

## Lymphoid Malignancies Group:

**Masao Nakagawa, M.D., Ph.D.**

**Assistant Professor**

**Internal Medicine, Health Care Center, Hokkaido University**

**Department of Hematology, Hokkaido University Graduate School of Medicine**

### EDUCATION:

Postdoctoral Training, National Cancer Institute, National Institutes of Health, Bethesda, MD (2011-2016)

Postdoctoral Training, Aichi Cancer Center Research Institute, Japan (2006-2011)

Ph.D. in Molecular Genetics and Hematology, Hokkaido University Graduate School of Medicine, Japan (2006)

M.D., Hokkaido University School of Medicine, Japan (1998)

### ACADEMIC SOCIETY MEMBERSHIP:

The American Society of Hematology

The Japanese Cancer Association

The Japanese Society of Hematology

The Japanese Society of Internal Medicine

### AWARDS AND FELLOWSHIP:

Research Fellowship of Uehara Memorial Foundation (2010)

The Center for Cancer Research (CCR) Federal Technology Transfer Award (2015)

The Fellows Award for Research Excellence (FARE) Travel Award (2016)

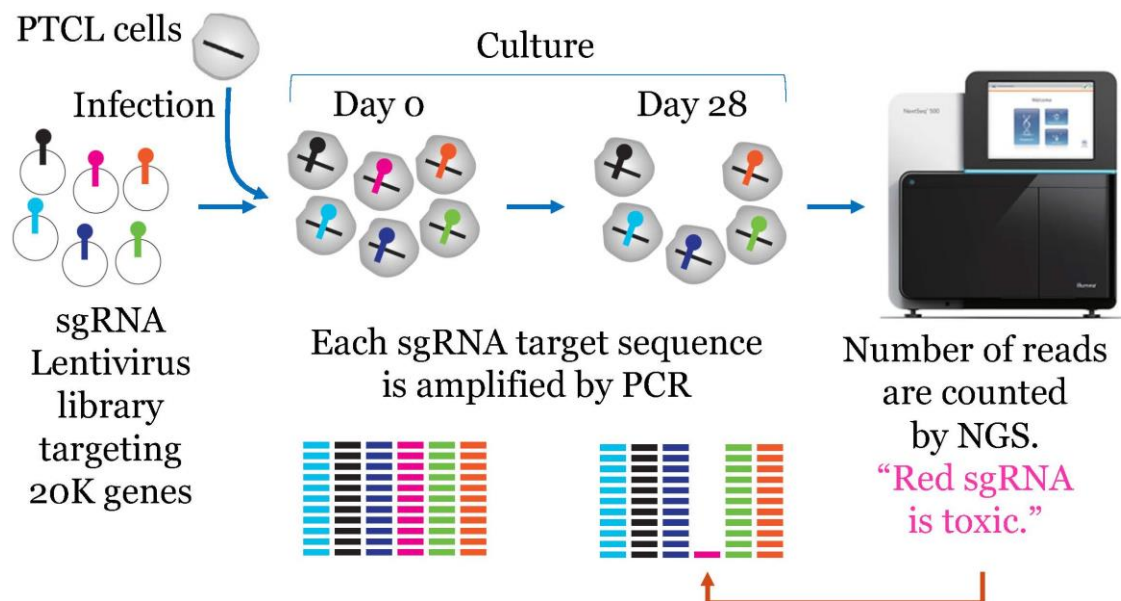
### RESEARCH INTERESTS:

Functional genomics for discovering the therapeutic molecular targets in PTCL

> Identifying the "Achilles' heel" genes in peripheral T-cell lymphomas as molecular targets for therapeutic intervention.

> Defining the molecular mechanisms of frequently mutated CCR4 gene in PTCL.

## CRISPR/Cas9/sgRNA library screening technology



## Overview

Human peripheral T-cell lymphomas (PTCL) is approximately 10 % of non-Hodgkin Lymphomas in worldwide. PTCL comprises heterogeneous diseases, where most are aggressive with less than 40% of 5-year overall survival with current treatment strategy. A discovery for new therapeutic modalities is urgent need.

