Department of Hematology

Principal Investigator: Norio Komatsu (Professor and Chairman)

The research in our department encompasses a wide range of topics on hematological malignancies, including myeloproliferative neoplasms (MPN), leukemias, lymphomas, myelodysplastic syndromes (MDS) and multiple myelomas (MM). We aim to clarify the molecular pathogeneses of these diseases and utilize this information for diagnosis and treatment. We have also been performing clinical studies based on molecular–targeted therapies and transplantation medicine.

Group Leaders and Research Topics
1) Norio Komatsu (Professor) and Marito Araki (Associate Professor)

We focus on studying Philadelphia chromosome-negative MPN. We developed original assay systems for the detection of JAK2 and MPL mutations that are frequently found in MPN patients. Utilizing these assays, we investigated clinical features associated with gene mutations in Japanese MPN patients and found that “triple-negative” MPN patients are substantially younger than those harboring JAK2, MPL or CALR mutation. This suggests that “triple-negative” Japanese MPN patients have a genetic background that promotes MPN development, which we are investigating by next-generation sequencing.

JAK2, MPL or CALR mutant proteins found in MPN have been shown to induce constitutive activation of cytokine–receptor signaling pathways that include erythropoietin and thrombopoietin. Understanding the cellular mechanisms by which mutant proteins transform cells is crucial to develop better diagnosis and treatment for MPN. Since we previously established a multi-potent hematopoietic model system, UT-7, and its sublines that respond to various cytokines, we utilize these cell lines to study JAK2, MPL and CALR mutant protein function in terms of cell proliferation and differentiation. More recently, we adopted iPS cell technology to advance our findings in a more relevant in vitro model system.

Publications:

Other research projects include understanding the molecular mechanisms of ATRA-induced granulocytic differentiation in acute promyeloid leukemia cells, and screening diagnostic markers for lymphoma by cap analysis of gene expression.

Publications:

2) Akihiko Goto (Senior Associate Professor)

Endoplasmic reticulum (ER) is responsible for protein folding, modification and trafficking. However, some newly synthesized proteins are not folded properly. Although the accumulation of unfolded proteins induces ER stress and triggers the unfolded protein response that acts against stress-mediated cell death, sustained ER stress leads to apoptosis. Proteasome and autophagy are two main protein degradation systems. We hypothesize that concomitant inhibition of proteasome and autophagy in cancer cells will induce enhanced ER stress by the accumulation of unfolded proteins, and result in pronounced cytotoxicity. Actually, in myeloma cells, we demonstrated that macrolide antibiotics block autophagy flux and lead to sensitization to proteasome inhibitor, bortezomib, via ER stress-mediated CHOP induction. Recently, we further delineated the role of aggresome as another target for ER stress-mediated apoptosis. I am currently focusing on other hematologic malignancies including MPN in order to elucidate the role of ER stress in biological and therapeutic aspects.

Publications:

3) Hironori Harada (Associate Professor)
The goal of my research is to clarify the molecular mechanisms of MDS and to establish molecular–targeted therapies for it. My group has been analyzing various gene mutations in myeloid neoplasms. We found that mutations of the RUNXI gene are frequently detected in patients with myeloid neoplasms. Furthermore, we have been investigating the pathogenesis of RUNXI mutants in mouse and human hematopoietic stem cells (HSC). As part of this effort, we have reported that RUNXI mutants induce MDS in collaboration with other gene abnormalities in a mouse BMT model. We are currently analyzing gene abnormalities including in the RUNX family, RNA splicing machinery and epigenetic regulators in the pathogenesis of various types of MDS. Nationwide research of familial MDS is ongoing.
Publications:

4) Masaru Tanaka (Associate Professor)
There are many disease entities in lymphoma, but only a few standard treatments for them. The mission of our group is to establish standard treatments for various types of them, especially for Hodgkin lymphoma and B-cell lymphomas. Our department is a member of the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG-LSG), which has conducted many clinical trials for various types of lymphoma. We are going to achieve our mission by participating in clinical trials of JCOG-LSG.

5) Makoto Sasaki (Associate Professor)
My group has been investigating lymphoid malignancies, especially focusing on MM and its clinical features. We aim to clarify (1) ideal chemotherapy for elderly myeloma patients in Japan, (2) clinical features of various infections and their countermeasures and (3) new diagnostic assays for MM. We established a multicenter multiple myeloma study group, the "Kanto-Tohoku MM Conference" (KT-MM), and have been continuously undertaking research and clinical studies around myeloma.

6) Yasuharu Hamano (Associate Professor)
We have been performing hematopoietic stem cell transplantation medicine. Our group aims to improve treatment outcome. Graft-versus-host diseases (GVHD) remain a major contributor to transplantation-related deaths. Nevertheless, optimal GVHD prophylaxis in cord blood transplantation (CBT) is not obvious. In our group, mycophenolate mofetil (MMF) was employed for GVHD prophylaxis in combination with calcineurin inhibitor. We found that MMF enables faster engraftment and causes less mucositis than methotrexate. MMF may be a feasible option for GVHD prophylaxis in CBT. We are currently analyzing the optimal MMF dose and simple surrogate parameters for therapeutic drug monitoring.

7) Jun Ando (Associate Professor)
I am interested in immunotherapy and gene therapy for lymphoma. My current research focuses on cytotoxic T lymphocyte (CTL) immunotherapy for lymphoma, as I was working as a postdoc of Prof. Rooney at Baylor College of Medicine. I learned how to make antigen–specific CTL, evaluate T-cell functions and to utilize these T cells for clinical therapy. About 30% of lymphomas in immunocompetent individuals carry the Epstein–Barr virus (EBV) genome and express four of about 90 potential viral antigens. We have targeted LMP1 and LMP2 for treatment. We are currently planning a clinical trial using LMP-specific CTL for EBV–associated lymphoma.

8) Tomoku Takaku (Associate Professor)
My research project involves analyzing the role of heparan sulfate proteoglycans (HSPG) in hematopoietic stem cell niche systems. All blood cells are produced by HSC, and the self-renewal of HSC is regulated by the signal from niche cells and signaling molecules included in the extracellular matrix (ECM). Among ECM components, HSPG are crucial controllers of the structural and functional organization of the bone marrow niche. We have been investigating the influence on hematopoiesis of a lack of HSPG in specific niche cells. It is considered that the eradication of leukemic stem cells is difficult by the current therapy. The final goal of our research is to eradicate leukemic stem cells through the analysis of hematopoietic niche systems.
Publications:

9) Hajime Yasuda (Associate Professor)
My research focuses on anemia attributed to vitamin B6 (VB6) deficiency in post–pancreaticoduodenectomy (PD) patients. VB6 deficiency can theoretically occur after PD because of malabsorption. VB6 deficiency causes anemia due to the impairment of heme synthesis. We recently reported two cases of post–PD patients with anemia due to VB6 deficiency, and this anemia resolved in both cases upon the supplementation of VB6. Anemia has been reported to be prevalent in long–term survivors of PD. We are currently planning to investigate VB6 levels along with other micronutrients necessary for hematopoiesis in long–term survivors of PD at our institution.
Publications: