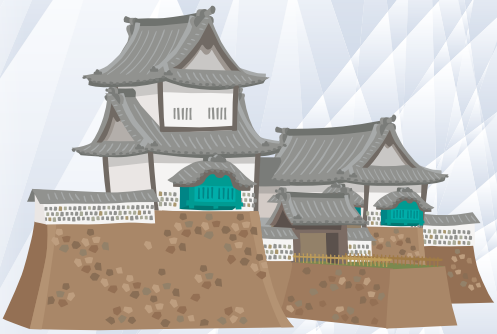
The 11th

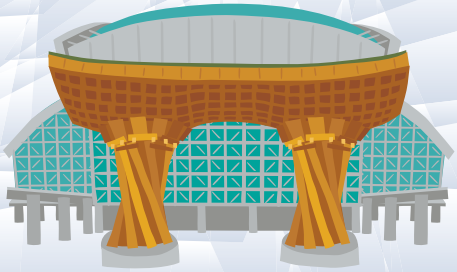
Kanazawa University
Cancer Research Institute (KU-CRI)
– Fudan University
Shanghai Cancer Center (FUSCC)

Joint Symposium on Tumor Biology 2023

13 September 2023

**Kanazawa University, Kakuma-campus,
Natural Science and
Technology Library 1F
Large Conference Room**





Organizers

Kanazawa University Cancer Research Institute
Fudan University Shanghai Cancer Center
Kanazawa Association of Tumor Biologists

Co-Organizers

NanoLSI WPI KANAZAWA UNIVERSITY
Institute for Frontier Science Initiative
okushin がんプロ

Symposium Office

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Kanazawa University Cancer Research Institute
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KANAZAWA UNIVERSITY

The 11th Kanazawa University Cancer Research Institute
(KU-CRI) – Fudan University Shanghai Cancer Center (FUSCC)

Joint Symposium
on Tumor Biology
2023

13 September 2023
Venue : Kanazawa University, Kakuma-campus,
Natural Science and Technology Library 1F Large Conference Room

— Organizers —

- Kanazawa University Cancer Research Institute
- Fudan University Shanghai Cancer Center
- Kanazawa Association of Tumor Biologists

