KANAZAWA UNIVERSITY

Cancer Research Institute
Kanazawa University

International Symposium

on Tumor Biology and Interdisciplinary Sciences in Kanazawa 2024

Program and Abstract

2024
11/6 (Wed) 9:50 - 17:30

NanoLSI 4F Main Conference Room

Contents

Session 1

10：00 ～ 12：00

Name

Eishu Hirata

Affiliation:

Division of Tumor Cell Biology and Bioimaging, Cancer Research Institute, Kanazawa University

Contact:

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Education:

2002	Kyoto University School of Medicine (MD)
2010	Kyoto University Graduate School of Medicine (PhD)

Professional Career:

2002 - 2006	Resident and Medical Staff in Kyoto University Hospital, Ako City Hospital, Kokura Memorial Hospital, and Shinko Hospital
2010	Assistant Professor, Kyoto University
2011	Research Fellow, Cancer Research UK London Research Institute
2015	Research Fellow, Francis-Crick Institute
2015	Senior Assistant Professor, Kanazawa Medical University
2018	Associate Professor, Kanazawa University
2024 - present	Professor, Kanazawa University

Scientific Activities:

2010 -	Board-certified Neurosurgeon, Japanese Neurosurgical Association
2022 -	Councilor, Japanese Cancer Association
2022 -	Board Member, Metastasis Research Society

Research Interests: Understanding and controlling the brain tumor microenvironment to cure brain tumors.

Publications:

1. Ishibashi and Hirata* et al., Astrocyte-induced mGluR1 activates human lung cancer brain metastasis via glutamate-dependent stabilization of EGFR. ***Developmental Cell.*** 59(5):1-16, 2024.
2. Hirata* et al., The brain microenvironment induces DNMT1 suppression and indolence of metastatic cancer cells. ***iScience.*** 23(9):101480, 2020.
3. Hirata et al., Intravital imaging reveals how BRAF inhibition generates drug tolerant microenvironments with high integrin β1/FAK signaling. ***Cancer Cell.*** 27: 1-15, 2015.

Multifaceted interactions between cancer cells and glial cells in brain metastasis.

Eishu Hirata

Division of Tumor Cell Biology and Bioimaging,
Cancer Research Institute of Kanazawa University

Adaptation of cancer cells to the brain tissue-specific microenvironment is essential for the formation of cancer brain metastasis, and it has been reported that bidirectional interactions, especially with glial cells, play important roles in the establishment and progression of brain metastasis from both positive and negative aspects [1-3]. However, the complex and multifaceted interactions are difficult to analyze in vivo, and there are limited methods to stably analyze the interactions between cancer cells and glial cells in vitro, which hinders our molecular understanding [4]. Recently, we have developed a simple and stable culture method of mouse glial cells, termed mixed-glial culture on/in soft substrate (MGS), which serves well as a platform to study cancer-glia interactions [5]. Using this method, we found that human lung cancer cells become overly dependent on metabotropic glutamate receptor 1 (mGluR1) signaling in the brain microenvironment. Mechanistically, interactions with astrocytes induce mGluR1 in cancer cells through the Wnt-5a / prickle planar cell polarity protein 1 (PRICKLE1) / RE1 silencing transcription factor (REST) axis. Induced mGluR1 directly interacts with and stabilizes the epidermal growth factor receptor (EGFR) in a glutamate-dependent manner, and these cells then become responsive to mGluR1 inhibition [5]. These results highlight increased dependence on mGluR1 signaling as an adaptive strategy and vulnerability of human lung cancer brain metastasis.

Furthermore, live imaging of the MGS co-culture system revealed the presence of microglia with strong tumor cytotoxicity. These cytotoxic microglia recognize and directly contact cancer cells to induce aggressive cell death, and we have recently gained some surprising insights into their molecular mechanisms.

References:

[1] Quail DF and Joyce JA., The Microenvironmental Landscape of Brain Tumors. ***Cancer Cell.*** 31(3):326-341 (2017).

[2] Hirata E et al., The brain microenvironment induces DNMT1 suppression and indolence of metastatic cancer cells. ***iScience.*** 23(9):101480 (2020).

[3] Ishibashi K et al., Multifaceted interactions between cancer cells and glial cells in brain metastasis. ***Cancer Science.*** (online ahead of print).

[4] Guttenplan KA and Liddelow SA. Astrocytes and microglia: Models and tools. ***Journal of Experimental Medicine.*** 216(1):71-83 (2018).

[5] Ishibashi K et al., Astrocyte-induced mGluR1 activates human lung cancer brain metastasis via glutamate-dependent stabilization of EGFR. ***Developmental Cell.*** 59(5):1-16. (2024).

