Institute for Genetic Medicine
HOKKAIDO UNIVERSITY

Institute for Genetic Medicine, Hokkaido University

2024►2025

Contents

Institute for Genetic Medicine Aim and Mission

Director, Institute for Genetic Medicine, Hokkaido University

Masaaki Murakami, D.V.M., Ph.D.

The Institute for Genetic Medicine (IGM) was established in April 2000 through the merger of the Hokkaido University Institute for Immunological Sciences (formerly knowns as the Institute of Tuberculosis Research), which has existed for more than 60 years, and the Cancer Research Center attached to the Faculty of Medicine, which has been around for more than 40 years. Currently, IGM consists of 15 laboratories and facilities that conduct medical and biological research in cooperation with the Hokkaido University School of Medicine, Graduate School of Medicine, Graduate School of Chemical Sciences and Engineering, Graduate School of Life Science, Graduate School of Infectious Diseases, and Hokkaido University Hospital. IGM is one of the largest centers for medical and life science research in Eastern Japan, with a total of approximately 200 members, including more than 50 undergraduate and graduate students from various countries. In addition, as one of the national Joint Usage/Collaborative Research Centers under the Ministry of Education, Culture, Sports, Science and Technology (MEXT), IGM has been recognized as a "Center for Advanced Research on Infectious Cancer Caused by Persistent Infection with Bacteria and Viruses (Center for Infectious Cancer Research, CICR)" since 2010.

Our approach to science is not bound by existing ideas or dogma. Instead, we encourage new hypotheses that are validated by experimentally, which has led us to discover new molecular mechanisms and biological concepts. The result of this approach is high impact papers, a generous amount of external funding (the amount of external funding received per faculty member at IGM is one of the highest in the university), and the education and training young researchers who will become leaders of their fields.

IGM's research focus includes infection, carcinogenesis, immunity/inflammation, and infectious cancer, which are the four stages in the development of infectious cancers. Part of this work involves research into new diagnostic, preventive, and therapeutic methods by investigating the functions of genes at the quantum, molecular, and individual levels to understand the causes of infectious cancers. Another important mission of IGM is to promote science to the general public. Thus, we regularly engage with nearby elementary, junior high, and senior high schools. We also sponsor a number of research gatherings, including the 10th Interdepartmental Symposium of Hokkaido University (2024), which was planned and organized by young researchers from 38 departments and over 800 participants; established the Azuma-Ichiro Fund to support young researchers' overseas travel; and participate in the annual university festival to provide school children with hands-on research experience.

Building upon our foundation of research, mentorship, and community engagement, IGM will continue to strive for innovative research that leads to new concepts in biology and medicine. We sincerely appreciate your continued support.

Oct. 2024

History

Institute of Immunological Science

1941. 2 Founded, Hoppou Foundation for Tuberculosis Research
1945. 8 Founded, Research Institute for Tuberculosis in Hoppou Foundation for Tuberculosis Reseach
1950. 4 Founded, Research Institute for Tuberculosis, Hokkaido University. Established, Research Section of Prophylaxis and Research Section of Bacteriology
1951. 3 Donated, Building of Research Institute for Tuberculosis (1,935m^2) from Hoppou Foundation for Tuberculosis Research
1951. 4 Established, Research Section of Chemistry and Research Section of Pathology in Research Institute for Tuberculosis
1953. 4 Established, Clinical Section in Research Institute for Tuberculosis
1954. 2 Started publishing periodically "Tuberculosis Research"
1968.11 Research Institute for Tuberculosis, Moved to North Building, Hokkaido University School of Medicine
1969. 4 Established, Research Section of Biochemistry in Research Institute for Tuberculosis, Hokkaido University
1974. 6 Research Institute for Tuberculosis, reorganized and Renamed, Institute of Immunological Science, Hokkaido University. Established, Research Section of Bacterial Infection, Research Section of Serology, Research Section of Chemistry, Research Section of Pathology and Research Section of Biochemistry in the Institute of Immunological Science
1975. 1 Started publishing periodically "Bulletin of the Institute of Immunological Science, Hokkaido University"
1976. 5 Established, Laboratory of Animal Experiment in Institute of Immunological Science
1980. 3 Started publishing periodically "Collected Papers from the Institute of Immunological Science, Hokkaido University"
1980. 4 Established, Research Section of Cellular Immunology in Institute of Immunological Science, Hokkaido University
1990. 3 Discontinued, Research Section of Cellular Immunology in Institute of Immunological Science, Hokkaido University
1990. 6 Established, Research Section of Immunopathogenesis in the Institute of Immunological Science, Hokkaido University

Cancer Institute, School of Medicine

1962. 4 Founded, Cancer Immunopathology Institute, Hokkaido University School of Medicine, Established, Division of Pathology in the Cancer Immunopathology Institute
1967. 4 Established, Division of Virology in Cancer Immunopathology Institute, Hokkaido University School of Medicine
1969. 4 Cancer Immunopathology Institute, Hokkaido University School of Medicine was renamed Cancer Institute, Hokkaido University School of Medicine
1971. 4 Established, Division of Biochemistry in Cancer Institute, Hokkaido University School of Medicine
1979. 4 Established, Division of Genetics in Cancer Institute, Hokkaido University School of Medicine
1986. 3 Discontinued, Division of Genetics in Cancer Institute, Hokkaido University School of Medicine
1986. 4 Established, Division of Molecular Genetics in Cancer Institute, Hokkaido University School of Medicine
1992. 4 Established, Division of Cell Biology in Cancer Institute, Hokkaido University School of Medicine
1996. 3 Discontinued, Division of Molecular Genetics in Cancer Institute, Hokkaido University School of Medicine
1996. 5 Established, Division of Gene Regulation and Division of Gene Therapy Development in Cancer Institute, Hokkaido University School of Medicine

Institute for Genetic Medicine

2000. 4 Founded, Institute for Genetic Medicine, Hokkaido University by integrating the Institute of Immunological Science, Hokkaido University and the Cancer Institute, Hokkaido University School of Medicine
2004. 4 Established, Department of Matrix Medicine as Endowed Department in Institute for Genetic Medicine, Hokkaido University
2006. 4 Established, Division of ROYCE' Health Bioscience as Endowed Department in Institute for Genetic Medicine, Hokkaido University
2008. 7 Laboratory of Animal Experiment for Disease Model was renamed Laboratory of Animal Experiments
Discontinued, Center for Virus Vector Development
Established, Center for Infection-associated Cancer
2010. 4 Authorized as a joint usage/research center for infection-associated cancers caused by sustained infection with bacteria and viruses.
Established, Joint Usage/Research Center Promotion Office in Institute for Genetic Medicine, Hokkaido University
Established, Joint Office for Promoting Interdisciplinary Research in Institute for Genetic Medicine, Hokkaido University
2011. 9 Established, Department of Probiotics Immunology as Endowed Department in Institute for Genetic Medicine, Hokkaido University
2012. 4 Division of Cancer Related Genes was renamed Division of Stem Cell Biology
2013. 9 Division of Tumor Virology was renamed Division of RNA Biofunction
2013.10 Discontinued, Department of ROYCE' Health Bioscience as Endowed Department in Institute for Genetic Medicine, Hokkaido University
2014. 2 Established, Biomedical Animal Research Laboratory as Frontier Research Unit in Institute for Genetic Medicine, Hokkaido University
2014. 3 Discontinued, Department of Matrix Medicine as Endowed Department in Institute for Genetic Medicine, Hokkaido University
2014. 4 Established, Vascular Biology as Frontier Research Unit in Institute for Genetic Medicine, Hokkaido University
2014. 5 Division of Molecular Immunology was renamed Division of Molecular Neuroimmunology
2014.10 Division of Immunoregulation was renamed Division of Functional Immunology
2015. 9 IGM was selected continuously as a joint usage/research center for infection-associated cancers caused by sustained infection with bacteria and viruses
2017. 4 Established, Liaison Labs in Research Center for Infection-associated Cancer
2017. 8 Division of Molecular Neuroimmnology was renamed Division of Molecular Psychoimmunology
2017. 8 Division of Molecular Virology was renamed Division of Developmental Immunology
2018. 5 Vascular Biology as Frontier Research Unit transferred to Faculty of Dental Medicine, Hokkaido University
2018. 9 Established, Division of Biomedical Oncology as Research Section of Disease Control in Institute for Genetic Medicine, Hokkaido University
2020. 3 Discontinued, Department of Probiotics Immunology as Endowed Department in Institute for Genetic Medicine, Hokkaido University
2020. 4 Established, Division of Genome Biology as Research Section of Pathophysiology in Institute for Genetic Medicine, Hokkaido University
2020. 5 Established, Department of Synbiotics as Endowed Department in Institute for Genetic Medicine, Hokkaido University
2020. 9 Discontinued, Division of Molecular Oncology as Research Section of Pathophysiology in Institute for Genetic Medicine, Hokkaido University
2020.10 Established, Division of Developmental Physiology as Research Section of Pathophysiology in Institute for Genetic Medicine, Hokkaido University
2020.10 Discontinued, Division of RNA Biofunction as Research Section of Molecular Pathogenesis in Institute for Genetic Medicine, Hokkaido University
2021. 3 Established, Laboratory of Molecular Cellular Biology as Frontier Research Unit in Institute for Genetic Medicine, Hokkaido University
2021. 3 Discontinued, Joint Office for Promoting Interdisciplinary Research in Institute for Genetic Medicine, Hokkaido University
2021. 9 Discontinued, Division of Cancer Biology as Research Section of Pathophysiology in Institute for Genetic Medicine, Hokkaido University
2022. 1 Established, Division of Hepatitis Virology as Research Section of Molecular Pathogenesis in Institute for Genetic Medicine, Hokkaido University
2022. 1 Established, Division of Biological Molecular Mechanisms as Research Section of Disease Control in Institute for Genetic Medicine, Hokkaido University
2022. 4 Established, Division of Microbial Oncology as Research Section of Pathophysiology in Institute for Genetic Medicine, Hokkaido University
2023. 3 Discontinued, Division of Functional Immunology as Research Section of Disease Control in Institute for Genetic Medicine, Hokkaido University