Recently, the Next generation sequencing technology enabled us to find frequently mutated genes in PTCL. In my previous work as a postdoctoral fellow in Lou Staudt Lab and Thomas Waldmann lab, we discovered frequent gain-of-function mutation in chemokine receptor CCR4 gene in Adult T-cell leukemia/lymphoma (ATLL) and provided functional evidences that inhibition of CCR4 signaling might have therapeutic potential for patients with ATLL. However most of other somatically mutated genes in PTCL were not fully characterized in terms of therapeutic targets. On the other hand, it has been recently known that the malignant cells potentially acquire the dependency on un-mutated genes which is the phenomenon called as "non-oncogene addiction". These observations indicate that non-biased and comprehensive functional investigation should be conducted in order to discover the therapeutic molecular targets in PTCL.

The goal of our laboratory is to understand the oncogenic molecular networks in PTCL which can be exploited for therapeutic intervention. To directly address this issue, our lab applies revolutionizing CRISPR/Cas9/sgRNA library screening technology to the following functional investigation.

- 1) Identifying indispensable pathways/molecules for the cellular proliferation/survival of PTCL cells, especially ATLL.
- 2) Discovering the pathways/molecules associated with drug-resistance or drug-sensitivity in PTCL cells.

## **FUNDED GRANTS:**

2011	Grant-in-Aid for Young Scientists (B), Research Project Number:23791095, JSPS, Japan.
2009-2010	Grant-in-Aid for Young Scientists (B), Research Project Number:21790930, JSPS, Japan.
2007-2008	Grant-in-Aid for Young Scientists (B), Research Project Number:19790678, JSPS, Japan.

## **PUBLICATION LIST:**

01. Chen, J., Zhang, Y., Petrus, MN., Xiao, W., Nicolae, A., Raffeld, M., Pittaluga, S., Bamford, RN., Nakagawa, M., Ouyanga, S., Epsteine, AL., Kadin, ME., Del Mistro, A., Woessnerh, R., Jaffe, ES., Waldmann, TA. Cytokine receptor signaling is required for the survival of ALK- anaplastic large cell lymphoma even in the presence of JAK1/STAT3 mutations. Proc. Natl. Acad. Sci. U S A, 2017. In Press.
02. Yang, Y., Kelly, P., Shaffer, AL., Schmitz, R., Yoo, HM., Liu, X., Huang, da W., Webster, D., Young, RM., Nakagawa, M., Ceribelli, M., Wright, GW., Yang, Y., Zhao, H., Yu, X., Xu, W., Chan, WC., Jaffe, ES., Gascoyne, RD., Campo, E., Rosenwald, A, Ott, G., Delabie, J., Rimsza, L., Staudt, LM. Targeting Non-proteolytic Protein Ubiquitination for the Treatment of Diffuse Large B Cell Lymphoma. Cancer Cell, 29:494-507, 2016.
03. Hodson, DJ., Shaffer, AL., Xiao, W., Wright, GW., Schmitz, R., Phelan, JD., Yang, Y., Webster, DE., Rui, L., Kohlhammer, H., Nakagawa, M., Waldmann, TA., Staudt, LM. Regulation of normal B-cell differentiation and malignant B-cell survival by OCT2. Proc. Natl. Acad. Sci. U S A, 113:E2039-46, 2016.
04. Nakagawa, M., Schmitz, R., Xiao, W., Goldman, CK., Yang, Y., Xu, W., Yu, X., Waldmann, TA., Staudt, LM. Gain-of-Function CCR4 Mutations in Adult T-cell Leukemia/Lymphoma. J. Exp. Med., 211:2497-505, 2014.