Contents

General Information

Date & Time

13 September 2023

Session 1　13:10~14:25

Session 2　14:45~16:00

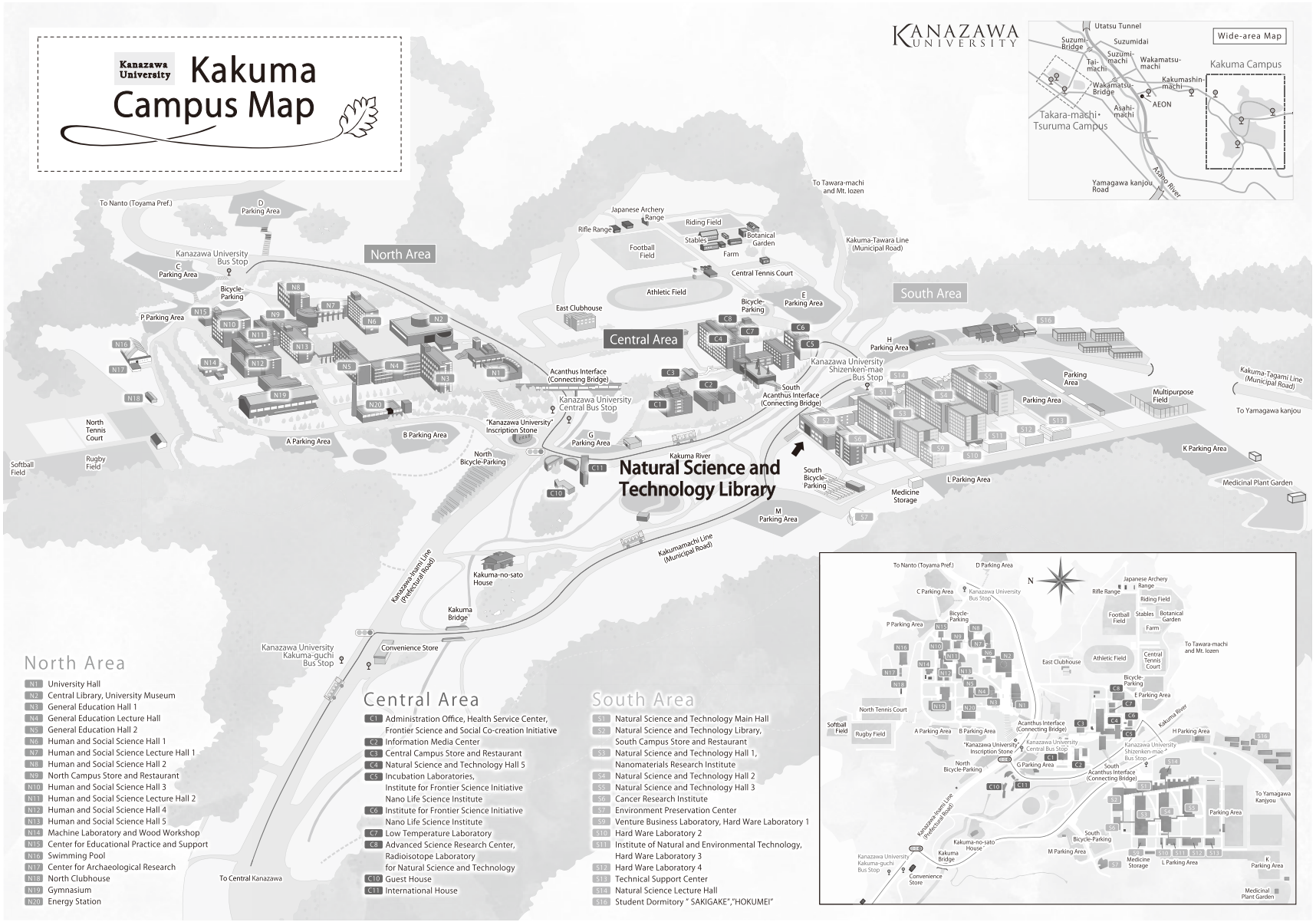
Venue

**Kanazawa University, Kakuma-campus,
Natural Science and Technology Library 1F
Large Conference Room**

〒920-1192
Kakuma-machi, Kanazawa-shi, Ishikawa, Japan
https://library.kanazawa-u.ac.jp/?page_id=19138&lang=en

Oral Presentation

Please bring your computer or USB during coffee break or before your session. If you use Macintosh computer, please bring adaptor for cable connection.
Please remain 5 min of your presentation time for active discussion.



North Area

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- N3 General Education Hall 1
- N4 General Education Lecture Hall
- N5 General Education Hall 2
- N6 Human and Social Science Hall 1
- N7 Human and Social Science Lecture Hall 1
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- N10 Human and Social Science Hall 3
- N11 Human and Social Science Lecture Hall 2
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- N15 Center for Educational Practice and Support
- N16 Swimming Pool
- N17 Center for Archaeological Research
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Central Area

- C1 Administration Office, Health Service Center, Frontier Science and Social Co-creation Initiative
- C2 Information Media Center
- C3 Central Campus Store and Restaurant
- C4 Natural Science and Technology Hall 5
- C5 Incubation Laboratories, Institute for Frontier Science Initiative Nano Life Science Institute
- C6 Institute for Frontier Science Initiative Nano Life Science Institute
- C7 Low Temperature Laboratory
- C8 Advanced Science Research Center, Radioisotope Laboratory for Natural Science and Technology
- C10 Guest House
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South Area

- S1 Natural Science and Technology Main Hall
- S2 Natural Science and Technology Library, South Campus Store and Restaurant
- S3 Natural Science and Technology Hall 1, Nanomaterials Research Institute
- S4 Natural Science and Technology Hall 2
- S5 Natural Science and Technology Hall 3
- S6 Cancer Research Institute
- S7 Environment Preservation Center
- S9 Venture Business Laboratory, Hard Ware Laboratory 1
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The 11th Kanazawa University Cancer Research Institute (KU-CRI) – Fudan University Shanghai Cancer Center (FUSCC) Joint Symposium on Tumor Biology 2023

Program

13:00 – 13:10 **Opening Remark**

Shinichi Nakamura,
Trustee (Research, Social Co-creation, and Graduate School Support) Kanazawa University

Session 1 Chair: Chiaki Takahashi

13:10 – 13:35 **Kunio Matsumoto**
Division of Tumor Dynamics and Regulation, Cancer Research Institute, WPI-Nano Life Science Institute, Kanazawa University
High-Performance MET Receptor Agonists Created by Molecular Technologies

13:35 – 14:00 **Huijuan Yang**
Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center
PI3K pathway alteration in gynecological malignancies -- its oncogenic mechanism and clinical translation

14:00 – 14:25 **Noriho Iida**
Department of Gastroenterology Kanazawa University Hospital
Gut microbiota of chronic liver disease patients promote liver carcinogenesis in TLR4-dependent manner

14:25 – 14:45 Break

Session 2 Chair: Dominic Voon

14:45 – 15:10 **Tong Tong**
Department of Radiology, Fudan University Shanghai Cancer Center
Department of Oncology, Shanghai Medical College, Fudan University
Prognostic value of the consensus molecular subtype 4 (CMS4) predicted by multiparametric radiomics-based machine learning in colorectal cancer: a multi-center retrospective study

15:10 – 15:35 **Yoshikazu Jomura**
Division of Cancer and Senescence Biology, Cancer Research Institute, Institute for Frontier Science Initiative, Kanazawa University
Identification and functional analysis of senescent cells in tumor microenvironment

15:35 – 16:00 **Yong Chen**
Melanoma Center, Department of Musculoskeletal Oncology, Fudan University Shanghai Cancer Center
The effect of the potential new drug MITF inhibitor on malignant melanoma and its synergistic mechanism with anti-PD1 immunotherapy