Chronological List of Director and Professor Emeritus

Successive Director of Research Institute for Tuberculosis

Morio YASUDA, M.D.,Ph.D.	1950. 4–1953. 3
Yoshio TAKAHASHI, M.D.,Ph.D.	1953. 4–1968. 3
Shichiro KAKIMOTO, Ph.D.	1968. 4–1971. 3
Yoshio TAKAHASHI, M.D.,Ph.D.	1971. 4–1974. 3

Successive Director of Institute of Immunological Science

Toru OHARA, M.D.,Ph.D.	1974. 4–1979. 4
Kazuo MORIKAWA, M.D.,Ph.D.	1979. 4–1985. 3
Ken-ichi YAMAMOTO, M.D.,Ph.D.	1985. 4–1988. 3
Ichiro AZUMA, Ph.D.	1988. 4–1994. 3
Mitsuaki KAKINUMA, M.D.,Ph.D.	1994. 4–1996. 3
Kazunori ONOÉ, M.D.,Ph.D.	1996. 4–2000. 3

Successive Director of Cancer Immunopathology Institute, School of Medicine

Katsuo TAKEDA, M.D.,Ph.D.	1962. 4–1965. 3
Sanshi ABE, M.D.,Ph.D.	1965. 4–1967.12
Hiroshi KOBAYASHI, M.D.,Ph.D.	1967.12–1969. 3

Successive Director of Cancer Institute, School of Medicine

Hiroshi KOBAYASHI, M.D.,Ph.D.	1969. 4–1973. 3
Toyoro OSATO, M.D.,Ph.D.	1973. 4–1975. 3
Akira MAKITA, M.D.,Ph.D.	1975. 4–1977. 3
Hiroshi KOBAYASHI, M.D.,Ph.D.	1977. 4–1981. 3
Toyoro OSATO, M.D.,Ph.D.	1981. 4–1985. 3
Akira MAKITA, M.D.,Ph.D.	1985. 4–1989. 3
Toyoro OSATO, M.D.,Ph.D.	1989. 4–1993. 3
Noboru KUZUMAKI, M.D.,Ph.D.	1993. 4–1997. 3
Masaki SAITO, M.D.,Ph.D.	1997. 4–1997.10
Masuo HOSOKAWA, M.D.,Ph.D.	1997.11–2000. 3

Successive Director of Institute for Genetic Medicine

Kazunori ONOÉ, M.D.,Ph.D.	2000. 4–2002. 3
Kenzo TAKADA, M.D.,Ph.D.	2002. 4–2006. 3
Toshimitsu UEDE, M.D.,Ph.D.	2006. 4–2010. 3
Kazuma TANAKA, Ph.D.	2010. 4–2012. 3
Akinori TAKAOKA, M.D.,Ph.D.	2012. 4–2016. 3
Masaaki MURAKAMI, V.M.D.,Ph.D.	2016. 4–2020. 3
Kazuma TANAKA, Ph.D.	2020. 4–2022. 3
Masaaki MURAKAMI, V.M.D.,Ph.D.	2022. 4–

Successive Director of Laboratory of Animal Experiment, Institute of Immunological Science

Kazuo MORIKAWA, M.D.,Ph.D.	1976. 5–1979. 3
Jun ARIMA, M.D.,Ph.D.	1979. 4–1981. 3
Ken-ichi YAMAMOTO, M.D.,Ph.D.	1981. 4–1985. 3
Ichiro AZUMA, Ph.D.	1985. 4–1988. 3
Harue OKUYAMA, M.D.,Ph.D.	1988. 4–1991. 2
Kazunori ONOÉ, M.D.,Ph.D.	1991. 2–1996. 3
Kazuyoshi IKUTA, M.D.,Ph.D.	1996. 4–1998.10
Toshimitsu UEDE, M.D.,Ph.D.	1998.11–2000. 3

Successive Director of Laboratory of Animal Experiments, Institute for Genetic Medicine

Toshimitsu UEDE, M.D.,Ph.D.	2000. 4–2004. 3
Kunimi KIKUCHI, M.D.,Ph.D.	2004. 4–2006. 3
Masanori HATAKEYAMA, M.D.,Ph.D.	2006. 4–2008. 6
Hisatoshi SHIDA, Ph.D.	2008. 7–2012. 3
Masami MORIMATSU, D.V.M.,Ph.D.	2012. 4–2013.10
Ken-ichiro SEINO, M.D.,Ph.D.	2013.11–2017.10
Akinori TAKAOKA, M.D.,Ph.D.	2017.11–2021. 3
Ken-ichiro SEINO, M.D.,Ph.D.	2022. 4-

Successive Director of Center for Virus Vector Development, Institute for Genetic Medicine

Kenzo TAKADA, M.D.,Ph.D.	2000. 4–2002. 3
Noboru KUZUMAKI, M.D.,Ph.D.	2002. 4–2006. 3
Hisatoshi SHIDA, Ph.D.	2006. 4–2008. 6

Successive Director of Center for Infection-associated cancer, Institute for Genetic Medicine

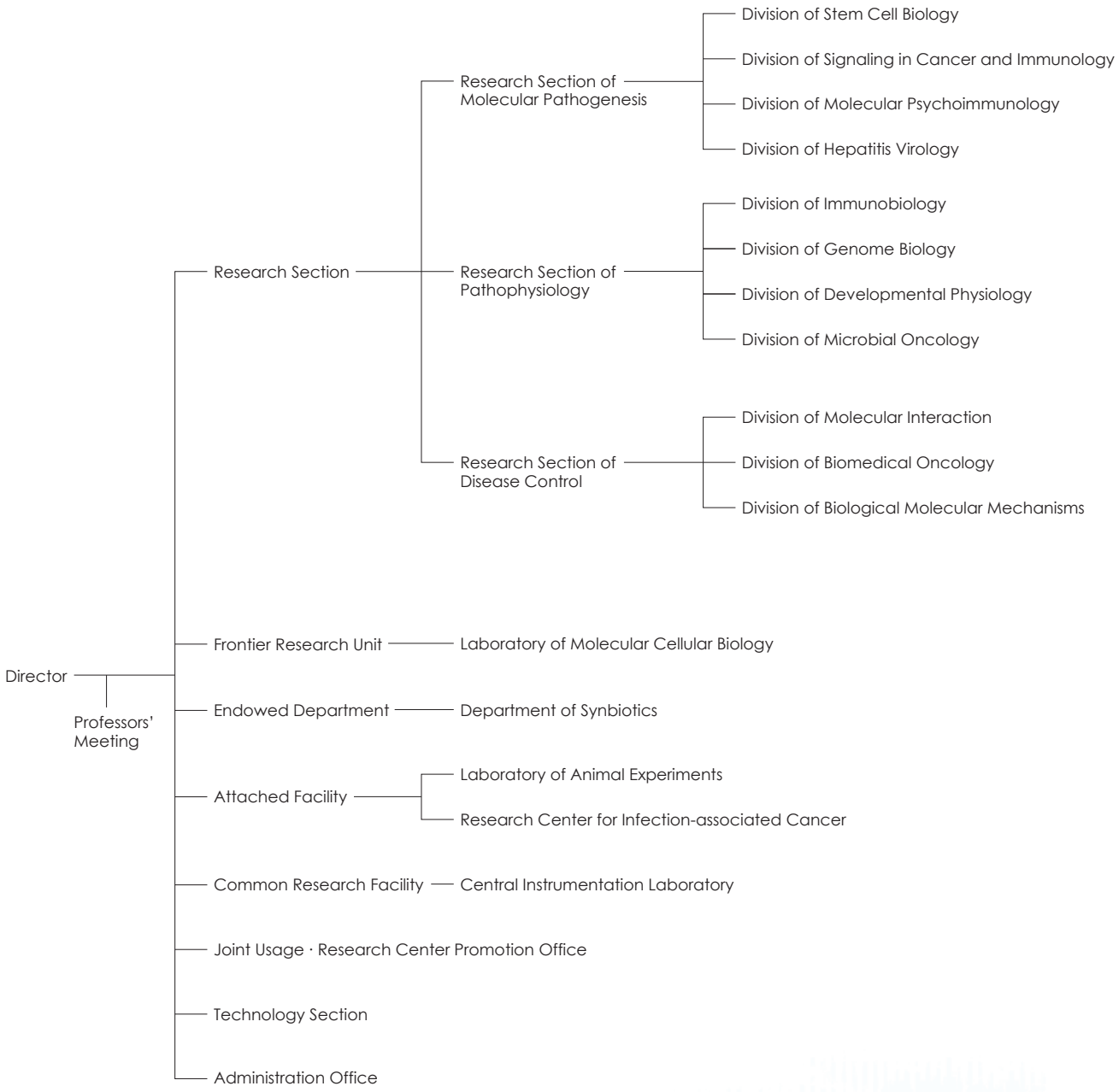
Masanori HATAKEYAMA, M.D.,Ph.D.	2008. 7–2009. 6
Akinori TAKAOKA, M.D.,Ph.D.	2009. 7–2012. 3
Kazuma TANAKA, Ph.D.	2012. 4–2014. 3
Toru KONDO, Ph.D.	2014. 4–2019. 3
Tetsuro HIROSE, Ph.D.	2019. 4–2020. 3
Masaaki MURAKAMI, V.M.D., Ph.D.	2020. 4–2022. 3
Masahiro SONOSHITA, Ph.D.	2022. 4–