05. Yu, P., Petrus, MN., Ju, W., Zhang, M., Conlon, KC., Nakagawa, M., Maeda, M., Bamford, RN., Waldmann, TA. Augmented efficacy with the combination of blockade of the Notch-1 pathway, bortezomib and romidepsin in a murine MT-1 adult T-cell leukemia model. *Leukemia*, 29:556-66, 2014.
06. Suguro, M., Yoshida, N., Umino, A., Kato, H., Tagawa, H., Nakagawa, M., Fukuhara, N., Karnan, S., Takeuchi, I., Hocking, TD., Arita, K., Karube, K., Tsuzuki, S., Nakamura, S., Kinoshita, T., Seto, M. Clonal heterogeneity of lymphoid malignancies correlates with poor prognosis. *Cancer Sci.*, 105:897-904, 2014.
07. Karube, K., Nakagawa, M., Tsuzuki, S., Takeuchi, I., Honma, K., Nakashima, Y., Shimizu, N., Ko, YH., Morishima, Y., Ohshima, K., Nakamura, S., Seto, M. Identification of FOXO3 and PRDM1 as tumor-suppressor gene candidates in NK-cell neoplasms by genomic and functional analyses. *Blood*, 118: 3195-204, 2011.
08. Nakagawa, M., Tsuzuki, S, Honma, K., Taguchi, O., Seto, M. Synergistic effect of *Bcl2*, *Myc* and *Ccnd1* transforms mouse primary B-cells into malignant cells. *Haematologica*, 96: 1318-1326, 2011.
09. Umino, A., Nakagawa, M., Utsunomiya, A., Tsukasaki, K., Taira, N., Katayama, N., Seto, M. Clonal evolution of adult T-cell leukemia/lymphoma takes place in lymph node. *Blood*, 117: 5473-5478, 2011.
10. Kato, H., Kagami, Y., Nakagawa, M., Karnan, S., Yatabe, Y., Nakamura, S., Morishima, Y., Seto, M. IL-4/CD40L Co-Stimulation Induces Long-Term Proliferation for CD10-Positive Germinal Center B Cell-Like Diffuse Large B-Cell Lymphoma. *The Open Leukemia Journal*, 3: 60-68, 2010.
11. Seto, M., Honma, K., Nakagawa, M. Diversity of genome profiles in malignant lymphoma. *Cancer Sci.*, 101: 573-578, 2010.
12. Honma, K. Tsuzuki, S. Nakagawa, M., Tagawa, H., Nakamura, S., Morishima, Y., Seto, M. TNFAIP3/A20 functions as a novel tumor suppressor gene in several subtypes of non-Hodgkin lymphomas. *Blood*, 114: 2467-2475, 2009.
13. Nakagawa, M., Nakagawa-Oshiro, A., Karnan, S., Tagawa, H., Utsunomiya, A., Nakamura, S., Takeuchi, I., Ohshima, K., Seto, M. Array CGH analysis of PTCL-U reveals a distinct subgroup with genetic alterations similar to lymphoma-type ATLL. *Clin. Cancer Res.*, 15: 30-38, 2009.
14. Takeuchi, I., Tagawa, H., Tsujikawa, A., Nakagawa, M., Katayama-Suguro, M., Guo, Y., Seto, M. The potential of copy number gains and losses, detected by array-based comparative genomic hybridization, for computational differential diagnosis of B-cell lymphomas and genetic regions involved in lymphomagenesis. *Haematologica*, 94: 61-69, 2009.
15. Hashino, S., Kobayashi, S., Takahata, M., Onozawa, M., Nakagawa, M., Kawamura, T., Fujisawa, F., Izumiyama, K., Kahata, K., Kondo, T., Asaka, M. Graft-versus-tumor effect after reduced-intensity allogeneic hematopoietic stem cell transplantation in a patient with advanced colon cancer. *Int. J. Clin. Oncol.*, 13: 176-180, 2008.
16. Hashino, S., Morita, L., Takahata, M., Onozawa, M., Nakagawa, M., Kawamura, T., Fujisawa, F., Kahata, K., Izumiyama, K., Yonezumi, M., Chiba, K., Kondo, T., Asaka, M. Administration of micafungin as prophylactic antifungal therapy in patients undergoing allogeneic stem cell transplantation. *Int. J. Hematol.*, 87: 91-97, 2008.
17. Honma, K., Tsuzuki, S., Nakagawa, M., Karnan, S., Aizawa, Y., Kim, WS., Kim, YD., Ko, YH., Seto, M. TNFAIP3 is the target gene of chromosome band 6q23.3-q24.1 loss in ocular adnexal marginal zone B cell lymphoma. *Genes Chrom. Cancer*, 47: 1-7, 2008.
18. Nakagawa, M., Hashino, S., Takahata, M., Kawamura, T., Fujisawa, F., Kahata, K., Kondo, T., Imamura, M., Ando, S., Asaka, M. Successful reduced-intensity stem cell transplantation with