Name

Fernando Calvo

Affiliation:

Tumor Microenvironment Team, Department of Cell & Molecular Signalling, Institute of Biomedicine and Biotechnology of Cantabria (Universidad de Cantabria/CSIC), Spain

Contact:

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Education:

2001	BSc Biochemistry, Universidad del Pais Vasco (Spain)
2008	PhD Biomedicine, Universidad de Cantabria (Spain)

Professional Career:

2001-2002	Industrial Placement Intern, AstraZeneca Pharmaceuticals, Alderly Edge, UK
2002-2008	PhD Student, Crespo Lab, Universidad de Cantabria, Spain
2009-2010	Research Fellow, Crespo Lab, Universidad de Cantabria/CSIC, Spain
2010-2013	Research Fellow, Sahai Lab, Cancer Research UK London Research Institute, UK
2013-2018	Team Leader, Institute of Cancer Research, UK
2018-2021	Ramón y Cajal Fellow and Team Leader, IBBTEC, Spain
2021-present	CSIC Tenured Scientific Leader, IBBTEC, Spain

Scientific Activities:

2021-	Commissioner, Spanish Agency for Research, Biomedicine-Cancer subgroup
2023-	Scientific Committee, GU-Alliance for Research and Development (GUARD) Consortium

Research Interests: Cancer Biology, Tumor Microenvironment, Cancer-associated fibroblasts, Cancer Therapeutics, Signaling and transcriptomics

Honors:

ERC Consolidator Grant (2021) | I3 Scientific Excellence Recognition (2021) | Eaton Foundation Fellow (2019) | Lab-AECC Award (2019) | BBVA Leonardo Awards (2019) | Ramón y Cajal Fellowship (2016) | CRUK Multidisciplinary Project Award (2016)

Publications:

1. Ferrari *et al*. (2019). “Dickkopf-3 links HSF1 and YAP/TAZ signalling to control aggressive behaviours in cancer-associated fibroblasts”. **Nature Communications** 10(1):130.

2. Calvo *et al*. (2013) “Mechanotransduction and YAP-dependent matrix remodelling is required for the generation and maintenance of cancer associated fibroblasts”. **Nature Cell Biology** 15(6):637-46.

3. Calvo *et al*. (2011). “RasGRF suppresses Cdc42-mediated tumour cell movement, cytoskeletal dynamics and transformation”. **Nature Cell Biology** 13(7):819-26.

Dissecting the mechanisms controlling the generation of tumor-promoting microenvironments by cancer-associated fibroblasts

Fernando Calvo

Tumor Microenvironment Team

Institute of Biomedicine and Biotechnology of Cantabria, Spain

Neoplasia is a slow process that involves the accumulation of genetic changes that promote cancer cell growth and survival. For tumors to progress to a malignant stage, other signals are required, and generally involve the generation of an environment in which cancer cells propagate and acquire more aggressive phenotypes Tumors are complex tissues comprising not only malignant cells but also non-cancerous stromal cells, including endothelial cells, fibroblasts, and immune cells, as well as the extracellular matrix (ECM) they produce. All these various components, collectively known as the tumor microenvironment, are not mere bystanders but instead critically regulate tumor initiation, malignant progression, metastasis and therapeutic efficacy [1]. Cancer-associated fibroblasts (CAFs) constitute a significant proportion of the stromal compartment in many solid malignancies and are key players in shaping the physical and chemical environment in tumors [2]. Thus, through remodeling of the ECM and signaling to cancer and stromal cells, CAFs actively influence tumor initiation, progression and dissemination. Altogether, it is increasingly acknowledged that targeting CAFs represents an alternative for therapeutic intervention that, contrary to immunotherapies or antiangiogenic therapies, has not been exploited in the clinic. Here, I will present our advances in the molecular and functional characterization of CAFs, describing how CAFs contribute to tumor progression and the signals and molecular mechanisms that lead to the emergence of tumor-promoting behaviors in otherwise healthy cells. In particular, I will delineate the importance of mechanotransduction in CAF biology [3,4] and describe recent findings on the unpredicted link between HSF1, Wnt signaling and YAP/TAZ relevant for the generation of tumor-promoting CAFs [5]. To conclude, unpublished data of ongoing projects in the lab will be presented. These include the description of novel functions and mechanisms employed by CAFs to promote tumor progression (*e.g.* abnormal vascularization, macrophage polarization)[6,7] and how emerging cellular processes influence CAF functions (*e.g.* stress, metabolic rewiring, epigenetic reprogramming).

References:

[1] Egeblad *et al*. Tumors as Organs: Complex Tissues that Interface with the Entire Organism. ***Dev Cell*** 18:884 (2010). **[2]** Sahai *et al.* A framework for advancing our understanding of cancer-associated fibroblasts. ***Nat Rev Cancer*** 20:174 (2020). **[3]** Calvo *et al.* Mechanotransduction and YAP-dependent matrix remodelling is required for the generation and maintenance of cancer-associated fibroblasts. ***Nat Cell Biol*** 15:637 (2013). **[4]** Calvo *et al.* Cdc42EP3/BORG2 and Septin Network Enables Mechano-transduction and the Emergence of Cancer-Associated Fibroblasts. *Cell Rep* 13:2699 (2015). **[5]** Ferrari *et al.* Dickkopf-3 links HSF1 and YAP/TAZ signalling to control aggressive behaviours in cancer-associated fibroblasts. ***Nat Commun*** 10:130 (2019). **[6]** Whisler *et al*. Emergent mechanical control of vascular morphogenesis. *Sci Adv* 9:eadg9781 (2023). **[7]** Coursier & Calvo. CAFs vs. TECs: when blood feuds fuel cancer progression, dissemination and therapeutic resistance. ***Cell Oncol*** Mar 7 (2024).

Name

Shunsuke Kitajima

Affiliation:

Division of Cell Biology, Cancer Institute, Japanese Foundation for Cancer Research

Contact:

E-mail: shunsuke.kitajima@jfcr.or.jp

Education:

2000-2004 Nagoya University School of Agricultural Science (B.S.)

2004-2006 Kyoto University Graduate School of Medicine (M.S.)

2006-2010 Kyoto University Graduate School of Medicine (Ph.D.)

Professional Career:

2010-2015 Cancer Research Institute, Kanazawa University, Postdoctoral Fellow/Assistant Professor

2015-2020 Dana-Farber Cancer Institute, Medical Oncology, Research Fellow

2020-Present The Cancer Institute of JFCR, Staff Scientist / Distinguished young researcher of JSPS

Scientific Activities:

2023- Present Councilor, Japanese Cancer Association

Research Interests:

My research interests focus on elucidating how the deregulation of oncogenes/tumor suppressor genes impacts the immune tumor microenvironment via the regulation of intracellular signaling, which determines drug sensitivity. By uncovering these molecular mechanisms, I aim to propose novel therapeutic strategies.

Honors:

2019 The Young Investigator Awards of the Japanese Cancer Association

Publications:

1. Tani and Kitajima* et. al., TREX1 inactivation unleashes cancer cell STING-interferon signaling and promotes anti-tumor immunity. ***Cancer Discovery***, 752-765, 2024 * Corresponding author
2. Kitajima* et. al., MPS1 inhibition primes immunogenicity of KRAS-LKB1 mutant lung cancer. ***Cancer Cell***, 40(10): 1128-1144, 2022. * Corresponding author
3. Kitajima et. al., Suppression of STING associated with LKB1 loss in KRAS-driven lung cancer. ***Cancer Discovery***, 9(1): 34-45, 2019
4. Kitajima et. al., Overcoming resistance to dual innate immune and MEK inhibition downstream of KRAS. ***Cancer Cell***, 34(3): 439-452, 2018

Targeting loss of cGAS/STING signaling in lung cancer

Shunsuke Kitajima

Division of Cell Biology

The Cancer Institute of Japanese Foundation for Cancer Research

Oncogenic KRAS remains an intractable therapeutic problem in non-small cell lung cancer (NSCLC), one of the leading causes of cancer deaths. Recently, the landscape of NSCLC therapy has dramatically changed with immune checkpoint blockade (ICB). Especially, KRAS-mutant NSCLC, which frequently occurs in patients with a smoking history and is associated with relatively high tumor mutation burdens (TMB), has been extensively analyzed for a response to PD-(L)1 blockade. These works have identified a clear relationship between STK11/LKB1 (LKB1) mutation and intrinsic resistance to this immunotherapy in KRAS-mutant NSCLC. Previously, we reported that KRAS-LKB1 mutant (KL) NSCLC shows marked epigenetic silencing of STING, an adaptor protein that links cytoplasmic double-stranded DNA accumulation to activation of downstream innate immune signaling. STING downstream cytokines such as IFN-β and CXCL10 are key molecules for activating dendritic cells and T-cell recruitment into the tumor microenvironment (TME), thus fostering anti-tumor immunity. Indeed, infiltration of CD8-positive T-cells into the TME is significantly lower in STING low KL-type NSCLC. These results uncover the key underlying mechanism to confer resistance to immune checkpoint blockade (ICB) in KL-type NSCLC and identify strategies to restore STING activity to overcome the resistance. Through a drug screen of cytotoxic chemotherapies or targeted DNA-damaging agents as well as a genetic screen, we identified several candidates as optimal targets to prime the STING pathway in KL cells. And this effect is markedly amplified by epigenetic de-repression of STING. To sum up, we introduce our recent approach to enhance the immunogenicity of KL cells and highlight the molecular mechanism by which the candidates efficiently activate the STING pathway and subsequent anti-tumor immunity.