Professor Emeritus

Kazuo MORIKAWA, M.D.,Ph.D.	1985. 4
Ken-ichi YAMAMOTO, M.D.,Ph.D.	1988. 4
Hiroyuki SHIOKAWA, Ph.D.	1988. 4
Harue OKUYAMA, M.D.,Ph.D.	1991. 3
Hiroshi KOBAYASHI, M.D.,Ph.D.	1991. 4
Akira MAKITA, M.D.,Ph.D.	1994. 4
Mitsuaki KAKINUMA, M.D.,Ph.D.	1998. 4
Ichiro AZUMA, Ph.D.	1999. 4
Masuo HOSOKAWA, M.D.,Ph.D.	2002. 4
Kunimi KIKUCHI, M.D.,Ph.D.	2006. 4
Noboru KUZUMAKI, M.D.,Ph.D.	2006. 4
Kazunori ONOÉ, M.D.,Ph.D.	2009. 4
Kenzo TAKADA, M.D.,Ph.D.	2011. 4
Tetsuya MORIUCHI, M.D.,Ph.D.	2011. 4
Toshimitsu UEDE, M.D.,Ph.D.	2013. 4
Hisatoshi SHIDA, Ph.D.	2013. 4
Masayuki NOGUCHI, Ph.D.	2019. 4
Kazuma TANAKA, Ph.D.	2024. 4

Organization

Data as of October 1, 2024



Number of Staff

Data as of October 1, 2024

Professor	12
Associate Professor	10
Lecturer	8
Assistant Professor	15
Administrative Officer	37
Technical Specialist • Technical Staff	7
Postdoctoral fellow	4
Research Fellow	5
Guest Researcher	15
Part-time Fellow	2
Research Support Assistant	5
Part-timer	28
Visiting Fellow	13
Research Fellowships for Young Scientists (PD)	2
Total	163

Number of Student

Data as of October 1, 2024

Graduate School of Medicine, Doctoral Program	19
Graduate School of Medicine, Master's Program	2
Graduate School of Chemical Sciences and Engineering, Doctor Course	1
Graduate School of Chemical Sciences and Engineering, Master Course	6
Graduate School of Life Science, Doctoral Course (Division of Clinical Pharmacy)	0
Graduate School of Life Science, Doctoral Course (Division of Life Science, Division of Soft Matter)	0
Graduate School of Life Science, Master's Course	5
Graduate School of Infectious Diseases, Doctoral Course	2
Research Student	2
Visiting Student	27
Total	64

Research Section of Molecular Pathogenesis

Division of Stem Cell Biology

Professor	Toru KONDO, Ph.D.
Lecturer	You Lee SON, Ph.D.
Assistant Professor	Naoto OIKAWA, Ph.D.
Postdoctoral Fellow	Shenshen DOU
Research Support Assistant	Seiko HORITA

Division of Signaling in Cancer and Immunology

Professor	Akinori TAKAOKA, M.D., Ph.D.
Associate Professor	Seiichi SATO, Ph.D.
Assistant Professor	Hiraku SUZUKI, DDS
Technical Specialist	Nozomi SAKURAI

Division of Molecular Psychoimmunology

Professor	Masaaki MURAKAMI, D.V.M., Ph.D.
Associate Professor	Shintaro HOJO, Ph.D.
Associate Professor	Shigeru HASHIMOTO, Ph.D.
Specially Appointed Lecturer	Shimpei KUBOTA, M.D., Ph.D.
Specially Appointed Lecturer	Yuta SHINOHARA, Ph.D.
Specially Appointed Lecturer	Jing Jing JIANG, M.D., Ph.D.
Specially Appointed Lecturer	Hiroki TANAKA, Ph.D.
Specially Appointed Assistant Professor	Rieko NISHI, M.D., Ph.D.
Specially Appointed Assistant Professor	Haruka HANDA, M.D., Ph.D.
Specially Appointed Assistant Professor	Kaoru MURAKAMI, DDS., Ph.D.
Postdoctoral Fellow	Teruhito YASUI, Ph.D.
Technical Specialist	Chiemi NAKAYAMA
Technical Staff	Naofumi SAKURAI
Technical Support Staff	Momoko TARU
Part-time Fellow	Kumiko TANAKA
Administrative Assistant	Mari OSAWA

Division of Hepatitis Virology

Professor	Kohji MORIISHI, D.V.M., Ph.D.
Associate Professor	Tomohisa TANAKA, D.V.M., Ph.D.

Research Section of Pathophysiology

Division of Immunobiology

Professor	Ken-ichiro SEINO, M.D., Ph.D.
Assistant Professor	Akihiro MORI, Ph.D.
Research Fellow	Yuichi IGARASHI, Ph.D.
Research Support Assistant	Rei OKABE

Division of Genome Biology

Professor	Ken-ichi NOMA, Ph.D.
Associate Professor	Shinya OTA, Ph.D.
Associate Professor	Hideki TANIZAWA, Ph.D.
Specially Appointed Assistant Professor	Yik-Lok CHUNG, Ph.D.
Technical Support Staff	Makiko FUKUUCHI
Technical Support Staff	Kusumastuti RATIH
Administrative Assistant	Michiko KANBAYASHI

Division of Developmental Physiology

Professor	Fumio MOTEGI, Ph.D.
Lecturer	Kenji KIMURA, Ph.D.
Lecturer	Yukako NISHIMURA, Ph.D.
Specially Appointed Assistant Professor	Kazunori YAMAMOTO, Ph.D.
Technical Specialist	Ami MATSUNO
Administrative Assistant	Saori MORITA

Division of Microbial Oncology

Associate Professor	Naoko KAMIYA, Ph.D.
Technical Support Staff	Eri MIZUNO

Research Section of Disease Control

Division of Biomedical Oncology

Professor	Masahiro SONOSHITA, Ph.D.
Assistant Professor	Takako OOSHIO, Ph.D.
Assistant Professor	Ryodai YAMAMURA, Ph.D.
Research Fellow	Yusuke SATOH
Technical Support Staff	Kanna KONDOH
Technical Support Staff	Mika YAMADA

Technical Support Staff	Tomomi HIRONAGA
Technical Support Staff	Eri TSURIBE
Technical Support Staff	Hiromi HAYASE
Technical Support Staff	Kanako MATSUDA
Research Support Assistant	Syunsuke MORI

