Stanford



Yusuke Nakauchi

Instructor, Institute for Stem Cell Biology and Regenerative Medicine

Bio

BIO

My research projects aim to investigate the biology of human leukemia. I believe my research will contribute to clarify the disease pathogenesis of leukemia and help identify the critical cells to target to both prevent the development of de novo leukemia and halt relapse.

ACADEMIC APPOINTMENTS

Instructor, Institute for Stem Cell Biology and Regenerative Medicine

HONORS AND AWARDS

- Allele-specific anti-HLA antibodies as theranostic agents in hematopoietic cell transplantation, SPARK (2023)
- 60th ASH Abstract Achievement Award (Oral Presentation), American Society of Hematology (2018)
- Stanford University School of Medicine, the Dean's Postdoctoral Fellowship, Stanford University (2016)
- Overseas Award, Nakayama Foundation for Human Science (2014)

BOARDS, ADVISORY COMMITTEES, PROFESSIONAL ORGANIZATIONS

- Associate Member, The American Association for Cancer Research (2015 present)
- Associate Member, The American Society of Hematology (2015 present)
- Member, The Japanese Society for Immunology (2011 present)
- Member, The Japanese Society of Hematology (2006 present)
- Member, The Japanese Society of Internal Medicine (2006 present)

PROFESSIONAL EDUCATION

- Doctor of Medicine, Asahikawa Medical University, Medicine (2005)
- Doctor of Philosophy, The University of Tokyo, Medicine (Pathology/ Immunology/Microbiology) (2014)

LINKS

- Majeti Lab, Stanford University School of Medicine: http://majetilab.stanford.edu
- The Institute of Medical Science, The University of Tokyo: http://stemcell-u-tokyo.org/en/sct/
- Asahikawa Medical University: http://www.jimu.asahikawa-med.ac.jp/english/index.html
- SPARK at Stanford: https://sparkmed.stanford.edu/

Research & Scholarship

CURRENT RESEARCH AND SCHOLARLY INTERESTS

From 2005 to 2010, my work as a clinical hematology fellow allowed me to experience first-hand how scientific advances that started in a laboratory can transform patients' lives. While many of my patients were cured of their disease with allogeneic hematopoietic stem cell transplantation, underscoring the importance of anti-tumor immunotherapy in eradicating leukemia, I witnessed face-to-face their suffering from the long-term consequence of graft-versus-host disease (GVHD). This experience was ultimately what drove me to engage in research to discover novel therapies. For this reason, I embarked on a Ph.D. program in 2010 to design antibody therapy to (i) target GVHD and (ii) target hematological malignancies. Under the mentorship of Professor Hiromitsu Nakauchi at the University of Tokyo, an international leader in hematopoiesis, I developed allele-specific anti-human leukocyte antigen (HLA) monoclonal antibodies for severe GVHD caused by HLA-mismatched hematopoietic stem cell transplantation (Nakauchi et al., Exp Hematol, 2015). This study was the first to find that anti-HLA antibodies can be used therapeutically against GVHD. That success gave me the motivation and confidence to further my research beyond targeting GVHD to targeting leukemic stem cells through my postdoctoral fellowship in the laboratory of Professor Ravindra Majeti here at Stanford University.

Many people suffer from leukemia each year, but we still don't know how to cure it completely. Recent advances in sequencing technologies have tremendously improved our understanding of the underlying mutations that drive hematologic malignancies. However, the reality is that most of the mutations are not easily "druggable," and the discovery of these mutations has not yet significantly impacted patient outcomes. This is perhaps the most crucial challenge facing a translational cancer researcher like myself. My current research is a major step toward my long-term goal of making personalized medicine a reality for patients with acute myeloid leukemia (AML) and other hematologic malignancies.

Since joining the Majeti lab, I have been targeting the ten-eleven translocation methylcytosine dioxygenase-2 (TET2) mutation, which is aberrant in leukemia at a high rate and has been studied using human-derived cells. TET2 is known to be involved in the clonal expansion of cells, and people with this mutation are more likely to suffer from hematologic malignancies. It is also known to be involved in the development of coronary artery disease, a gene that has attracted much attention in recent studies. In my field, it is an essential gene involved in the abnormal proliferation of hematopoietic stem cells. Focusing on this gene, I mapped TET2-dependent 5hmC, epigenetic and transcriptional programs matched to competitive advantage, myeloid skewing, and reduced erythroid output in TET2-deficient hematopoietic stem and progenitor cells (HSPC). Vitamin C and azacitidine restore the 5hmC landscape and phenotypes in TET2-mutant HSPCs. These findings offer a comprehensive resource for TET-dependent transcriptional regulation of human hematopoiesis and shed light on the potential mechanisms by which TET deficiency contributes to clonal hematopoiesis and malignancies. Of course, these findings would also be of value in understanding the biology of normal hematopoietic stem cells (HSCs) and various other TET2-related cancers.

And from now on, I would like to use the single-cell transplantation techniques mastered in the Majeti lab to study the behavior of normal and aberrant human HSCs using various new methods, ultimately preventing the progression of AML.

In my clinical experience, I have lost many AML patients. With the regret and sadness of losing these patients in my heart, I hope to one day contribute to developing treatments that will fundamentally change how the world treats leukemia.

Publications

PUBLICATIONS

• Genome engineering with Cas9 and AAV repair templates generates frequent concatemeric insertions of viral vectors. *Nature biotechnology* Suchy, F. P., Karigane, D., Nakauchi, Y., Higuchi, M., Zhang, J., Pekrun, K., Hsu, I., Fan, A. C., Nishimura, T., Charlesworth, C. T., Bhadury, J., Nishimura, T., Wilkinson, et al 2024

- Genetically Corrected RAG2-SCID Human Hematopoietic Stem Cells Restore V(D)J-Recombinase and Rescue Lymphoid Deficiency. *Blood advances* Pavel-Dinu, M., Gardner, C. L., Nakauchi, Y., Kawai, T., Delmonte, O. M., Palterer, B., Bosticardo, M., Pala, F., Viel, S., Malech, H. L., Ghanim, H. Y., Bode, N. M., Kurgan, et al 2023
- Simplified Intrafemoral Injections Using Live Mice Allow for Continuous Bone Marrow Analysis Journal of Visualized Experiments Nakauchi, Y., Ediriwickrema, A., Martinez-Krams, D., Zhao, F., Rangavajhula, A., Karigane, D., Majeti, R. 2023
- RUNX1 loss renders hematopoietic and leukemic cells dependent on interleukin-3 and sensitive to JAK inhibition. *The Journal of clinical investigation* Fan, A. C., Nakauchi, Y., Bai, L., Azizi, A., Nuno, K. A., Zhao, F., Köhnke, T., Karigane, D., Cruz-Hernandez, D., Reinisch, A., Khatri, P., Majeti, R. 2023
- Dysregulated lipid synthesis by oncogenic IDH1 mutation is a targetable synthetic lethal vulnerability. *Cancer discovery* Thomas, D., Wu, M., Nakauchi, Y., Zheng, M., Thompson-Peach, C. A., Lim, K., Landberg, N., Kohnke, T., Robinson, N., Kaur, S., Kutyna, M., Stafford, M., Hiwase, et al 2022
- The cell type specific 5hmC landscape and dynamics of healthy human hematopoiesis and TET2-mutant pre-leukemia. *Blood cancer discovery* Nakauchi, Y., Azizi, A., Thomas, D., Corces, M. R., Reinisch, A., Sharma, R., Cruz Hernandez, D., Kohnke, T., Karigane, D., Fan, A., Martinez-Krams, D., Stafford, M., Kaur, et al 2022
- Integrated analysis of patient samples identifies biomarkers for venetoclax efficacy and combination strategies in acute myeloid leukemia. *Nature cancer* Zhang, H. n., Nakauchi, Y. n., Köhnke, T. n., Stafford, M. n., Bottomly, D. n., Thomas, R. n., Wilmot, B. n., McWeeney, S. K., Majeti, R. n., Tyner, J. W. 2020; 1 (8): 826–39
- Hematopoietic Stem Cells Harrison's Principles of Internal Medicine (Japanese 5th Edition) Nakauchi, Y., Nakauchi, H.
 MEDSI.2017; 19: 89e1-4
- Effective treatment against severe graft-versus-host disease with allele-specific anti-HLA monoclonal antibody in a humanized mouse model. *Experimental hematology*

Nakauchi, Y., Yamazaki, S., Napier, S. C., Usui, J., Ota, Y., Takahashi, S., Watanabe, N., Nakauchi, H. 2015; 43 (2): 79-88 e1 4