References:

[1] Tani and Kitajima* et. al., TREX1 inactivation unleashes cancer cell STING-interferon signaling and promotes anti-tumor immunity. ***Cancer Discovery***, 752-765, 2024. PMID:38227896

[2] Kitajima et. al., MPS1 inhibition primes immunogenicity of KRAS-LKB1 mutant lung cancer. ***Cancer Cell***, 40(10): 1128-1144, 2022. PMID:36150391

[3] Kitajima et. al., Suppression of STING associated with LKB1 loss in KRAS-driven lung cancer. ***Cancer Discovery***, 9(1): 34-45, 2019. PMID:30297358

[4] Kitajima et. al., Overcoming resistance to dual innate immune and MEK inhibition downstream of KRAS. ***Cancer Cell***, 34(3): 439-452, 2018. PMID:30205046

Session 2

13：00 ～ 15：00

Name

Kazuo Okamoto

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Division of Immune Environment Dynamics, Cancer Research Institute, Kanazawa University

Contact:

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Education:

2000	Graduated from the Faculty of Science, Kyoto University
2006	Graduate School of Biostudies, Kyoto University (PhD)

Professional Career:

2006-2010	Postdoctoral Fellow, Tokyo Medical and Dental University
2010-2015	Group leader, JST, ERATO, Takayanagi Osteonetwork Project
2010-2012	Assistant Professor, Tokyo Medical and Dental University
2012-2016	Assistant Professor, Graduate School of Medicine, The University of Tokyo
2016-2024	Project Associate Professor, Graduate School of Medicine, The University of Tokyo
2024-	Professor, Cancer Research Institute of Kanazawa University

Scientific Activities:

2019-	The Japanese Society for Bone and Mineral Research, Public relations committee & Councilor
2021-	The Japanese Society for Immunology, Councilor
2021-	The Japanese Society of Inflammation and Regeneration, Councilor & FLY-IR Committee Chairman
2022-	MEXT, National Institute of Science and Technology Policy (NISTEP), S&T Experts Investigators

Research Interests: *Immunology, Bone, RANKL, Bone metastasis, Inflammation*

Honors:

2016	Young Investigator Award, the Japanese Society for Immunology
2017	Research Encouragement Award, the Japanese Society for Bone and Mineral Research
2024	Distinguished Scientist Award, the Japanese Society for Bone and Mineral Research

Publications:

1. Asano, Okamoto et al, ***Nature Metabolism***, 1: 868-875, 2019

2. Inoue, Okamoto et al, ***Nature Immunology***, 19: 1265-1276, 2018

3. Okamoto et al, ***Nature***, 464: 1381-1385, 2010

Unraveling tumor assault on bone–immune microenvironment

Kazuo Okamoto

Division of Immune Environment Dynamics,

Cancer Research Institute of Kanazawa University

Bone is often thought of as a solid and static tissue, but in fact, its homeostasis is maintained by the breakdown of old bone tissue and its replacement with new bone. This process, called bone remodeling, is controlled by the optimal balance between bone formation by osteoblasts and bone resorption by osteoclasts. The bone homeostasis is well known to be regulated by the endocrine system, but it also closely interacts with the immune system. Bone cells and immune cells share a variety of regulatory molecules including cytokines, chemokines and receptors as well as the tissue microenvironment [1]. Thus, the effects of abnormal immune activation such as autoimmunity can spill over into the skeletal system. Similarly, tumor can cause persistent disruption of bone remodeling, leading to irreversible bone damage. In the context of bone metastasis, aberrant expression of RANKL, which is an essential cytokine for osteoclastogenesis, induced by the metastatic tumor cells causes the pathological bone resorption, resulting in skeletal tumor progression as well as skeletal disorders [2, 3]. Now, a fully human anti-RANKL neutralizing antibody denosumab is used in the treatment of skeletal-related events by bone metastasis [4]. In addition, the bone marrow is the primary lymphoid organ where hematopoietic stem cells and immune progenitors are maintained, and the interplay between bone marrow mesenchymal cells and immune cells establish the environment for bone marrow hematopoiesis. Thus, pathological disruption of the bone marrow microenvironment can affect the immune system through the hematopoietic alterations [5]. Elucidation of the unique tumor microenvironment established by the multicellular network of immune, bone and tumor cells would help provide a more comprehensive understanding of the pathogenesis of bone metastases and new insights to guide the development of cancer immunotherapy.

References:

[1] Okamoto K *et al,* Osteoimmunology: the conceptual framework unifying the immune and skeletal systems. ***Physiological Reviews***, 97: 1295-1349, 2017(review)

[2] Asano T, Okamoto K *et al,* Soluble RANKL is physiologically dispensable but accelerates tumor metastasis to bone. ***Nature Metabolism,*** 1: 868-875, 2019

[3] Nakai Y, Okamoto K *et al,* Efficacy of an orally active small-molecule inhibitor of RANKL in bone metastasis. ***Bone Research***, 7: 1, 2019

[4] Okamoto K *et al,* Role of RANKL in cancer development and metastasis. ***Journal of Bone and Mineral Metabolism***, 39: 71-81, 2021(review)

[5] Terashima A, Okamoto K *et al,* Sepsis-induced osteoblast ablation causes immunodeficiency. ***Immunity,*** 44: 1434-43, 2016

Name:

Sophie Acton

Affiliation:

Laboratory for Molecular Cell Biology,

Faculty of Life Sciences,

University College London

Contact:

E-mail: s.acton@ucl.ac.uk

Education:

2004 University of Bath (MPharmacol)

2008 University College London (PhD Biochemistry)

Professional Career:

2008	Research Fellow, Dana-Farber Cancer Institute, Harvard Medical School
2012	Research Fellow, Francis-Crick Institute
2016	Cancer Research UK Career Development Fellow, University College London
2022	Cancer Research UK Senior Cancer Research Fellow, University College London
2024-present	Professor of Immunology, University College London

Scientific Activities:

2023-present	Cancer Research UK Discovery Research Committee Member
2024-present	Senior Editor – Discovery Immunology (British Society for Immunology)

Research Interests: *please write down your research interests within 5.*

Lymphoid tissue biology, Stromal immunology, Tumour microenvironment, Inflammation.

Publications:

1. Horsnell *et al.* Lymph node homeostasis and adaptation to immune challenge resolved by fibroblast network mechanics. ***Nat Immunol***. 2022 Aug;23(8):1169-1182.
2. Martinez *et al.* Fibroblastic Reticular Cells Control Conduit Matrix Deposition during Lymph Node Expansion. ***Cell Reports.*** 2019 Nov 26;29(9):2810-2822.e5.
3. Acton *et al.* Dendritic cells control fibroblastic reticular network tension and lymph node expansion. ***Nature***. 2014 Oct 23;514(7523):498-502.

Harnessing The Lymphoid Tissue Niche To Boost Anti-Tumor Immune Responses

Sophie Acton
Laboratory for Molecular Cell Biology
Faculty of Life Sciences
University College London

Emergent physical properties of tissues are not readily understood by reductionist studies of their constituent cells. We show molecular signals controlling cellular, physical, and structural properties and collectively determine tissue mechanics of lymph nodes through stromal cell and immune cell crosstalk. Lymph nodes paradoxically maintain robust tissue architecture in homeostasis yet are continually poised for extensive expansion upon immune challenge. Perturbation of fibroblast mechanics through genetic deletion of podoplanin attenuates T cell activation. We find that increased tissue tension through the fibroblastic stromal meshwork is required to trigger the initiation of fibroblast proliferation and restore homeostatic cellular ratios and tissue structure through lymph node expansion. We have recently developed genetic tools to conditionally manipulate gene expression in fibroblastic stroma and find that expression of Podoplanin (PDPN) in the fibroblastic reticular cells (FRCs) supporting lymph node architecture to be a key signalling molecule regulating tissue mechanics, immune cell regulation and stromal remodelling. Further, we determine a novel mechanism driving protrusion formation in FRCs which is triggered via PDPN clustering which is coordinated through RhoA and PKN2. This mechanism of reactive protrusion formation is essential for lymph node structure and integrity through tissue remodelling.

Our understanding of stromal/immune cell crosstalk extends beyond secondary lymphoid tissues to the tumour microenvironment where many of the same cellular players interact to regulate anti-tumour immune function and tumour progression. We find certain subsets of fibroblasts in tumours that acquire phenotypes similar to fibroblastic reticular cells in lymph nodes. These stromal cells can determine local immune cell filtration and organisation and importantly control tumour growth.

1. Horsnell *et al.* Lymph node homeostasis and adaptation to immune challenge resolved by fibroblast network mechanics. ***Nat Immunol***. 2022 Aug;23(8):1169-1182.
2. Martinez *et al.* Fibroblastic Reticular Cells Control Conduit Matrix Deposition during Lymph Node Expansion. ***Cell Reports.*** 2019 Nov 26;29(9):2810-2822.e5.
3. Acton *et al.* Dendritic cells control fibroblastic reticular network tension and lymph node expansion. ***Nature***. 2014 Oct 23;514(7523):498-502.
4. Millward *et al.* PKN2 signalling induces stromal cell protrusions to preserve lymph node structural integrity. ***Preprint – Research Square*** 10.21203/rs.3.rs-4921177/v1

Name

Atsushi Okuma

Affiliation:

Hitachi Kobe Laboratory, Center for Exploratory Research, Research & Development Group, Hitachi, Ltd.

Contact:

E-mail: atsushi.okuma.xq@hitachi.com

Education:

2013 Graduate School of Life Sciences, Tohoku University (PhD)

Professional Career:

2013.4–2017.3 Postdoctoral fellow: The Cancer Institute of Japanese Foundation for Cancer Research

2017.4–2017.7 Specially Appointed Assistant Professor: Research Institute for Microbial Diseases, Osaka University

2017.8–2019.5 Postdoctoral fellow: Department of Biomedical Engineering, Boston University

2019.6-present Chief Researcher: Research & Development Group, Hitachi, Ltd.

Research Interests:

Cells act as rigorous micro-size machines, which sense environment (input), integrate the signals (process), and respond (output). I am interested in how to "hack" the machinery of cells and what we can do with "hacked" cells. I am currently working on a DesignCell® project at Hitachi, Ltd that is uncovering the design principles of genetic engineering of mammalian cells. In the project, our team is trying to establish AI- and robotics-aided semi-automated platform to make engineered cells with desired functions.

Publications:

1. Atsushi Okuma. "Generation of CAR-T cells by lentiviral transduction" **Mammalian Cell Engineering: Methods and Protocols**, 2021: 2312: 3-14.