● Division of Biological Molecular Mechanisms

Professor	Nobuo NODA, Ph.D.
Associate Professor	Yuko FUJIOKA, Ph.D.
Specially Appointed Lecturer	Takuma TSUJI, Ph.D.
Assistant Professor	Daisuke NOSHIRO, Ph.D.
Specially Appointed Assistant Professor	Yuta OGASAWARA, Ph.D.
Specially Appointed Assistant Professor	Eigo TAKEDA, Ph.D.
Postdoctoral Fellow	Ryouhei SASAKI
Postdoctoral Fellow	Hasan MOYNUL
Research Fellowships for Young Scientists (PD)	Suguru NISHINAMI
Research Fellowships for Young Scientists (PD)	Yutarou HAMA
Research Fellow	Sekiko KURAZONO
Part-time Fellow	Konomi MARUMO
Technical Support Staff	William CALDWELL ELIJAH
Technical Support Staff	Ayaka SAITO
Research Support Assistant	Eriko ITOH
Administrative Assistant	Keina YODA

Frontier Research Unit

● Molecular Cell Biology

Associate Professor	Tomohiko OKAZAKI, Ph.D.
Assistant Professor	Nao MORIMOTO, Ph.D.
Technical Support Staff	Noriko KATO
Technical Support Staff	Fumi YAMAMOTO

Endowed Department

● Department of Synbiotics

Specially Appointed Professor	Tadaaki MIYAZAKI, Ph.D.
Specially Appointed Professor	Koichi SATO, M.Eco.
Specially Appointed Assistant Professor	Keiko TADA, Ph.D.
Research Fellow	Yuki MIYAZAKI
Research Fellow	Natsuki ZIN
Administrative Assistant	Nana SAKURAI

Attached Facility

● Laboratory of Animal Experiments

Professor	Ken-ichiro SEINO, M.D., Ph.D.
Associate Professor	Kumiko YOSHIMATSU, D.V.M., Ph.D.
Technical Specialist	Koki OTAKI
Technical Support Staff	Noriko MIMA
Technical Support Staff	Kyouko TAKAHASHI
Technical Support Staff	Naomi HOSOYA
Technical Expert	Hiroyuki MUROTA

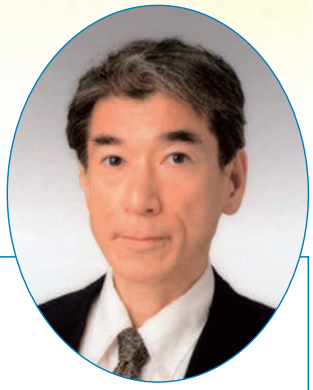
● Research Center for Infection-associated Cancer

Professor	Masahiro SONOSHITA, Ph.D.
Specially Appointed Professor	Masanori HATAKEYAMA, Ph.D.
Professor	Masaaki MURAKAMI, D.V.M., Ph.D.
Professor	Kohji MORIISHI, D.V.M., Ph.D.
Associate Professor	Naoko KAMIYA, Ph.D.
Associate Professor	Kumiko YOSHIMATSU, D.V.M., Ph.D.
Technical Specialist	Susumu ISHIKAWA
Technical Specialist	Satoko ISHIGAKI
Research Support Assistant	Tomoko KURIBAYASHI

● Joint Usage/Research Center Promotion Office

Professor	Masahiro SONOSHITA, Ph.D.
Professor	Masaaki MURAKAMI, D.V.M., Ph.D.
Associate Professor	Kumiko YOSHIMATSU, D.V.M., Ph.D.
Technical Specialist	Susumu ISHIKAWA
Technical Specialist	Satoko ISHIGAKI
Research Support Assistant	Tomoko KURIBAYASHI

*No faculty members have been assigned to Division of Molecular Interaction.



Professor Toru KONDO, Ph.D.

Research Project

Characterization of novel genes involved in age-related disorders, including glioma, and the development of new therapeutic methods for these diseases.

Outline

Our research objectives are to characterize the glioma-initiating cells (GIC), find GIC-specific factors, and develop new therapeutic strategies for glioma.

We characterize novel senescence-related factors and investigate their functions in the age-related disorders.

We also investigate the relationship between obesity and age-related diseases.

Contents and Result

Development of novel miR-dependent genome-editing Adeno-associated virus that selectively eradicates glioblastoma-initiating cells.

Glioblastoma (GBM), one of the most malignant human cancers, frequently recurs despite multimodal treatment with surgery and chemo/radiotherapies. One of the reasons of why GBM recues is likely the existence of GBM-initiating cells (GICs) that have strong proliferative and tumorigenic abilities and are resistant to various types of chemotherapies and radiotherapy. It is therefore crucial to find novel methods that specifically kill GICs by targeting their characteristics. Previously, we have identified various factors, such as membrane proteins, transcription factors and microRNA (miR), which increase or decrease in GICs compared with normal neural stem cells (NSC), and demonstrated their functions in GICs. On the process developing novel methods for GBM therapy, we noticed that these factors are considerably expressed in the cells of non-central nervous system, suggesting the concerned side effects if we target these factors for therapy. To overcome this hurdle, we combined our previous findings with the genome-editing system and developed new miR-dependent genome-editing Adeno-associated virus (AAV) coated with brain-tropic capsid, resulting the selective killing of GIC brain tumors in vivo.

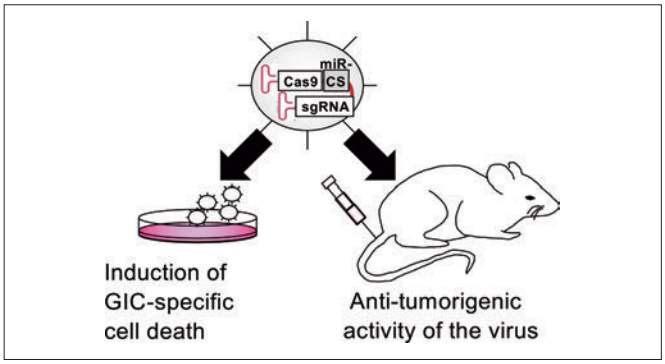


Fig. 1 Anti-tumorigenic activity of the brain tropic AAV encoding the miR-dependent genome-editing system

Brain tropic AAV encoding both Cas9 expression cassette, which regulates endogenous miR, and sgRNA targeting GIC factor not only killed GIC selectively in culture but also prevented GIC tumor in brain when administers intravenously.

EVA1-Antibody Drug Conjugate as a new therapeutic strategy for eliminating glioblastoma-initiating cells.

Since the identification of glioblastoma (GBM)-initiating cells (GICs) as a crucial target for GBM therapy, we, along with other scientists, have been characterizing GICs and identified potential targets for their eradication. Among the factors, we particularly focused on a membrane protein Epithelial V-like antigen 1 (EVA1) and generated a set of high affinity antibodies. Among the antibodies, we successfully identified the anti-EVA1X Ab (EVA1X) as a promising therapeutic candidate for EVA1-expressing cancers. EVA1X showed strong antibody-dependent cell cytotoxicity and complement-dependent cytotoxicity to GICs. In

http://www.igm.hokudai.ac.jp/stemcell/

addition, when combined with cytotoxic drug MMAE, EVA1X-MMAE exerted strong cytotoxicity to GICs and prevented their tumorigenesis in vivo.

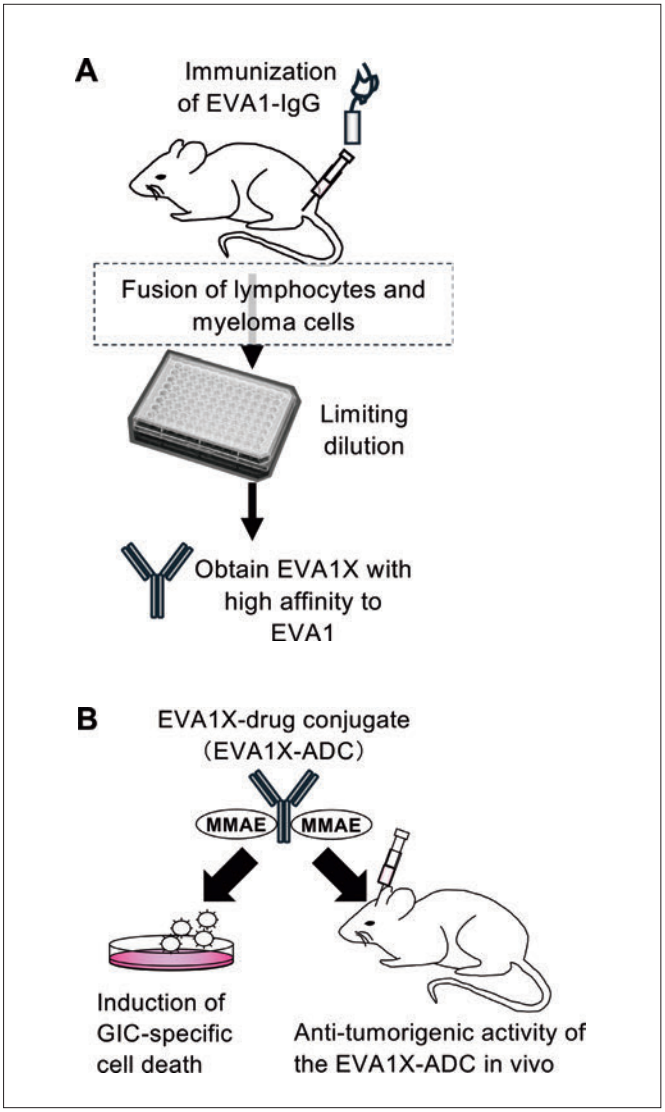


Fig. 2. Generation of EVA1X with high affinity to EVA1 and the selective anti-tumorigenic activity of EVA1X-ADC

(A) Generation of EVA1X. (B) EVA1X-ADC not only killed GIC selectively in culture but also eliminated GIC brain tumor when injected into brain.

Identification of novel target for obesity regulation and its functional analysis

There are two general classes of adipocytes; energy-storing white adipocytes and energy-expending brown adipocytes. Obesity triggers adipose tissue remodeling with changes in the number and size of the adipocytes, which ultimately lead to chronic low-grade inflammation of the adipose tissue. Thus, obesity is associated with the development of metabolic diseases such as type 2 diabetes and cardiovascular disease. Our recent study explored the role of X, a cell surface molecule specifically expressed in brown adipocytes, in obesity regulation using X-deficient mice. Interestingly, while X deficiency did not affect the thermogenic function of brown adipocytes, which was considered its primary target, it significantly altered the function of visceral adipose tissue. We are currently preparing a manuscript for publication that elucidates the mechanisms by which X influences functional changes in visceral adipose tissue associated with obesity.

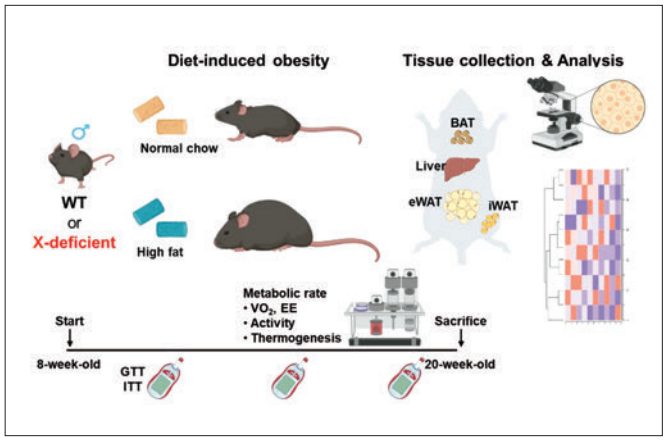


Fig. 3. Obesity induction in gene X-deficient mice.

WT and X-deficient mice were fed either a normal chow or a high fat diet for 12 weeks. Various metabolic functions were assessed, including glucose/insulin tolerance test (GTT/ITT), oxygen consumption (VO_2), and energy expenditure (EE). After 12 weeks, adipose tissues from the interscapular (brown adipose tissue, BAT), inguinal (iWAT), and epididymal (eWAT) regions, as well as the liver, were collected for histological analysis and RNA sequencing.

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Selected Paper(2022.6-2024.9)

1. Al-Akashi Z, Zujur D, Kamiya D, Kato T, **Kondo T**, & Ikeya M. (2023). Selective Vulnerability of Human-Induced Pluripotent Stem Cells to Dihydroorotate Dehydrogenase Inhibition during Mesenchymal Stem/Stromal Cell Purification. **Front. Cell. Dev. Biol.** (section Stem Cell Research), 11, 1089945.

2. Wada H, Otsuka R, Germeraad W, Murata T, **Kondo T**, & Seino K. (2023). Tumour cell-induced macrophage senescence plays a pivotal role in tumour initiation followed by stable growth in immunocompetent condition. **J. ImmunoTherapy of Cancer** 11, e006677.

3. (2024). Combination of the endothelin blocker and sustained IGF expression improves survival and functions in degenerating photoreceptor cells. **Cell. Mol. Life Sci.** 81, 51.

Professor Akinori TAKAOKA, M.D., Ph.D.

Research Project

Innate recognition during microbial infection and cancer development

Outline

How does the host cell recognize the invasion of pathogenic microbes? Part of the sewer lies in the pattern recognition receptors in the innate immune system. These receptors, such as Toll-like receptors (TLRs) and retinoic acid-inducible gene-I (RIG-I), are innate sensors that mediate signal transductions inside the cells to activate the induction of cytokines and chemokines (Figure 1). This leads to the activation of innate immune responses and the subsequent adaptive immune responses for the elimination of pathogens. Furthermore, PRRs can also sensor molecular patterns derived from host cells when the cells undergo necrosis/apoptosis, which may reflect aberrant inflammatory responses in autoimmune diseases. The team is trying to explore such DNA and RNA sensor(s) and to elucidate underlying mechanisms of disease pathogenesis at a molecular level, in terms of the function of the sensing molecules in the immune system. In particular, the laboratory focuses on microbial infections, cancer, and autoimmune diseases.

Contents and Result

Elucidation of pathogen recognition mechanism

The immune system is an essential system for protecting the living body from the invasion of pathogenic microorganisms and maintaining the homeostasis of the living body, and is roughly divided into innate immunity and acquired immunity. Of these, the innate immune system, which first "recognizes" pathogenic microorganisms, is extremely important in that it initiates activation of the immune system. According to many research results, in this pathogen recognition process, pattern recognition receptors (PRRs) are called pathogen-associated molecular patterns (PAMPs), which are different from the host, and are specific to microorganisms such as nucleic acids and lipids. It was clarified that it is caused by recognizing the constituent molecules of. In virus infection, virus-derived nucleic acids (RNA / DNA) often become PAMPs. In various viral infections, nucleic acid recognition sensor molecules and their signal transduction pathways as shown in Fig. 1 have been clarified so far. In our laboratory, we are proceeding with the identification of new nucleic acid recognition sensor molecules and the analysis of the control mechanism of their signal transduction pathways.

Regulatory mechanism by aryl hydrocarbon receptor in type I IFN-mediated antiviral innate defense

Our research group has clarified the role of aryl hydrocarbon receptor (AHR) in virus-induced innate immune response (Yamada et al., Nat. Immunol., 2016). AHR is a ligand-activated transcription factor that mediates the toxicity of many environmental xenobiotics including dioxins, and also has important biophysiological roles. However, its role in innate immune responses during viral infection is not fully understood. Type I interferons (IFNs) are produced in response to viral

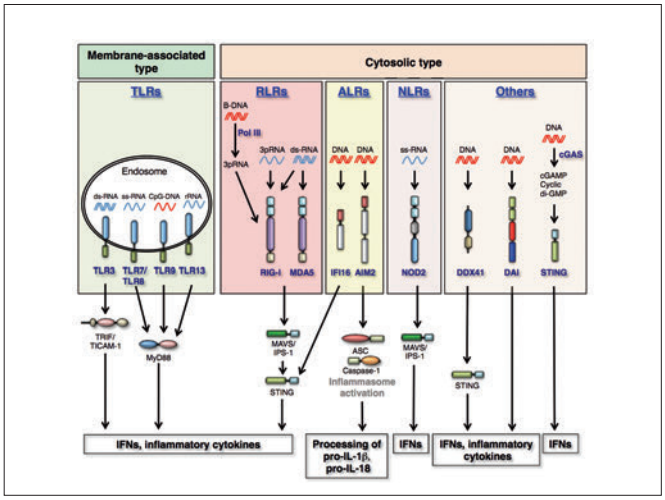

Figure 1. Nucleic acid-mediated activation of innate immune signaling.
Nucleic acid sensors are mainly divided into two groups; membrane-associated type and cytosolic type. Nucleic acid-ligand binding to sensors results in their association with their adaptor proteins such as TRIF, MyD88, MAVS or STING, leading to the induction of IFNs and inflammatory cytokines. On the other hand, some types of DNA also activate inflammasome, leading to the maturation of IL-1β and IL-18. Abbreviations: TLRs, Toll-like receptors; RLRs, RIG-I-like receptors; NLRs, NOD-like receptors; ALRs, AIM2-like receptors; ds-RNA, double-stranded RNA; ss-RNA, single-stranded RNA; rRNA, ribosomal RNA; Pol III, RNA polymerase III; 3pRNA, 5'-triphosphate RNA; cGAMP, cyclic GMP-AMP; IFNs, interferons.

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infection and are crucial cytokines for the activation of antiviral immune responses. The induction of type I IFNs is triggered by the detection of the viral nucleic acids through pattern recognition receptors. In this study, we show that constitutive AHR signaling in the steady state modulates type I IFN response during infection with various types of virus. The type I IFN response was markedly enhanced in AHR-deficient mouse embryonic fibroblasts (MEFs) during infection with various types of virus. Such an excessive response was also observed upon pharmacological inhibition with an AHR antagonist or a TDO/IDO inhibitor. Furthermore, we identified TIPARP as an AHR target gene that is essential for AHR-mediated regulation of type I IFN production. Mechanistic studies revealed that TIPARP interacts and post-translationally ADP-ribosylates TBK1, resulting in the inhibition of its kinase activity. Thus, our findings demonstrate a novel link between AHR signaling and innate signaling for the modulation of IFN-mediated antiviral response during viral infection, suggesting a physiological role of constitutive activation of the AHR-TIPARP axis mediated by endogenous ligands such as tryptophan metabolites, in restraining the IFN-dependent host antiviral defense system (Figure 2).

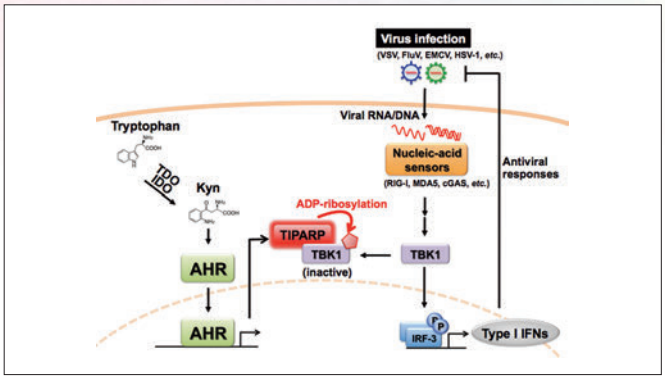

Figure 2.

The schematic representation of constitutive AHR signaling for the TIPARP-mediated modulation of antiviral IFN response.

AHR signaling activated by endogenous ligands (Kyn, *etc.*) constitutively upregulates the levels of TIPARP, which interacts with TBK1 for the downregulation of TBK1 activity by ADP-ribosylation. This AHR-TIPARP axis plays a key role for tuning nucleic acid sensor-mediated type I IFN induction. TDO, tryptophan-2,3-dioxygenase; IDO, indoleamine-2,3-dioxygenase; Kyn, kynurenine; TIPARP, TCDD-inducible poly(ADP-ribose) polymerase; TBK1, TANK-binding kinase 1; IRF-3, interferon regulatory factor-3; IFN, interferon.

A novel mechanism of innate immune antiviral response against SARS-CoV-2

COVID-19, caused by SARS-CoV-2, which is a positive-sense, single-stranded RNA betacoronavirus, remains an ongoing global pandemic. Although most people infected with SARS-CoV-2 show a mild and self-limited course, there are also a few severe and critical patients with exacerbated inflammatory response. The wide spectrum of clinical manifestations of COVID-19 suggests that individual immune responses to the underlying pathogen may play some crucial roles in determining the clinical course. However, the innate immune responses against SARS-CoV-2 remains poorly understood. Here we showed that retinoic acid-inducible gene-I (RIG-I) but not MDA5 or TLR3 sufficiently restrains SARS-CoV-2 replication in human lung cells in a type I/III interferon (IFN)-independent manner. RIG-I inhibits viral RNA-dependent RNA polymerase (RdRp)-mediated first step of replication through the preferential binding of RIG-I helicase domain to the 3- untranslated region of the viral genomic positive-sense RNA. This new mode of RIG-I recognition fails to activate the conventional downstream MAVS/IPS-1-dependent signaling, which is in accordance with lack of cytokine induction after SARS-CoV-2 infection. Consistently, genetic ablation of RIG-I expression allows lung cells to produce viral particles. Furthermore, SARS-CoV-2 can replicate in chronic obstructive pulmonary disease (COPD) patient-derived cells with low levels of RIG-I expression. Treatment with all-trans retinoic acid (ATRA), which upregulate RIG-I expression, significantly reduced viral titers in the cells. These data have defined RIG-I expression levels as one of the intrinsic determinants for the defense in human lung cells at least during the initial process of SARS-CoV-2 infection. It has been reported that nearly 40-45% people infected with SARS-CoV-2 show asymptomatic with no robust upregulation of innate cytokines. In this respect, the balance between RIG-I expression levels and the amount of invading virus would regulate the fate of viral replication, which might determine cytokine responses and the related patient outcomes.

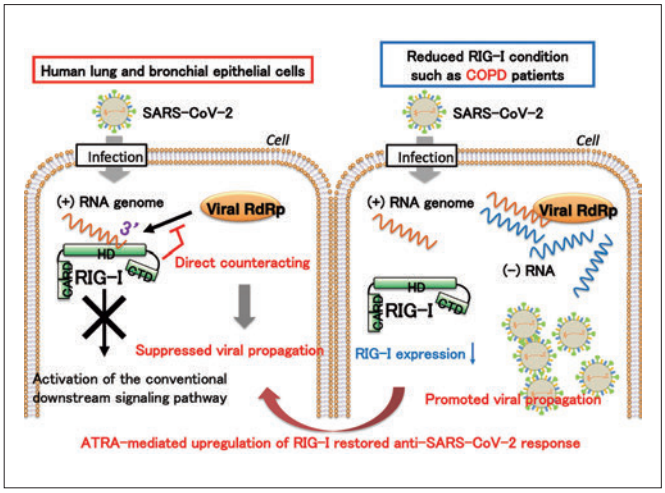

Figure 3.

The schematic representation of a novel defense mechanism of RIG-I for SARS-CoV-2

RIG-I sufficiently restrains SARS-CoV-2 replication in human lung and bronchial epithelial cells without its canonical downstream pathway. Mechanistically, RIG-I inhibits viral RdRp-mediated replication through the preferential binding of RIG-I helicase domain to the 3-untranslated region of the viral genomic RNA. In RIG-I-reduced condition such as COPD, SARS-CoV-2 can replicate. Re-expression of RIG-I by treatment with ATRA significantly suppresses viral replication.

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Research Section of Molecular Pathogenesis | Division of Molecular Psychoimmunology

Professor Masaaki MURAKAMI, D.V.M., Ph.D.

Research Project

Pathological Regulation of Chronic Inflammatory Diseases through IL-6 Amplifier and Gateway Reflex Mechanisms

Outline

We discovered two unique concepts of inflammation induction, "IL-6 amplifier" in 2008 and "gateway reflex" in 2012, and have analyzed the molecular mechanisms involved in the formation and exacerbation of pathologies in various inflammatory diseases. "IL-6 amplifier" is an overactivation mechanism of NF-κB present in non-immune cells, while the "gateway reflex" involves specific nerve circuit activation, forming vascular gates through IL-6 amplifier at particular vascular sites, allowing immune cells, including autoreactive T-cells, to infiltrate tissues. Currently, we organize the research projects on microinflammation control in AMED Moonshot Goal 7 and the Stress R&D area under AMED's Advanced R & D Programs for Medical Innovation. We conduct the research on the following four items in collaboration with Murakami's laboratories at National Institute for Quantum and Radiological Science and Technology (QST) and National Institute of Natural Sciences, in order to achieve 'realization of automatic medicine at the time of unwellness' and "elucidating molecular pathogenic mechanisms and developing biomarker detection technologies for stress-related diseases" .

(i) IL-6 amplifier: Investigating the pathological role of IL-6 amplifier in various inflammatory diseases such as autoimmune diseases and infections, and identifying biomarkers and therapeutic targets using IL-6-amplifier regulatory and inducible factors.

(ii) Gateway reflex: Elucidating the mechanisms of onset and exacerbation of various autoimmune and stress-related diseases, including mental and neurological disorders, through the activation of specific neural circuits.

(iii) Quantum Immunology: Developing super-sensitive, high-precision detection systems for perivascular microinflammation, tissue-specific autoreactive T cells, and infectious microbial subtypes that cause various diseases, including autoimmune and stress-related conditions.

(iv) Space Immunology: Analyzing the pathogenesis of immune diseases based on the gravity gateway reflex and space experiments.

Contents and Result

IL-6 amplifier

In 2008, we discovered the "IL-6 amplifier" as a molecular mechanism underlying chronic inflammatory diseases, including autoimmune diseases (Fig. 1). IL-6 amplifier is a mechanism to induce tissue-specific chronic inflammation by synergistically enhancing the production of inflammatory cytokines, chemokines and growth factors such as IL-6, TNF-α and IL-17, upon a simultaneous activation of NF-κB and STAT3 transcription factors in tissue-specific non-immune cells such as synovial fibroblasts and tubular epithelial cells, as well as in ubiquitously present non-immune cells such as vascular endothelial cells and fibroblasts. Previous studies have shown that IL-6 amplifier is essential for pathogenesis in mouse models of chronic inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, and graft rejection. In addition, a functional screening of IL-6 amplifier-related genes across the entire genome and matching with the human disease-related gene database revealed that approximately 1,700 positive regulators and target genes of IL-6 amplifier may be deeply involved in diverse chronic inflammatory diseases in humans. Indeed, IL-6 amplifier-related factors were detected at high levels in samples from patients with chronic inflammatory diseases, and blood levels of their target molecules were significantly higher than in healthy individuals.

