology and Oncology, IMSUT Hospital, we evaluated the optimal tissue culture conditions for 3 to 9 days of ex vivo coculture with chemotherapeutic drugs/ epigenetic compounds. As a result, we were able to establish an in-house tissue culture medium that could maintain the hematopoietic stem cell and progenitor cell-like fractions of AML cells throughout the ex vivo drug treatment period. While processing these cells, we also established a high-throughput assay system using automated technologies.

These efforts are highly expected to become a tool for elucidating the pathophysiology of hematologic malignancies and developing further therapeutics.

1. Clinical precision research for hematological diseases by genomic and multi omics analysis

Kimihito Cojin Kawabata[1], Hironobu Komori[1,2], Hayato Tsuji[1,2], Yoshiharu Takama[1,2], Seiko Kato[1], Maiko Morita[1], Kiyoko Izawa[1], Sanae Suzuki[1], Tetsushi Oka[2], Yoshimasa Ono[2], Kenji Wakabayashi[2], Gen Kudo[2], Satoshi Takahashi[1].

[1] IMSUT, [2] Daiichi Sankyo RD Novare Co., Ltd.

Currently, our entire research network is already working within or outside IMSUT on whole genome, RNA expression, transcriptome, DNA methylation, and genome structure analysis of malignant hematopoietic cells, aiming to compare the analysis at the single cell level with the actual clinical course of the

patient. Our group is now focused on installing the DSS part of the project based on good scientific evidence.

In order to validate the tissue culture conditions of primary AML specimens by our group and collaborators, or potentially optimize them for the precision research platform, we repeated the testing of clinical specimens kindly provided by the Department of Hematology and Oncology based on the goodwill of patients. The initial culture conditions for side-by-side comparison were based on previous experiences with ex vivo culture of AML specimens (Kawabata et.al, Blood, 2021, and MS in preparation), and each of the key questions "What is the optimal concentration of serum?" and "Is the use of a serum substitute beneficial for tumor specimens?" were carefully tested. After careful evaluation and further discussion of these data, we were able to find the optimal in-house tissue culture medium for primary AML specimens cultured for up to 9 days while maintaining a certain level of immature components (such as CD34 positive fraction). Those pilot experiments are extremely important because the information obtained from these cultured cells will be used in DSS and omics research. We are now able to treat the specimens for 6 days under these "tentative" optimal culture conditions and have already started this DSS culture system with several AML samples. The next step is to attempt long-term culture and expand the valuable but quantitatively limited primary cultures ex vivo.

Finally, by integrating this information, we plan to advance more precise pathological analysis, search for factors involved in drug sensitivity, and then translate the results back to the clinic to create an analysis system that will assist in real-time decision-making on treatment strategies. In addition to these clinical implications, the project will also shed light on multiple hotspots, including biomarker discovery, the immune environment of hematologic malignancies, detection of minimal residual disease, and even basic biology such as epigenetic regulation.

2. Generation of antigen-specific T cells derived from cord blood

Morita Maiko[1], Kimihito Cojin Kawabata[1], Kiyoko Izawa[1], Satoshi Yamazaki[1,2], Ai Tachikawa-Kawana[1,3], Patrick Hanley[4], Catherin Bollard[4], Seiko Kato[1], Satoshi Takahashi[1]

[1] IMSUT, [2] University of Tsukuba, [3] National Institute of Infectious Diseases, [4] Children's National Research Institute

This project aims to establish a method other than gene transfer to generate and amplify viral antigen-specific T cells from naïve T cells derived from umbilical cord blood.

Previous studies have shown that cGAMP, a type of STING ligand, triggers a type IFN response and promotes cross-priming of antigen-specific CD8 + T cells by mature DCs. It has also been reported that cGAMP induces the transcription factor T-bet, which is required for the development of effector CD8 + T cells. When naïve T cells derived from cord blood were cultured with cGAMP and viral antigen peptides twice for 14 days, a significant production of inflammatory cytokines such as IFN-γ and TNF-α was observed. As the next step, we plan to examine culture conditions, such as cytokines and supplements combined with cGAMP, to explore more effective methods of producing and amplifying viral antigen-specific T cells.

Future clinical studies are planned to advance this research and improve the safety of cord blood transplantation by promoting immune reconstitution against viral infection after transplantation.

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