16:00 – 16:10 Closing Remark

Takeshi Suzuki
Director General, Cancer Research Institute, Kanazawa University

Session 1

High-Performance MET Receptor Agonists Created by Molecular Technologies

Kunio Matsumoto
Division of Tumor Dynamics and Regulation
Cancer Research Institute,
WPI-Nano Life Science Institute,
Kanazawa University, Japan

Cytokines and growth factors have remarkable biological activities, and therefore some growth factors have been applied as essential "biologics" (biological drugs) for disease treatment. However, these bioactive proteins generally have short half-lives when in circulation and show poor penetration across the blood–brain-barrier (BBB), properties that limit their utility in the treatment of chronic or brain diseases. HGF (hepatocyte growth factor) exerts biological activities via the MET transmembrane receptor. Recently, therapeutic efficacy of intrathecal administration of recombinant HGF protein for the treatment of spinal cord injury was verified. Therefore, MET receptor activation by agonistic molecules created by new drug modalities as well as native HGF is expected to be applicable to the treatment of various diseases. Since growth factor receptors are activated through dimer/oligomer formation, molecules capable of dimerizing or oligomerizing receptors are expected to be agonistic. We obtained macrocyclic peptides that bind to the extracellular region of MET receptor with high affinity and specificity, using RaPID (Random Peptide Integrative Discovery) technology. By crosslinking MET-binding peptides, we succeeded to obtain a "synthetic HGF" that has the same biological activity as HGF. Synthetic growth factors have been in market for preparation of stem cells in regenerative medicine. By grafting the sequence of MET-binding cyclic peptide into the loop of the Fc region of IgG molecule, we created MET receptor agonist with antibody-like long-term blood stability, as well as MET-activating ability comparable to HGF. Furthermore, we succeeded in creating MET-agonist that can efficiently cross the blood-brain barrier (BBB) and reach neurons. Technology that creates growth factors and cytokines that have extended biochemical stability and ability to reach specific cells, by using a highly versatile method but with a minimum structural modification, is expected to extend the usefulness of biologics.

Kunio Matsumoto
Division of Tumor Dynamics and Regulation
Cancer Research Institute,
WPI-Nano Life Science Institute,
Kanazawa University, Japan

EDUCATIONS/TRAINING

1983	B.Sci.	Faculty of Science, Kanazawa University
1986	Ph.D	Graduate School of Science, Osaka University

POSITIONS AND HONORS

2007-	Professor	Cancer Research Institute, Kanazawa University
1995-2007	Associate Professor	Osaka University Graduate School of Medicine
1993-1995	Assistant Professor	Osaka University Graduate School of Medicine
1990-1993	Assistant Professor	Department of Biology, Kyushu University
1986-1990	Assistant Professor	Osaka University Medical School

1992 Academic Incitement Award of Japanese Industrial Hygiene Dermatology Association
1996 JB Award from the Japanese Biochemical Society
1997 Incitement Award of the Japanese Cancer Association
2001 The Most Valuable Article Award for 30 Anniversary Memorial of Nikkei Science Journal
2001 The 3rd Bio-Business Competition JAPAN, The Special Award by Referees
2006 Nature Medicine-AnGes MG BioMedical Award (Main Award)
2014 The Commendation for Science and Technology by MEXT (the Minister of Education, Culture, Sports, Science and Technology), Prizes for Science and Technology
2022 Kanazawa City Cultural Award

RECENT PUBLICATIONS

1. Ito K[†], Sakai K[†], Suzuki Y, Ozawa N, Hatta T, Natsume T, Matsumoto K[§], Suga H[§]. Artificial human Met agonists based on macrocycle scaffolds. ***Nat Commun,*** 6: 6373, 2015. ([†]equal contribution; [§]corresponding authors)
2. Sakai K, Passioura T, Sato H, Ito K, Furuhashi H, Umitsu M, Takagi J, Kato Y, Mukai H, Warashina S, Zouda M, Watanabe Y, Yano S, Shibata M, Suga H, Matsumoto K. Macrocyclic peptide-based inhibition and imaging of hepatocyte growth factor. ***Nat Chem Biol,*** 15: 598-606, 2019.
3. Mihara E, Watanabe S, Bashiruddin NK, Nakamura N, Matoba K, Yumi Sano, Maini R, Yin Y, Sakai K, Arimori T, Matsumoto K, Suga H, Takagi J. Lasso-grafting of macrocyclic peptide pharmacophores yields multi-functional proteins. ***Nat Commun,***12: 1543, 2021.
4. Sakai K[†], Sugano-Nakamura N, Mihara E, Rojas-Chaverra NM, Watanabe S, Sato H, Imamura R, Voon DC, Sakai I, Yamasaki C, Tateno C, Shibata M, Suga H, Takagi J[†], Matsumoto K[†]. Designing receptor agonists with enhanced pharmacokinetics by grafting macrocyclic peptides into fragment crystallizable regions. ***Nat Biomed Eng,*** 7: 164-176, 2023. ([†]corresponding authors)
5. Warashina S[§], Sato H[§], Zouda M, Takahashi M, Wada Y, Passioura T, Suga H, Watanabe Y, Matsumoto K[†], Mukai H[†]. Two-chain mature hepatocyte growth factor-specific positron emission tomography imaging in tumors using ^{64}Cu-labeled HiP-8, a non-standard macrocyclic peptide probe. ***Mol Pharmaceutics,*** 20: 2029-2038, 2023. ([§]equal contribution; [†]corresponding authors)

PI3K pathway alteration in gynecological malignancies -- its oncogenic mechanism and clinical translation

Huijuan Yang
Department of Gynecological Oncology
Fudan University Shanghai Cancer Center

PI3K pathway is highly activated by PIK3CA mutation, amplification or PTEN loss in gynecological malignancies, which affects cell proliferation, stemness, metabolism and immune microenvironment. Our series studies focused on the biological function of PIK3CA mutation, and hope further to transform them into clinic. Firstly, PIK3CA was determined as the gene with highest mutation rate (13.6%) among targetable oncogenic mutations in 285 Chinese cervical cancers[1]. Furthermore, we demonstrated that the hotspots are located at E545/2K in 777 cervical cancers, which is different from that in breast cancer [2]. While it is revealed nearly 40%-50% of endometrial and ovarian clear cell carcinomas detected with PIK3CA mutation from TCGA database. Functionally, PIK3CA-E545K enhances glycolysis and radio-resistance by activating β-catenin-mediated SIRT3/GLUT4 axis and p53/bcl2/bax pathway[3,4]. In addition, PIK3CA-E545K mutation inhibits SIRT4 expression, leading to more glutamine uptaking and utilization, which decreases radiosensitivity in cervical cancer[5]. Several clinical trials conducted in our cancer center suggested that single PI3Kα inhibitor, such as WX390, CYH33, is tolerable and effective in gynecological malignancies. In terms of immune microenvironment, our study revealed that PIK3CA-E545K mutation transcriptional upregulates PD-L1 expression and represses CD8+ T cells infiltrating in cervical cancer, PI3Kα inhibitor markedly increases the anti-tumor efficacy of PD-1 antibody in xenografts by activating CD8+ T cells differentiation and proliferation, especially in that with PIK3CA mutation (revision in Immunology). Besides, we found that PI3K/AKT pathway is highly activated in immune subtype of ovarian clear cell carcinoma[6]. Our clinical trial on combination of PI3Kα inhibitor and PD-1 antibody in relapsed gynecological malignancy is ongoing.

Huijuan Yang
Department of Gynecological Oncology
Fudan University Shanghai Cancer Center

EDUCATIONS/TRAINING

1994	Bachelor of Medicine	School of Medicine, Shanghai Medical University (Merged to Fudan University since 2000)
1997	Doctor of Medicine	School of Graduate Studies, Shanghai Medical University
2004	Doctor of Philosophy	Department of Obstetrics & Gynecology, Faculty of Medicine, University of Hong Kong

POSITIONS AND HONORS

2014-	Consultant	Department of Gynecologic Oncology, Fudan University Shanghai Cancer Hospital
2007-2014	Associate Consultant	Department of Gynecologic Oncology, Fudan University Shanghai Cancer Hospital
2000-2007	Attending Physician	Department of Gynecologic Oncology, Fudan University Shanghai Cancer Hospital
1994-2000	Resident	Department of Gynecologic Oncology, Fudan University Shanghai Cancer Hospital
2021	Shanghai Medical Science and Technology Prize 2021 (3rd prize)	
2022	Shanghai Medical Science and Technology Prize 2022 (1st prize)	
2022	Shanghai Anticancer Science and Technology Prize 2022 (3rd prize)	

RECENT PUBLICATIONS

1. Jiang W, Ouyang X, Ji Z, Shi W, Wu Y, Yao Q, Wang Y, Yang W, Xiang L, Yang H. The PIK3CA-E545K-SIRT4 signaling axis reduces radiosensitivity by promoting glutamine metabolism in cervical cancer. ***Cancer Lett***. 2023 Mar 1;556:216064.
2. Yang H, Ye S, Li Q, Wu Y, Jiang W, Zhou S, Zhou X, Yang W, Tu X, Shan B, Huang S et al: Integrative genomic and transcriptomic analysis reveals immune subtypes and prognostic markers in ovarian clear cell carcinoma. ***British journal of cancer*** 2022, 126(8):1215-1223.
3. Yang H (corresponding author), Ye S, Goswami S, Li T, Wu J, Cao C, Ma J, Lu B, Pei X, Chen Y, Yu J, Xu H, Qiu L, Afridi S, Xiang L, Zhang X (corresponding author). Highly immunosuppressive HLADRhi regulatory T cells are associated with unfavorable outcomes in cervical squamous cell carcinoma. ***Int J Cancer***. 2020 146(7):1993-2006.
4. Jiang W, Wu Y, He T, Zhu H, Ke G, Xiang L, Yang H (corresponding author). Targeting of β-catenin reverses radioresistance of cervical cancer with the PIK3CA E545K mutation. ***Mol Cancer Ther***. 2020 Feb;19(2):337-347.doi: 10.1158/1535-7163.MCT-19-0309.
5. Jiang W, He T, Liu S, Zheng Y, Xiang L, Pei X, Wang Z, Yang H (corresponding author). The PIK3CA E542K and E545K mutations promote glycolysis and proliferation via induction of the β-catenin/SIRT3 signaling pathway in cervical cancer. ***J Hematol Oncol***. 2018 Dec 14;11(1):139. doi: 10.1186/s13045-018-0674-5.