• Concurrent administration of intravenous systemic and intravitreal methotrexate for intraocular lymphoma with central nervous system involvement *INTERNATIONAL JOURNAL OF HEMATOLOGY*

Nakauchi, Y., Takase, H., Sugita, S., Mochizuki, M., Shibata, S., Ishiwata, Y., Shibuya, Y., Yasuhara, M., Miura, O., Arai, A. 2010; 92 (1): 179-185

- IDH1-Mutant Preleukemic Hematopoietic Stem Cells Can Be Eliminated by Inhibition of Oxidative Phosphorylation. *Blood cancer discovery* Landberg, N., Köhnke, T., Feng, Y., Nakauchi, Y., Fan, A. C., Linde, M. H., Karigane, D., Lim, K., Sinha, R., Malcovati, L., Thomas, D., Majeti, R. 2024: OF1-OF18
- IDH1-mutant preleukemic hematopoietic stem cells can be eliminated by inhibition of oxidative phosphorylation. *Blood cancer discovery* Landberg, N., Köhnke, T., Feng, Y., Nakauchi, Y., Fan, A. C., Linde, M. H., Karigane, D., Lim, K., Sinha, R., Malcovati, L., Thomas, D., Majeti, R. 2023
- Simplified Intrafemoral Injections Using Live Mice Allow for Continuous Bone Marrow Analysis. *Journal of visualized experiments : JoVE* Nakauchi, Y., Ediriwickrema, A., Martinez-Krams, D., Zhao, F., Rangavajhula, A., Karigane, D., Majeti, R. 2023
- Engineering Sequential Mutations into Human HSPCs Yields an Aggressive Myeloid Malignancy Allowing for Interrogation of Preleukemic Transformation

Collins, C. T., Nakauchi, Y., Koehnke, T., Chavez, J. S., Choi, S., Sharma, R., Zhao, F., Majeti, R. AMER SOC HEMATOLOGY.2023

• BCOR Loss Confers Increased Stemness and Partially Rescues RUNX1-Deficient Phenotypes in Human Hematopoietic Stem and Progenitor Cells Jackson, K. K., Fan, A. C., Karigane, D., Zhao, F., Collins, C. T., Nakauchi, Y., Kayamori, K., Rangavajhula, A. S., Koehnke, T., Majeti, R.

AMER SOC HEMATOLOGY.2023

• Gene Correction of DNMT3A:R882H in Primary Human AML Demonstrates That This Mutation Is Not Required for Disease Maintenance, but Is Associated with Increased Leukemia Stem Cell Frequency

Koehnke, T., Karigane, D., Hilgart, E., Kayamori, K., Fan, A. C., Collins, C. T., Suchy, F. P., Rangavajhula, A. S., Feng, Y., Nakauchi, Y., Martinez-Montes, E., Koldobskiy, M., Feinberg, et al

AMER SOC HEMATOLOGY.2023

• Intra-Leukemic IFN. Signaling Mediates Cell Cycle Suppression and Chemoresistance in AML Karigane, D., Fan, A. C., Kayamori, K., Nakauchi, Y., Koehnke, T., Rangavajhula, A. S., Ediriwickrema, A., Majeti, R. AMER SOC HEMATOLOGY.2023

• Targeting IDH1-Mutated Pre-Leukemic Hematopoietic Stem Cells in Myeloid Disease, Including CCUS and AML Landberg, N., Koehnke, T., Nakauchi, Y., Fan, A., Karigane, D., Thomas, D., Majeti, R. AMER SOC HEMATOLOGY.2022: 2234-2235

• Reengineering Ponatinib to Minimize Cardiovascular Toxicity CANCER RESEARCH Hnatiuk, A. P., Bruyneel, A. N., Tailor, D., Pandrala, M., Dheeraj, A., Li, W., Serrano, R., Feyen, D. M., Vu, M. M., Amatya, P., Gupta, S., Nakauchi, Y., Morgado, et al 2022; 82 (15): 2777-2791