2. Jang Hwan Cho*, Atsushi Okuma*, et al., "Engineering advanced logic and distributed computing in human CAR immune cells" **Nat Commun.**, 2021 Feb 4; 12(1): 792.

3. Jang Hwan Cho*, Atsushi Okuma*, et al., "Engineering Axl specific CAR and SynNotch receptor for cancer therapy." **Sci Rep.**, 2018 Mar 1; 8(1): 3846.

4. Atsushi Okuma, et al., "p16Ink4a and p21Cip1/Waf1 promote tumour growth by enhancing myeloid-derived suppressor cells chemotaxis." **Nat Commun.**, 2017 Dec 12; 8(1): 2050.

5. Atsushi Okuma, et al., "Accelerated Apoptosis by Disruption of the STAT3-IκB-ζ Axis in Epithelial Cells Induces Sjögren's Syndrome-like Autoimmune Disease." **Immunity**, 2013 Mar 21; 38(3):450-60.

Design chimeric antigen receptors, design cell functions

Atsushi Okuma

Center for Exploratory Research, Research & Development Group, Hitachi, Ltd.

Chimeric antigen receptor (CAR) T cell therapy has achieved promising outcomes in B cell malignancies and multiple myeloma. However, its efficacy against most solid tumors remains elusive. The majority of CAR-T studies utilize a limited pattern of CAR designs, similar to the approved CD19 CARs, differing mainly in the binder domain, while proposing additional tools and techniques to overcome immunosuppressive solid tumor microenvironment, although the design of the CD19 CAR is not clearly optimal for other CARs against other tumors. To maximize the inherent efficacy of the CAR, we have developed the DesignCell® platform that can rapidly optimize sequences of any type of CARs. Our platform incorporates an AI system capable of generating CAR designs with expected functionality, a pooled screening system specialized for evaluating CAR T cells in a single cell manner, and an automated high-throughput arrayed screening system for phenotyping CAR T cells. First, in order to handle CAR libraries with enormous diversity, we constructed a pooled screening system in which each cell carries a different CAR, and the phenotype is linked to the CAR design by sequencing the CAR after a single cell analysis. Second, we have modified the arrayed screening process from the production to the evaluation of CAR T cells to be high-throughput compatible, and automated it with robotic handling system, because arrayed screening provides normalized data for hundreds or thousands of cells, so we can use reliable labeled data sets with less host cell bias for supervised learning. Finally, to reduce the required data from experiments, we developed methods to generate superior protein sequences using machine learning and protein language model. Altogether, we have enabled the rapid design of an optimal CAR through an iterative process of the generation of CAR sequences by AI and the experimental CAR T cell evaluation.

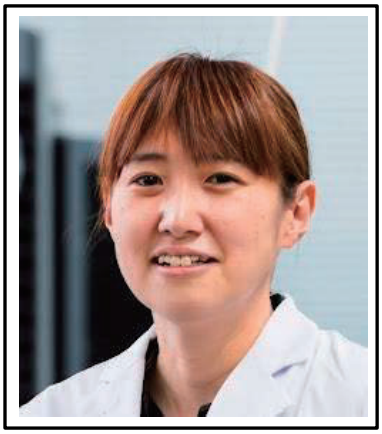
References:

[1] Atsushi Okuma. “Generation of CAR-T cells by lentiviral transduction” **Mammalian Cell Engineering: Methods and Protocols**, 2021: 2312: 3-14.

[2] Jang Hwan Cho*, Atsushi Okuma*, et al., “Engineering advanced logic and distributed computing in human CAR immune cells” **Nat Commun.**, 2021 Feb 4; 12(1): 792.

Session 3

15：20 ～ 17：20



Name

Ayako Suzuki

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Education:

2015	Graduate School of Frontier Sciences, The University of Tokyo (PhD)

Professional Career:

2015	Specially Appointed Assistant Professor, The University of Tokyo
2015-2018	Staff Scientist, National Cancer Center
2018-2021	Specially Appointed Associate Professor, The University of Tokyo
2021-present	Associate Professor, The University of Tokyo

Scientific Activities:

2024-	Councilor, Japanese Cancer Association

Research Interests: Understanding aberrant genomic, epigenomic and transcriptomic features and their changes associated with lung cancer progression

Publications:

1. Haga Y, Sakamoto Y, Kajiya K, Kawai H, Oka M, Motoi N, Shirasawa M, Yotsukura M, Watanabe S, Arai M, Zenkoh J, Shiraishi K, Seki M, Kanai A, Shiraishi Y, Yatabe Y, Matsubara D, Suzuki Y, Noguchi M, Kohno T, Suzuki A. Whole-genome sequencing reveals the molecular implications of the stepwise progression of lung adenocarcinoma. ***Nat Commun*** 14:8375, 2023.

2. Suzuki A, Onodera K, Matsui K, Seki M, Esumi H, Soga T, Sugano S, Kohno T, Suzuki Y, Tsuchihara K. Characterization of cancer omics and drug perturbations in panels of lung cancer cells. ***Sci Rep*** 9:19529, 2019.