Gut microbiota of chronic liver disease patients promote liver carcinogenesis in TLR4-dependent manner

Noriho Iida
Department of Gastroenterology
Kanazawa University Hospital, Japan

Carcinogenesis has long been suspected to be related in part to the composition of gut flora, and liver carcinogenesis has also been related to gut commensal bacteria. The goal of this work is to further elucidate mechanisms underlying liver carcinogenesis induced by gut commensal microbiota in humans as well as in rodent models.

C57BL6 mice were transplanted with feces of Hepatitis C virus-related chronic liver disease with hepatocellular carcinoma patients (HCC, n=23) or without HCC (CLD, n=21), or healthy donors (HD, n=24). After injecting diethylnitrosamine (DEN) and CCl4, liver gene expression or tumor incidence was evaluated. Mice transplanted with feces of HCC or CLD highly bear liver tumors after induction with diethylnitrosamine and CCl4 (tumor incidence in HCC, 91.6%; CLD, 68.7%). In contrast, feces from HD induced less liver tumors (11.1%). Metagenome analysis of microbiota of the mice revealed that Enterococcus faecalis was abundant in mice with microbiota of CLD or HCC. Inoculation of Enterococcus faecalis to mice increased liver tumors, tumorigenic gene expression in the liver, and plasma lipopolysaccharide (LPS). Deletion of TLR4 or Myd88 abrogated the increase of liver tumors in E. faecalis-inoculated mice. Hepatocyte-specific tlr4-deleted mice, not myeloid-cells-specific tlr4-deleted mice, abrogated tumorigenic gene expression in the liver.

Dysbiotic gut microbiota of chronic liver disease patients promote liver carcinogenesis in a TLR4-Myd88-dependent manner.

Noriho Iida
Department of Gastroenterology
Kanazawa University Hospital, Japan

EDUCATIONS/TRAINING

2001	M.D.	Kanazawa University, School of Medicine
2009	Ph.D	Kanazawa University, Graduate School of Medicine
2009-14	Postdoctoral fellow	National Cancer Institute, NIH, USA

POSITIONS AND HONORS

2022-	Senior Assistant Professor	Department of Gastroenterology, Kanazawa University Hospital
2019	Assistant Professor	Department of Gastroenterology, Kanazawa University Hospital
2018	Assistant Professor	Graduate School of Medicine, Kanazawa University
2013	Assistant Professor (Tenure-track)	Graduate School of Medicine, Kanazawa University

RECENT PUBLICATIONS

1. Ziyu Wang, Noriho Iida, Jun Seishima, Hirofumi Okafuji, Masahiro Yutani, Yukako Fujinaga, Yusuke Hashimoto, Haruyoshi Tomita, Eishiro Mizukoshi, Shuichi Kaneko. Patient-derived Enterococcus faecium with inflammatory genotypes promote colitis. ***J Gastroenterol***. 2022;57:770-783.
2. Eishiro Mizukoshi, Hidetoshi Nakagawa, Toshikatsu Tamai, Masaaki Kitahara, Kazumi Fushimi, Kouki Nio, Takeshi Terashima, Noriho Iida, Kuniaki Arai, Tatsuya Yamashita, Taro Yamashita, Yoshio Sakai, Masao Honda, Shuichi Kaneko. Peptide vaccine-treated, long-term surviving cancer patients harbor self-renewing tumor-specific CD8+ T cells. ***Nat Commun***. 2022;13:3123.
3. Hirofumi Okafuji, Noriho Iida, Kazuya Kitamura, Jun Seishima, Ziyu Wang, Masahiro Yutani, Takatoshi Yoshio, Tatsuya Yamashita, Yshio Sakai, Masao Honda, Taro Yamashita, Yukako Fujinaga, Reiko Shinkura, Yasuhito Hamaguchi, Eishiro Mizukoshi and Shuichi Kaneko. Oral Corticosteroids Impair Mucin Production and Alter the Posttransplantation Microbiota in the Gut. ***Digestion*** 2022;103:269-286.
4. Noriho Iida, Eishiro Mizukoshi, Tatsuya Yamashita, Masahiro Yutani, Jun Seishima, Ziyu Wang, Kuniaki Arai, Hikari Okada, Taro Yamashita, Yoshio Sakai, Yusuke Masuo, Rina Agustina, Yukio Kato, Yukako Fujinaga, Masanobu Oshima, Masao Honda, Francois Lebreton, Michael S Gilmore and Shuichi Kaneko. Chronic liver disease enables gut Enterococcus faecalis colonization to promote liver carcinogenesis. ***Nature Cancer*** 2021;2:1039-1054.

Session 2

Prognostic value of the consensus molecular subtype 4 (CMS4) predicted by multiparametric radiomics-based machine learning in colorectal cancer: a multi-center retrospective study

Tong Tong
Department of Radiology
Fudan University Shanghai Cancer Center
Department of Oncology, Shanghai Medical College, Fudan University

Gene expression profiles are widely recognized to be associated with tumor heterogeneity and therapeutic response in colorectal cancer (CRC). The consensus molecular subtype (CMS) is a novel classification system that reflects the genetic characteristics of the tumor. Among the four subtypes, CMS4 is associated with the worst prognosis. Patients with CMS4 are generally resistant to adjuvant chemotherapy treatment and have a higher likelihood of having micro metastases at the time of initial diagnosis due to its "early dissemination" pattern. Therefore, early detection of CMS4 is crucial for administering effective treatment protocols at an early stage. In CMS4 CRC, the upregulation of the EMT pathway and overexpression of TGF-β result in a histomorphology phenotype characterized by high tumor mesenchymal content and an angiogenesis-driven microenvironmental vascular abundance. These features may be reflected in MRI image features to some extent. Therefore, it is feasible to achieve early detection of CMS classification using an MRI-based radiomics approach. Among all cases, 59 (26%) cases were classified as CMS4. We found that the contrast-enhanced (CE) mode achieved better performance than T2-weighted (T2WI) model in both the test set (0.815 vs 0.790) and external validation set (0.741 vs 0.702). After merging the two models, the predictive performance of the Merged model was further improved, with the AUCs of 0.855 and 0.759 in the test set and external validation set. The genetic phenotype of CMS4 colorectal cancer may be potentially associated with morphological features. Multiparametric radiomics-based machine learning shows promising potential in distinguishing CMS4 from other subtypes of CRC.

Tong Tong
Department of Radiology
Fudan University Shanghai Cancer Center

EDUCATIONS/TRAINING

1998-2003	Bachelo	Shanghai Medical School, Fudan University
2003-2008	Doctorate	Shanghai Medical School, Fudan University
2014	Visiting Scholar	Memorial Sloan Kettering Cancer Center, USA

POSITIONS AND HONORS

	Chief Physician	Department of Radiology, FUSCC
	PhD Supervisor	Imaging and Nuclear Medicine, Fudan University
	Member	Magnetic Resonance Committee, Chinese Society of Radiology Youth Group Committee, Shanghai Society of Radiology
	Member	National Natural Science Foundation of China General Project
	Project Leader	National Natural Science Foundation of China Youth Project
2020-2023	Project Leader	Shanghai Science and Technology Commission Project
2020-2022	Project Leader	"Excellence 2025" Program, Fudan University
2017	Third Prize, Shanghai Anti-Cancer Science and Technology Award, Shanghai Anti-Cancer Association.	
2016	Third Prize, Fudan University Shanghai Cancer Center "Tianheng Cup", FUSCC.	

RECENT PUBLICATIONS

1. Liu Z, Wang Y, Shen F, Zhang Z, Gong J, Fu C, Shen C, Li R, Jing G, Cai S, Zhang Z, Sun Y, Tong T*. Radiomics based on readout-segmented echo-planar imaging (RS-EPI) diffusion-weighted imaging (DWI) for prognostic risk stratification of patients with rectal cancer: a two-centre, machine learning study using the framework of predictive, preventive, and personalized medicine. ***EPMA J***. 2022 Nov 12;13(4):633-647. (JCR:Q1;IF=8.834)
2. Li M, Gong J, Bao Y, Huang D, Peng J, Tong T*. Special issue "The advance of solid tumor research in China": Prognosis prediction for stage II colorectal cancer by fusing computed tomography radiomics and deep-learning features of primary lesions and peripheral lymph nodes. ***Int J Cancer***. 2023 Jan 1;152(1):31-41. (JCR:Q1;IF=7.316)
3. Cai C, Hu T, Gong J, Huang D, Liu F, Fu C, Tong T*. Multiparametric MRI-based radiomics signature for preoperative estimation of tumor-stroma ratio in rectal cancer. ***Eur Radiol***. 2021 May;31(5):3326-3335. (JCR:Q1;IF=5.315)
4. Dai W, Mo S, Han L, Xiang W, Li M, Wang R, Tong T*, Cai G. Prognostic and predictive value of radiomics signatures in stage I-III colon cancer. ***Clin Transl Med***. 2020 Jan;10(1):288-293. (JCR:Q1;IF=11.492)
5. Hu T, Wang S, Huang L, Wang J, Shi D, Li Y, Tong T*, Peng W. A clinical-radiomics nomogram for the preoperative prediction of lung metastasis in colorectal cancer patients with indeterminate pulmonary nodules. ***Eur Radiol***. 2019 Jan;29(1):439-449. (JCR:Q1;IF=5.315)

Identification and functional analysis of senescent cells in tumor microenvironment

Yoshikazu Johmura
Division of Cancer and Senescence Biology
Cancer Research Institute
Institute for Frontier Science Initiative
Kanazawa University, Japan

Healthy life expectancy and average life expectancy have diverged by 9.2 years for men and 12.5 years for women as of 2018 in Japan, and extending healthy life expectancy is an urgent issue to realize a sustainable society. Fundamental solutions require an understanding of the regulatory mechanisms of individual aging and chronic inflammatory diseases, and the development of therapeutic and preventive technologies.