- IL-3 SELECTIVELY RESCUES RUNX1-DEFICIENT HUMAN HSPCS WITH DYSREGULATED JAK/ STAT SIGNALING Fan, A., Azizi, A., Nuno, K., Nakauchi, Y., Zhao, F., Cruz-Hernandez, D., Reinisch, A., Majeti, R. ELSEVIER SCIENCE INC.2022: S84
- IL-3 RESCUES PROLIFERATIVE DEFECTS IN INFLAMMATION-SENSITIVE RUNX1 DEFICIENT HUMAN HEMATOPOIETIC STEM AND PROGENITOR CELLS

Fan, A., Azizi, A., Dutta, R., Nakauchi, Y., Nuno, K., Zhao, F., Reinisch, A., Majeti, R. ELSEVIER SCIENCE INC.2020: S59

- Enasidenib drives human erythroid differentiation independently of isocitrate dehydrogenase 2. *The Journal of clinical investigation* Dutta, R. n., Zhang, T. Y., Köhnke, T. n., Thomas, D. n., Linde, M. n., Gars, E. n., Stafford, M. n., Kaur, S. n., Nakauchi, Y. n., Yin, R. n., Azizi, A. n., Narla, A. n., Majeti, et al 2020
- Use of polyvinyl alcohol for chimeric antigen receptor T-cell expansion. *Experimental hematology* Nishimura, T., Hsu, I., Martinez-Krams, D. C., Nakauchi, Y., Majeti, R., Yamazaki, S., Nakauchi, H., Wilkinson, A. C. 2019
- IDH1 Mutant AML Is Susceptible to Targeting De Novo Lipid Synthesis Independent of 2-Hydroxyglutarate and Has a Distinct Metabolic Profile from IDH2 Mutant AML

Thomas, D., Nakauchi, Y., Wu, M., Zheng, M., Sinha, S., Dill, D., Peltz, G., Majeti, R. AMER SOC HEMATOLOGY.2018

- An Engineered Cell-Traceable Model of Reticular Dysgenesis in Human Hematopoietic Stem Cells Linking Metabolism and Differentiation Wang, W., Awani, A., Reich, L., Nakauchi, Y., Thomas, D., Dever, D. P., Porteus, M., Weinacht, K. G. AMER SOC HEMATOLOGY.2018
- Azacitidine and Ascorbate Inhibit the Competitive Outgrowth of Human TET2 Mutant HSPCs in a Xenograft Model of Pre-Leukemia Nakauchi, Y., Thomas, D., Sharma, R., Corces, M., Reinisch, A., Cruz, D., Koehnke, T., Karigane, D., Fan, A., Majeti, R. AMER SOC HEMATOLOGY.2018
- Large-Scale Clonal Analysis Resolves Aging of the Mouse Hematopoietic Stem Cell Compartment. *Cell stem cell* Yamamoto, R. n., Wilkinson, A. C., Ooehara, J. n., Lan, X. n., Lai, C. Y., Nakauchi, Y. n., Pritchard, J. K., Nakauchi, H. n. 2018; 22 (4): 600–607.e4
- Establishment of a Therapeutic Anti-Pan HLA-Class II Monoclonal Antibody That Directly Induces Lymphoma Cell Death via Large Pore Formation. *PloS one*

Matsuoka, S., Ishii, Y., Nakao, A., Abe, M., Ohtsuji, N., Momose, S., Jin, H., Arase, H., Sugimoto, K., Nakauchi, Y., Masutani, H., Maeda, M., Yagita, et al 2016; 11 (3): e0150496

• A Safeguard System for Induced Pluripotent Stem Cell-Derived Rejuvenated T Cell Therapy STEM CELL REPORTS Ando, M., Nishimura, T., Yamazaki, S., Yamaguchi, T., Kawana-Tachikawa, A., Hayama, T., Nakauchi, Y., Ando, J., Ota, Y., Takahashi, S., Nishimura, K., Ohtaka, M., Nakanishi, et al 2015; 5 (4): 597-608

PRESENTATIONS

- Novel Strategy to Treat Graft-versus-Host Disease with Allele-Specific Anti-HLA Monoclonal Antibody 18th Annual Winter Meeting of the Korean Society of Blood and Marrow Transplantation (2/14/2014 2/15/2014)
- Novel Therapeutic Approach To Graft-Versus-Host Disease With Allele-Specific Anti-HLA Monoclonal Antibody 55th American Society of Hematology Annual Meeting and Exposition (12/7/2013 - 12/10/2013)
- TET2 Disruption Alters Human Hematopoietic Stem/ Progenitor Cells Differentiation and Self-Renewal