- cord blood for a poor-prognosis adult with refractory chronic active Epstein-Barr virus infection. *Int. J. Hematol.*, 85: 443-445, 2007.
19. Fukuhara, N., Nakamura, T., Nakagawa, M., Tagawa, H., Takeuchi, I., Yatabe, Y., Morishima, Y., Nakamura, S., Seto, M. Chromosomal imbalances are associated with outcome of *Helicobacter pylori* eradication in t(11;18)(q21;q21) negative gastric MALT lymphomas. *Genes Chrom. Cancer*, 46: 784-790, 2007.
  20. Onozawa, M., Hashino, S., Takahata, M., Fujisawa, F., Kawamura, T., Nakagawa, M., Kahata, K., Kondo, T., Ota, S., Tanaka, J., Imamura, M., Asaka, M. Relationship between preexisting anti-varicella-zoster virus (VZV) antibody and clinical VZV reactivation in hematopoietic stem cell transplantation recipients. *J. Clin. Microbiol.*, 44: 4441-4443, 2006.
  21. Nakagawa, M., Seto, M., Hosokawa, Y. Molecular pathogenesis of MALT lymphoma: two signaling pathways underlying anti-apoptotic effect of API2-MALT1 fusion protein. *Leukemia*, 20: 929-936, 2006.
  22. Nakagawa, M., Hosokawa, Y., Yonezumi, M., Izumiyama, K., Suzuki, R., Tsuzuki, S., Asaka, M., Seto, M. MALT1 contains nuclear export signals and regulates cytoplasmic localization of BCL10. *Blood*, 106: 4210-4216, 2005.
  23. Hosokawa, Y., Suzuki, H., Nakagawa, M., Lee, T.H., Seto, M. API2-MALT1 fusion protein induces transcriptional activation of the API2 gene through NF-kappaB binding elements: Evidence for a positive feed-back loop pathway resulting in unremitting NF-kappaB activation. *Biochem. Biophys. Res. Commun.*, 334: 51-60, 2005.
  24. Nakagawa, M., Kameoka, Y., Suzuki, R. Nucleophosmin in acute myelogenous leukemia. *N. Engl. J. Med.*, 352: 1819-1820, 2005.
  25. Izumiyama, K., Nakagawa, M., Yonezumi, M., Kasugai, Y., Suzuki, R., Suzuki, H., Tsuzuki, S., Hosokawa, Y., Asaka, M., Seto, M. Stability and subcellular localization of API2-MALT1 chimeric protein involved in t(11;18) (q21;q21) MALT lymphoma. *Oncogene*, 22: 8085-8092, 2003.
  26. Nakagawa, M., Miyagishima, T., Kamata, T., Arai, S., Miura, Y., Onishi, S., Kishimoto, A., Kamishima, Y., Choi, G.H., Kudo, M., Okabe, M. Refractory idiopathic cold agglutinin disease successfully treated with intermittent high-dose cyclophosphamide. *Rinsho Ketsueki*, 42: 713-715, 2001.