One of the most important risk factors for the development of cancer is aging. The incidence of many cancers increases with age, and the pattern is similar to those of typical age-related diseases. It is becoming clear that the accumulation of 'senescent cells' that are induced by various stressors including DNA damage and show characteristics such as irreversible arrest of cell proliferation and secretion of bioactive molecule (SASP) is important for anti-tumorigenesis as well as the onset and progression of aging-related diseases. Importantly, recent studies indicate that the elimination of senescent cells accumulated in the body during aging ameliorates age-related diseases including cancer, thus promoting the healthy lifespan. Therefore, cellular senescence likely plays both positive and negative roles in cancer. Recently, we generated a p16Ink4a-CreERT2-tdTomato mouse to analyze the in vivo characteristics of senescent cells. Our new mouse model and single-cell analyses suggest that in vivo senescent cells exhibited heterogeneous senescence-associated phenotypes during aging. Currently, we are trying to apply this approach to some cancer models, and we found that cancer-related senescent cells also are composed of several cell types and have various characteristics. Further analysis will provide a molecular basis for context-dependent effects of cellular senescence in cancer.

Yoshikazu Johmura
Division of Cancer and Senescence Biology
Cancer Research Institute
Institute for Frontier Science Initiative
Kanazawa University, Japan

EDUCATIONS/TRAINING

2005	M.S.	Graduate School of Pharmaceutical Science, Nagoya City University
2008	Ph.D.	Graduate School of Pharmaceutical Science, Nagoya City University

POSITIONS AND HONORS

2023-	Unit Leader	Institute for Frontier Science Initiative, Kanazawa University
2022-	Professor	Cancer Research Institute, Kanazawa University
2016-2022	Assistant Professor	Institute of Medical Science, University of Tokyo
2011-2016	Assistant Professor	Department of Medical Sciences, Nagoya City University
2008-2011	Postdoctoral Researcher	National Cancer Institute, NIH

RECENT PUBLICATIONS

1. LONRF2 is a protein quality control ubiquitin ligase whose deficiency causes late-onset neurological deficits Li D, *Johmura Y, … *Nakanishi M. ***Nature Aging*** 2023, in press. (*corresponding authors)
2. Wang TW, Johmura Y*, Suzuki N, Omori S, Migita T, Yamaguchi K, Hatakeyama S, Yamazaki S, Shimizu E, Imoto S, Furukawa Y, Yoshimura A, Nakanishi M*. Blocking PD-L1 boosts senescence surveillance and improves aging phenotypes. ***Nature*** 2022, 611(7935), 358-364. (*corresponding authors)
3. Reyes NS, Krasilnikov M, Allen NC, Lee JY, Hyams B, Zhou M, Ravishankar S, Cassandras M, Wang C, Khan I, Matatia P, Johmura Y, Molofsky A, Matthay M, Nakanishi M, Sheppard D, Campisi J, Peng T*. Sentinel p16INK4a+ cells in the basement membrane form a reparative niche in the lung. ***Science***. 2022, 14;378(6616):192-201. (*corresponding author)
4. *Johmura Y, Yamanaka T, Omori S, Wang TW, Sugiura Y, Matsumoto M, Suzuki N, Kumamoto S, Yamaguchi K, Hatakeyama S, Takami T, Yamaguchi R, Shimizu E, Ikeda K, Okahashi N, Mikawa R, Suematsu M, Arita M, Sugimoto M, Nakayama KI, Furukawa Y, Imoto S, *Nakanishi M. Senolysis by glutaminolysis inhibition ameliorates various age-associated disorders. ***Science***. 2021, 371(6526), 265–270. (*corresponding authors)
5. Omori S, Wang TW, *Johmura Y, Kanai T, Nakano Y, Kido T, Susaki EA, Nakajima T, Shichino S, Ueha S, Ozawa M, Yokote K, Kumamoto S, Nishiyama A, Sakamoto T, Yamaguchi K, Hatakeyama S, Shimizu E, Katayama K, Yamada Y, Yamazaki S, Iwasaki K, Miyoshi C, Funato H, Yanagisawa M, Ueno H, Imoto S, Furukawa Y, Yoshida N, Matsushima K, Ueda HR, Miyajima A, *Nakanishi M. Generation of a p16 Reporter Mouse and Its Use to Characterize and Target p16 high Cells In Vivo. ***Cell Metabolism***. 2020, 32(5), 814–828. (*corresponding authors)

