Hematology

The aim of the research being undertaken in our department is to elucidate the causal mechanisms and optimal treatment of hematological disorders, such as bone marrow failure syndrome, leukemia, lymphoma and myeloma. Our main research fields include; 1. Clinical research for the analysis of gene mutations in hematological disorders, introduction of novel drugs against new molecular targets, and gene-transduced cell therapy, 2. Bone marrow microenvironments, such as stromal cells and extracellular vesicles (EVs), 3. reactive oxygen species in tumor cells, 4. graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS) after stem cell transplantation.

Professor
Masayoshi Kobune, M.D., Ph.D.
Interests:
Bone marrow failure syndrome
Hematological tumor stem cell biology

Assistant Professor
Satoshi Iyama, M.D., Ph.D.
Interests:
Acute leukemia
Transplantation immunity
Immunotherapy

Instructor
Hiroto Horiguchi, M.D., Ph.D.
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Interests:
Lymphoma and myeloma
Thrombosis and hemostasis

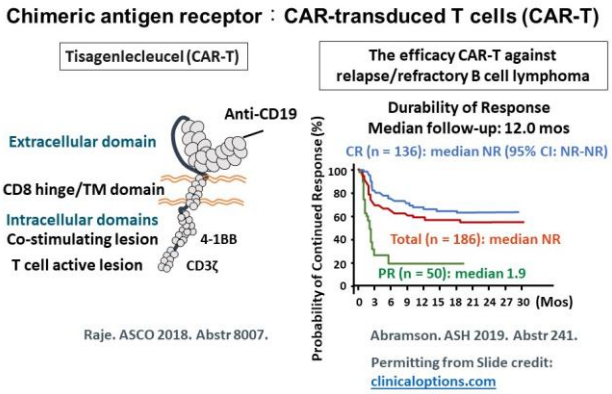
1. Clinical research

Following clinical reseaches are now onging.

a) Hematologic Malignancies (HM)-SCREEN-Japan 02: A multi-center collaborative study aimed at exploring the feasibility of implementing a specific gene genome sequencing kit. The focus is on optimizing the diagnosis of acute myeloid leukemia (AML).

b) Genetic Testing for Blood Disorders: This clinical trial involves genetic testing by using Allele-Specific-PCR or NGS for lymphoplasmacytic lymphoma and myelodysplastic syndromes (MDS) to enhance diagnostic accuracy and aid in treatment selection.

c) CTL019 Phase IIIb Trial (CAR-T) evaluates the safety and efficacy of Tisagenlecleucel, a gene therapy using out of specification products for relapsed/refractory lymphoma.

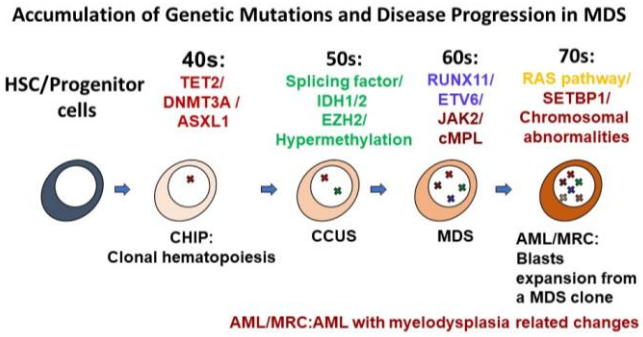


d) Clovalimab: A multicenter, randomized, phase III clinical trial evaluating the efficacy and safety of clovalimab over eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH).

e) Nipocalimab: A multi-center, randomized, double-blind, placebo-controlled trial for Warm Autoimmune Hemolytic Anemia (wAIHA).

2. Bone marrow (BM) failure syndrome

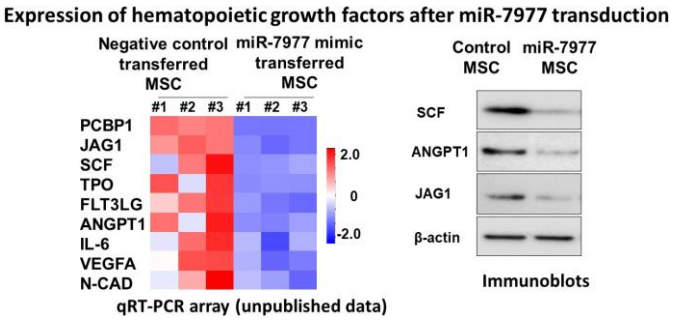
Multiple genomic mutations in bone marrow hematopoietic stem/progenitor cells are implicated in the development of MDS. Among these, founder gene mutations, including TET2, DNMT3A, and ASLX1, are associated with preclinical clonal hematopoiesis, even observable in the bone marrow of healthy volunteers. Subsequently, driver gene mutations have been identified as determinants of the disease-specific phenotype and facilitators of the clonal evolution of MDS stem/progenitor cells.
Additionally, our research revealed that MDS clones highly produce erythroferron, which reduces the production of hepatic hepcidin. Consequently, in some categories of MDS patients, iron absorption from the intestine could be elevated. We are further investigating the role of reactive oxygen species and dysfunction of BM stromal cells.



3. AML and acute lymphoid leukemia (ALL)

The diagnosis and standard chemotherapy for acute leukemia have recently been established, leading to a remarkable improvement in overall survival. However, a subset of elderly patients with acute leukemia has shown resistance to standard therapy. Recently, BCL2 and FLT3 inhibitors have been found to be effective for refractory AML. Further, multi-specific antibody including blinatumomab have been found to be quite effective for acute ALL. Additionally, we have revealed that EVs released from AML cells contain hsa-miR-7977, which targets a splicing factor, PCBP1, and the HIPPO-YAP signaling pathway in mesenchymal stem cells (MSC). The MSC exposed to EVs exhibited a disturbance in the expression of several cytokines and contributed to the upregulation of leukemia-supporting stroma growth.

4. Relapse/Refractory lymphoma



The majority type of lymphoma has been believed to be curable and controllable diseases. However, some types of lymphoma including T cell lymphoma, double-hit lymphoma and Burkitt lymphoma were not always controllable disorders. Therefore, we analyzed the efficacy and safety of novel antibodies such as anti-CCR4, new CD20 antibody, bite-antibody and low molecular compaund such as IMIDs and HDAC inhibitors.

5. Multiple myeloma (MM) and new molecular targets

Recent advance of therapeutic approach using proteasome inhibitors (PI), immunomodulatory drugs (IMiDs) and Anti-CD38 antibody open the new era in the treatment of MM. However, because these drugs have been developed in a short period of time, optimal combination of these drugs and whole therapeutic strategy have not yet been clarified. In this regard, we confirmed the efficacy and safety of reduced dose of VRD (sVRD or VRD-Lite) as a maintenance therapy for Japanese patients. Moreover, we explored new compounds to treat relapse/refractory MM and found that iron chelator deferasirox and small molecule CP-31398 induces reactive oxygen species-dependent apoptosis in MM. In addition, we first identified that high expression of nucleoporin 133 in CD138+ cells was an independent poor prognostic factor in newly diagnosed MM.

6. Transplantation immunity and supportive therapy

Steroid-resistant GVHD are involved in poor prognosis after stem cell transplantation (SCT). We found that Narrowband ultraviolet B phototherapy ameliorates acute GVHD via upregulation of regulatory T cells. We developed the new supportive therapy for mucosal injury after SCT. We further introduced MSC therapy and JAK2 inhibitors to overcome GVHD.

List of Main Publications (2018.9 – 2023.8)

See QR code below