3. Suzuki A, Makinoshima H, Wakaguri H, Esumi H, Sugano S, Kohno T, Tsuchihara K, Suzuki Y. Aberrant transcriptional regulations in cancers: genome, transcriptome and epigenome analysis of lung adenocarcinoma cell lines. ***Nucleic Acids Res*** 42(22):13557-13572, 2014,

Elucidation of molecular changes associated with lung cancer progression by spatial omics analyses

Ayako Suzuki

Department of Computational Biology and Medical Sciences,
Graduate School of Frontier Sciences, The University of Tokyo

Recently, various spatial omics measurement methods, especially spatial transcriptome platforms, have been developed, and these techniques enable measuring omics features in cancers at single-cell resolution with keeping spatial and histopathological information of cancer tissues. During lung cancer progression, cancer cells expand with acquisition of aberrant omics features including gene expression changes associated with proliferation, dedifferentiation and invasion. Further, microenvironmental cells, such as fibroblasts and immune cells, would also affect these changes as a stress and selection pressure. For understanding how cancer tissues acquire heterogeneous and malignant phenotypes that may cause therapeutic difficulties, comprehensive omics profiling of local tissue regions is needed.

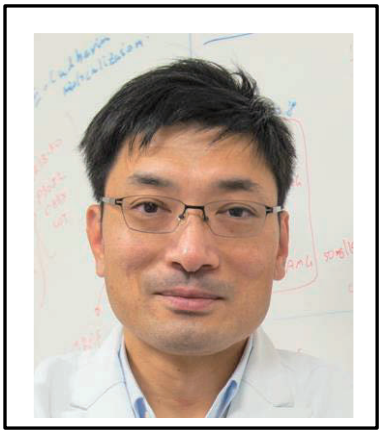
To elucidate how omics statuses of cancer cells change during lung cancer progression and what microenvironmental factors would be involved in transition of transcriptomic features of cancer cells, we have conducted spatial omics analyses using lung cancer tissues. We first conducted spatially-resolved whole-transcriptome analysis Visium for exploration of aberrant transcriptome networks and these related microenvironment states, and then moved to *in situ* gene expression analysis Xenium for verification of the identified events at a single-cell level. Especially when focusing on the tissue regions showing transcriptomically proliferative/invasive features, both inflammatory and anti-inflammatory factors co-located in non-invasive cases at the very early stages of lung cancers while immunosuppressive microenvironment was already built by anti-inflammatory factors in invasive cases.

References:

[1] Nagasawa S, Zenkoh J, Suzuki Y, Suzuki A. Spatial omics technologies for understanding molecular status associated with cancer progression. ***Cancer Sci*** doi: 10.1111/cas.16283, 2024.

[2] Nagasawa S, Kashima Y, Suzuki A, Suzuki Y. Single-cell and spatial analyses of cancer cells: toward elucidating the molecular mechanisms of clonal evolution and drug resistance acquisition. ***Inflamm Regen*** 41:22, 2021.

[3] Haga Y, Sakamoto Y, Kajiya K, Kawai H, Oka M, Motoi N, Shirasawa M, Yotsukura M, Watanabe S, Arai M, Zenkoh J, Shiraishi K, Seki M, Kanai A, Shiraishi Y, Yatabe Y, Matsubara D, Suzuki Y, Noguchi M, Kohno T, Suzuki A. Whole-genome sequencing reveals the molecular implications of the stepwise progression of lung adenocarcinoma. ***Nat Commun*** 14:8375, 2023.



Name

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Education:

1999 M.D., Nagoya City University School of Medicine

2006 Ph.D.., Nagoya City University Graduate School of Medicine

Professional Career:

1999-2001	Resident in Internal Medicine, Kanto Teishin Hospital, Tokyo, Japan
2001-2003	Fellow in Medical Oncology, Division of Oncology/Hematology, Department of Medicine, National Cancer Center Hospital East, Chiba, Japan
2008-2012	Research Fellow, Center for Cancer Research, Massachusetts General Hospital and Harvard Medical School, Boston, MA
2012-2018	Division of Medical Oncology, Cancer Research Institute, Kanazawa University (2012-2016 Assistant, 2016-2018 Associate Professor
2018-present	Chief, Division of Molecular Therapeutics, Aichi Cancer Center Research Institute
2021-present	Director, Precision Medicine Center, Aichi Cancer Center Hospital

Scientific Activities:

2007 Diplomate, Subspecialty Board of Medical Oncology, Japanese Society of Medical Oncology

2016 Fellow of the Japanese Society of Internal Medicine

Present: Japanese Cancer Association (Councilor), Japanese Society of Medical Oncology (Councilor)
The Japanese Association for Molecular Target Therapy of Cancer (Director)

Editorial board: JCO precision oncology, Cancer Science

Research Interests: *RAS/RAF mutated cancer, ctDNA analysis, Tumor agonistic clinical trial.*

Honors:

2006 IASLC Fellowship/Young Investigator Award, International Association for the Study of Lung Cancer.

2014 Incitement Award from Japan Cancer Association

2021 JCA-Mauvernay Award form Japan Cancer Association

Mechanisms of resistance to KRAS inhibitors

Hiromichi Ebi

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KRAS inhibitors are now introduced into clinical practice, however, resistance mechanisms can limit their effectiveness. Initially, tumors rely on mutant KRAS, but as they progress, they may shift to alternative pathways, resulting in intrinsic resistance. This resistance can stem from mechanisms like epithelial-to-mesenchymal transition (EMT), YAP activation, or KEAP1 mutations. KRAS inhibition often triggers cellular rewiring to counteract therapeutic pressure. For instance, feedback reactivation of signaling pathways such as MAPK, mediated by receptor tyrosine kinases, supports tumor survival. KRAS inhibition also causes metabolic reprogramming and protein re-localization. The re-localization of E-cadherin and Scribble from the membrane to the cytosol causes YAP to translocate to the nucleus, where it drives MRAS transcription, leading to MAPK reactivation. Emerging evidence indicates that changes in cell identity, such as mucinous differentiation, shifts from alveolar type 2 to type 1 cells, or lineage switching from adenocarcinoma to squamous cell carcinoma, also contribute to resistance. In addition to these non-genetic mechanisms, secondary mutations in KRAS or alterations in upstream/downstream signaling proteins can cause acquired resistance. Overcoming these resistance mechanisms involves enhancing the efficacy of drugs targeting mutant KRAS, developing broad-spectrum inhibitors, combining therapies targeting multiple pathways, and integrating immune checkpoint inhibitors.

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Education:

2002 Department of Pharmaceutical Science, Setsunan University (BS)

2016 Okayama University Graduate School of Medicine (PhD)

Professional Career:

2002 Pharmacist, Department of Clinical Pharmacy, Okayama University Hospital

2005 Pharmacist, Pharmacy, Kousei Hospital

2007 Pharmacist, Department of Clinical Pharmacy, Okayama University Hospital

2016 Scientist, Department of Hematology, Respiratory and Oncology, Okayama University

2017 Research Coordinator, Biobank, Okayama University Hospital

2017 Research Fellow, Massachusetts General Hospital Cancer Center, Harvard Medical School

2022-present Instructor, Massachusetts General Hospital Cancer Center, Harvard Medical School

Scientific Activities:

2024 Faculty, International Association for the Study of Lung Cancer

Research Interests: Understanding the molecular mechanisms of cancer evolution and developing new therapies

Honors:

2015 Presentation Award, Japanese Society of Medical Oncology (JSMO)

2015 Travel Grant Award, European Society for Medical Oncology (ESMO) Asia

2016 Okayama Medical Association Award, Okayama University

2016 Young Investigator Award, Japanese Lung Cancer Society

2016 JCA Scholar-in-Training Award, AACR-JCA Joint Conference

2020 Postdoctoral Fellowship Award, MGH ECOR Fund for Medical Discovery (FMD)

2020 Pilot Grant Program Award, Lung Cancer Research Foundation (LCRF)

2023 Publication Award, United Japanese researchers Around the world (UJA)

Publications:

1. Isozaki et al., Therapy-induced APOBEC3A drives evolution of persistent cancer cells. ***Nature***. 620(7973):393-401, 2023.
2. Piotrowska*, Isozaki* et al., Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and clinical validation of combined EGFR and RET inhibition with osimertinib and BLU-667 for acquired RET fusion. ***Cancer Discov.*** 8(12):1529-1539,2018.
3. Isozaki et al., Non-small cell lung cancer cells acquire resistance to the ALK inhibitor alectinib by activating alternative receptor tyrosine kinases. ***Cancer Res.*** 76(6):1506-16, 2016.

Therapy-induced tumor evolution in non-small cell lung cancer.

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Acquired drug resistance to anticancer targeted therapies remains an unsolved clinical problem. Although many drivers of acquired drug resistance have been identified, the underlying molecular mechanisms shaping tumor evolution during treatment are incompletely understood. Genomic profiling of patient tumors has implicated apolipoprotein B messenger RNA editing catalytic polypeptide-like (APOBEC) cytidine deaminases in tumor evolution; however, their role during therapy and the development of acquired drug resistance is undefined. Here we report that lung cancer targeted therapies commonly used in the clinic can induce cytidine deaminase APOBEC3A (A3A), leading to sustained mutagenesis in drug-tolerant cancer cells persisting during treatment. Therapy-induced A3A promotes the formation of double-strand DNA breaks, increasing genomic instability in drug-tolerant persisters. Deletion of A3A reduces APOBEC mutations and structural variations in persister cells and delays the development of drug resistance. APOBEC mutational signatures are enriched in tumors from patients with lung cancer who progressed after extended responses to targeted therapies. This study shows that induction of A3A in response to targeted therapies drives evolution of drug-tolerant persister cells, suggesting that suppression of A3A expression or activity may represent a potential therapeutic strategy in the prevention or delay of acquired resistance to lung cancer targeted therapy.

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