In recent years, Genome-Wide Association Study accompanied with a widespread use of next-generation se-

http://www.igm.hokudai.ac.jp/neuroimmune/index.html

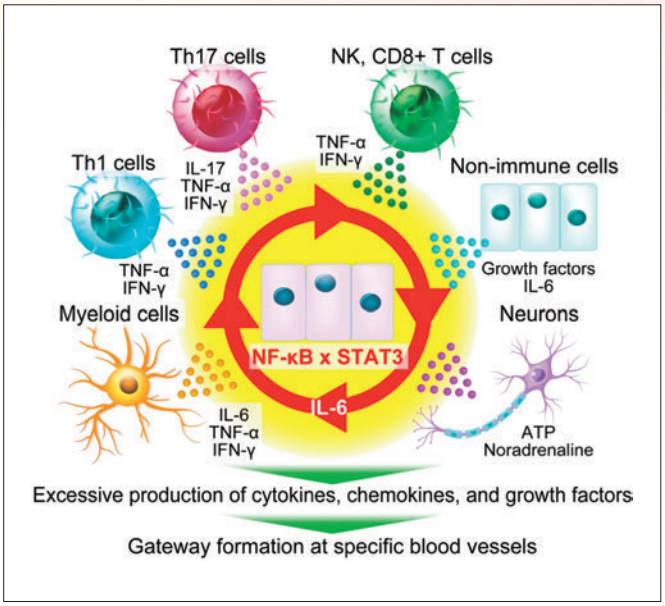

Fig. 1: IL-6 amplifier

In tissue-specific non-immune cells such as synovial fibroblasts and tubular epithelial cells, as well as in ubiquitous non-immune cells such as vascular endothelial cells and fibroblasts, cytokine stimulation-dependent simultaneous activation of NF-κB and STAT3 pathways results in a local synergistic enhancement of the production of inflammatory mediators. The amplification of inflammation by IL-6 amplifier has been implicated in the pathogenesis or exacerbation of various inflammatory diseases, such as autoimmune diseases and cytokine storms that cause COVID-19 severity.

quencing has demonstrated that disease-related genes and single nucleotide polymorphisms (SNPs) are genetically associated with disease in a number of cases. However, even if SNPs in identified disease-related genes can be genetically proven to be associated with diseases, it is still unclear how they alter the function of the related genes and contribute to pathogenesis. We have pursued our research under the working hypothesis that SNPs in disease-associated genes may have some effect on IL-6 amplifier and contribute to the development and exacerbation of chronic inflammatory diseases. As a result, we have reported that these SNPs positively or negatively regulate IL-6 amplifier and induce or suppress excessive inflammatory responses in inflammatory diseases such as keloids, Sjogren's syndrome, Dupuytren's contracture, and pancreatitis after endoscopic retrograde cholangiopancreatography. In the future, we will contribute to public welfare by identifying novel diagnostic markers and drug targets through clarification of the molecular mechanisms how IL-6 amplifier's target molecules and SNPs are associated with the pathological conditions of autoimmune diseases such as rheumatoid arthritis, systemic scleroderma, moyamoya disease, and COVID-19 to further clarify how IL-6 amplifier target molecules and SNPs are involved in the pathogenesis of these diseases.

Gateway reflex

In 2012, we discovered a molecular mechanism by which

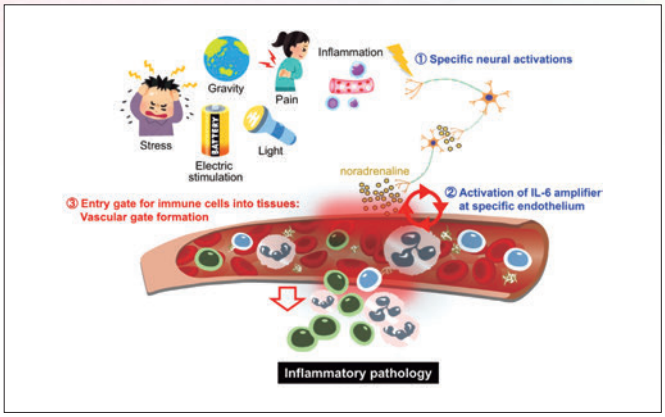

Fig. 2: Gateway reflex

Six types of environmental stimuli (gravity, electric stimulation, pain, chronic stress, light, and inflammation) cause or suppress (only light stimulation) tissue-specific inflammatory diseases by triggering or inhibiting (only light stimulation) IL-6 amplifier in specific vascular regions, through an activation of specific neural circuits for a vascular gate formation for autoreactive T-cells to pass through the blood barrier into the CNS or retina. This mechanism is called gateway reflex, which we have intensively studied.

activation of specific neuronal circuits can alter specific vascular conditions through IL-6 amplifier, leading to the development of tissue-specific autoimmune diseases, which we named the "gateway reflex" (Fig. 2). To date, we have reported six gateway reflexes triggered by environmental or artificial stimuli. The first one we found was gravity-related, in which gravitational loading on the soleus muscle activates specific sensory and sympathetic circuits, induces noradrenaline-mediated IL-6 amplifier in the dorsal vessels of the fifth lumbar spinal cord (L5), and promotes entry of pathogenic immune cells into the central nervous system (CNS) via the blood brain barrier (BBB) (gravitational gateway reflex). This mechanism can be reproduced by artificial electric stimulation, whereby electrical stimulation of specific muscles activates specific neuronal circuits and promotes the formation of vascular gates at specific vascular sites in their vicinity (electricity gateway reflex). In addition, pain-induced activation of neural circuits has been shown to trigger recurrent CNS inflammation by forming vascular gates on the "ventral" side, different from those formed in the L5 dorsal vessels by gravitational stimulation (pain gateway reflex). In 2017, mild stress that does not cause health problems even when autoreactive T cells are present in the bloodstream, activates neural pathways in the brain involved in stress, which in turn triggers microinflammation in specific blood vessels in the brain, abnormally activating normally quiescent neural pathways and causing sudden death due to cardiac dysfunction (stress gateway reflex). On the other hand, studies in mouse models of uveitis (EAU) have shown that bright light stimulation reduces the expression of α1 noradrenergic receptors in retinal vascular endothelial cells, which in turn inhibits the entry of autoreactive T cells into the retina, thereby reducing disease onset (light gateway reflex). In 2022, we also reported that the gate-

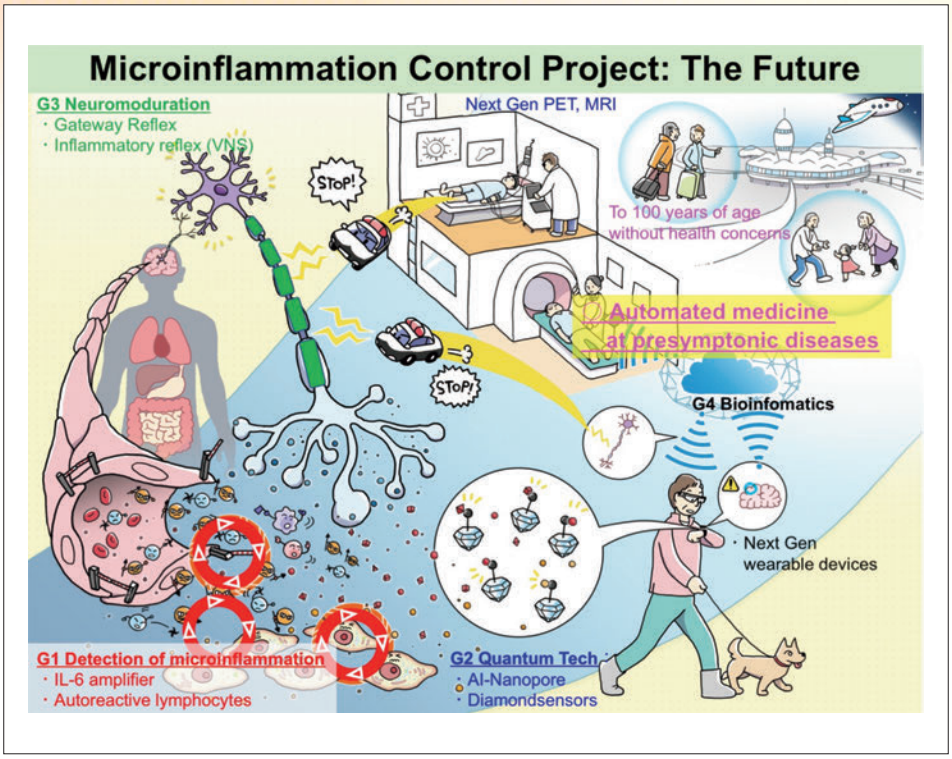

Fig. 3: Development of detection systems for tissue-specific autoreactive T-cells and therapies for perivascular microinflammation