The effect of the potential new drug MITF inhibitor on malignant melanoma and its synergistic mechanism with anti-PD1 immunotherapy

Yong Chen
Melanoma Center
Department of Musculoskeletal Oncology
Fudan University Shanghai Cancer Center

Microphthalmia transcription factor (MITF) regulates melanocyte development and is the "lineage-specific survival" oncogene of melanoma. MITF is essential for melanoma initiation, progression, and relapse and has been considered an important therapeutic target; however, direct inhibition of MITF through small molecules is considered impossible, due to the absence of a ligand-binding pocket for drug design. Here, our structural analyses show that the structure of MITF is hyperdynamic because of its out-of-register leucine zipper with a 3-residue insertion. The dynamic MITF is highly vulnerable to dimer-disrupting mutations, as we observed that MITF loss-of-function mutations in human Waardenburg syndrome type 2 A are frequently located on the dimer interface and disrupt the dimer forming ability accordingly. These observations suggest a unique opportunity to inhibit MITF with small molecules capable of disrupting the MITF dimer. From a high throughput screening against 654,650 compounds, we discovered compound TT-012, which specifically binds to dynamic MITF and destroys the latter's dimer formation and DNA-binding ability. Using chromatin immunoprecipitation assay and RNA sequencing, we showed that TT-012 inhibits the transcriptional activity of MITF in B16F10 melanoma cells. In addition, TT-012 inhibits the growth of high-MITF melanoma cells, and inhibits the tumor growth and metastasis with tolerable toxicity to liver and immune cells in animal models. We also verified the anti-MM activity of TT-012 through PDX model. Nest, we constructed C57BL/6 mice transplanted tumor model using mice-derived malanoma cell line B16. Using this model, we verified the immune activity of TT-012 to improve the tumor immune microenvironment. We also clarified the synergistic anti-tumor effect and safety of TT-012 combined with anti-PD1 immunotherapy. Single cell RNA seq was performed to explore the mechanisms of this synergistic anti-tumor effect. In this process, we intend to keep optimizing MITF inhibitors, synthesize TT-012 derivatives, and strive to obtain relevant potential drug molecules.

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EDUCATIONS/TRAINING

2003	M.S.	Nankai University, Tianjin, China
2011	M.D., Ph.D.	Tianjin Medical University, Tianjin, China
2013	Soudavor Fellowship	Memorial Sloan Kettering Cancer Center, New York, USA
2014	Visiting Scholar	Institute of Gustave Roussy, Paris, France

POSITIONS AND HONORS

	Vice Chairman	Melanoma Committee of China Anti-Cancer Association
	Chairman	Melanoma Committee of Shanghai Anti-Cancer Association
	Chairman	Melanoma Center, FUSCC
	Vice Chairman	Department of Musculoskeletal Oncology, FUSCC
	Attending Surgeon	FUSCC
2008	The 3rd class excellent paper in 5th Chinese conference on oncology	
2021	The 2nd Prize of Science and Technology Award of China Anti-Cancer Association	

RECENT PUBLICATIONS

1. Liu Z., Chen K., Dai J., Xu P., Sun W., Liu W., Zhao Z., Bennett SP., Li P., Ma T., Lin Y., Kawakami A., Yu J., Wang F., Wang C., Li M., Chase P., Hodder P., Spicer TP., Scampavia L., Cao C., Pan L., Dong J., Chen Y., Yu B., Guo M., Fang P., Fisher DE., Wang J. A unique hyperdynamic dimer interface permits small molecule perturbation of the melanoma oncoprotein MITF for melanoma therapy. ***Cell Res***. 33(1):55-70. (2023)
2. Sun W., Jin Y., Wei C., Xu Y., Liu W., Zhong J., Zou Z., Lin X., Xiang Y., Chen Y. CDCA2 promotes melanoma progression by inhibiting ubiquitin-mediated degradation of Aurora kinase A. ***Eur J Cancer***. 188:49-63. (2023)
3. Zhong J., Sun W., Hu T., Wang C., Yan W., Luo Z., Liu X., Xu Y., Chen Y. Comparative analysis of adjuvant therapy for stage III BRAF-mut melanoma: A real-world retrospective study from single center in China. ***Cancer Med***. 12(10):11475-11482. (2023)
4. Guo X., Yin X., Xu Y., Li L., Yuan M., Zhao H., Jiang Y., Shi X., Bi H., Liu Y., Chen Y., Xu Q. TMED3 promotes the development of malignant melanoma by targeting CDCA8 and regulating PI3K/Akt pathway. ***Cell Biosci***. 13(1):65. (2023)
5. He Y., Dong Y., Chen Y., Zhang G., Zhang H., Lei G., Du Y., Chen X., Ye Y., Liu H. Multi-omics characterization and therapeutic liability of ferroptosis in melanoma. ***Signal Transduct Target Ther***. 7(1):268. (2022)


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