In microinflammation control project on AMED Moonshot Goal 7, an ultra-sensitive detection system will be developped utilizing quantum technologies, which can diagnose microinflammation in unwell state that is an 'unaffected' stage of disease, but could lead to chronic inflammation (e.g. immune disorders, dementia, and atherosclerosis) in the future. Furthermore, development of neuromodulation technology will enable patient's condition to be back from an unaffected state to a healthy state by nipping the 'disease bud (microinflammation)'.

way reflex is also involved in diseases characterized by symmetrical remote inflammation, such as rheumatoid arthritis, where IL-6 amplifier generated in one ankle joint induces the production of the neurotransmitter ATP, resulting in sequential cross-talk between sensory nerves and interneurons. The results revealed that the IL-6 amplifier is induced in the opposite ankle joint in an ATP-dependent manner, resulting in the remote triggering of arthritis (remote inflammation gateway reflex). Regarding the pain gateway reflex, we also found that GM-CSF, which is constitutively produced from blood vessels, is involved in the long-term survival of peripherally derived myeloid cells involved in recurrent CNS inflammation.

Thus, since the nervous and vascular systems run throughout the body, the study of gateway reflexes can explain disease-related molecular mechanisms and functional coordination mechanisms between organs from the viewpoint of neural circuit regulation. Currently, we conduct research to discover new gateway reflex mechanisms and to elucidate the onset and exacerbation mechanisms of stress-related diseases, including neuropsychiatric disorders.

Quantum immunology

Aging and stress cause not only immune disorders such as rheumatoid arthritis, but also metabolic syndrome, dementia, and other chronic inflammation-related diseases that are inevitable in today's aging society. Previous studies, especially ours, have shown that chronic inflammation develops when pathogenic immune cells cause microinflammation around specific blood vessels and invade various organs and tissues through blood vessels. However, preventive measures to detect and eliminate these microinflammations at an early stage have not yet been established. Based on our original and pioneering research results of "IL-6 amplifier" and "gateway reflex," we believe that ultra-early detection of microinflammation, the etiological factor of tissue-specific inflammatory diseases, is possible by measuring biomarkers that reflect "inflammatory conditions around vascular gates" and "tissue-specific autoreactive T-cell activation. Currently, as part of the research and development of the AMED Moonshot Project and stress-related projects, we are attempting to develop an ultra-sensitive and ultra-precise detection system for microinflammation and stress-related factors from an unaffected state by utilizing T cell activation marker molecules and MHC tetramers modified by highly sensitive quantum sensor technology such as nanodiamond sensor. We also aim to elucidate the pathogenesis of chronic inflammation by analyzing the antigen specificity of T-cell receptors (Fig. 3). In addition, by applying our recently published AI nanopore technology, which enables rapid identification of SARS-CoV-2 variants, we aim to develop a highly sensitive

technique for measuring pathogens such as viruses and bacteria that cause various infectious diseases, as well as tissue-specific autoantibodies produced by activated B-cells, which are characteristic of autoimmune diseases. Moreover, our AMED Moonshot R&D will create a neuromodulation technology to control the pathogenesis of various inflammatory diseases via local vascular gate control by artificially inducing neural activation utilizing the aforementioned gateway reflex mechanism.

Space immunology

Gravity is an unavoidable physical stimulus for all terrestrial organisms, including humans, and thus there are likely to be response mechanisms associated with important biological functions during evolution. We demonstrated that an increase or decrease in gravitational load defines the degree of disease pathogenesis as gravity gateway reflex mechanism in 2012, by applying a tail suspension method in ground-based experiments to reduce the gravitational load on the hindlimbs of mice models of autoimmune diseases. However, since the tail suspension method might cause stress to the mice, due to unusual postures and restrictions on behaviors, and it was unclear how much whole-body microgravity influences on inflammatory response of the disease. Therefore, we sent the mice induced autoimmune disease to the International Space Station (ISS) for about a month in 2019 to verify what changes occurred in the lesion sites of the mice after their return, comparing them with ground experiments, and obtained results supporting the gravity gateway reflex. As a result, our project received an "A grade" in the project evaluation.

Previous studies have indicated that astronauts experience vision loss due to long stays in space, suggesting that the space environment may affect the optic nerve and retina. We have considered the possibility that these pathologies may also be related to gateway reflex caused by light and gravity, and have conducted research using the mice returned from the ISS. We expect to create space immunology field by clarifying how the space environment alters the gateway reflex and inflammatory response. In 2025, we will organize the annual meeting of International Society for Gravitational Physiology scheduled to be held at Hokkaido University.

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Selected Paper (2020.10-2022.5)

1. Furukawa R, Kuwatani M, Jiang JJ, Tanaka Y, Hasebe R, Murakami K, Tanaka K, Hirata N, Ohki I, Takahashi I, Yamasaki T, Shinohara Y, Nozawa S, Hojyo S, Kubota SI, Hashimoto S, Hirano S, Sakamoto N, Murakami M. GGT1 is a SNP eQTL gene involved in STAT3 activation and associated with the development of Post-ERCP pancreatitis. ***Sci Rep.*** 28; 14(1): 12224, 2024

2. Murakami K, Kubota SI, Tanaka K, Tanaka H, Akabane K, Suzuki R, Shinohara Y, Takei H, Hashimoto S, Tanaka Y, Hojyo S, Sakamoto O, Naono N, Takaai T, Sato K, Kojima Y, Harada T, Hattori T, Fuke S, Yokota I, Konno S, Washio T, Fukuhara T, Teshima T, Taniguchi M, Murakami M. High-precision rapid testing of omicron SARS-CoV-2 variants in clinical samples using AI-nanopore. ***Lab Chip.*** 23(22): 4909-4918, 2023

3. Matsuyama S, Yamamoto R, Murakami K, Takahashi N, Nishi R, Ishii A, Nio-Kobayashi J, Abe N, Tanaka K, Jiang JJ, Kawamoto T, Iwanaga T, Shinohara Y, Yamasaki T, Ohki I, Hojyo S, Hasebe R, Kubota SI, Hirata N, Kamimura D, Hashimoto S, Tanaka Y, Murakami M. GM-CSF Promotes the Survival of Peripheral-Derived Myeloid Cells in the Central Nervous System for Pain-Induced Relapse of Neuroinflammation. ***J Immunol.*** 211(1): 34-42, 2023

Research Section of Molecular Pathogenesis | Division of Hepatitis Virology

Professor Kohji MORIISHI, D.V.M., Ph.D.

Research Project

1. Elucidation of the mechanisms of infection with hepatitis B and C viruses and the pathogenesis of related liver diseases and study on development of novel antiviral strategies
2. Development of antiviral drugs for SARS-coronavirus-2.

Outline

Hepatitis B and C viruses are thought to be the cause of more than half of the approximately 30,000 liver cancer deaths in Japan each year. Although the development of antiviral drugs has made it possible to eliminate hepatitis C virus, problems such as hepatocarcinogenesis and re-infection remain after HCV elimination. On the other hand, although antiviral agents that are reverse transcriptase inhibitors are available as current hepatitis B therapy, complete elimination of the viral genome is not accomplished due to cccDNA formation and host genome insertion, and the development of new antiviral agents is still required. There is also a need for new hepatitis B vaccine development for reasons such as the inability of some populations to induce sufficient immunity. Our aims are to elucidate the mechanisms of infection and virulence of both viruses and to develop novel antiviral agents and vaccines against hepatitis B virus. In addition, research on SARS-CoV-2 is also being conducted to discover and develop novel antiviral agents for COVID-19 therapy through the development of viral replicons.

Contents and Result

Development of antiviral against SARS-Coronavirus-2.

SARS-Coronavirus-2 (SARS-CoV-2), the virus responsible for COVID-19, has posed a threat worldwide since 2019, but as of 2024, it has decreased in virulence and adapted to humanity. In the last two decades, pandemic or endemic outbreaks of similar beta-coronaviruses have been repeated worldwide; SARS-CoV-1 had been settled within a year because of its high virulence and low transmissibility. MERS-Coronavirus, on the other hand, continues to spread sporadically around the world, especially in the Middle East area. The drugs that first appeared as anti-SARS-CoV-2 agents were based on basic research on an-

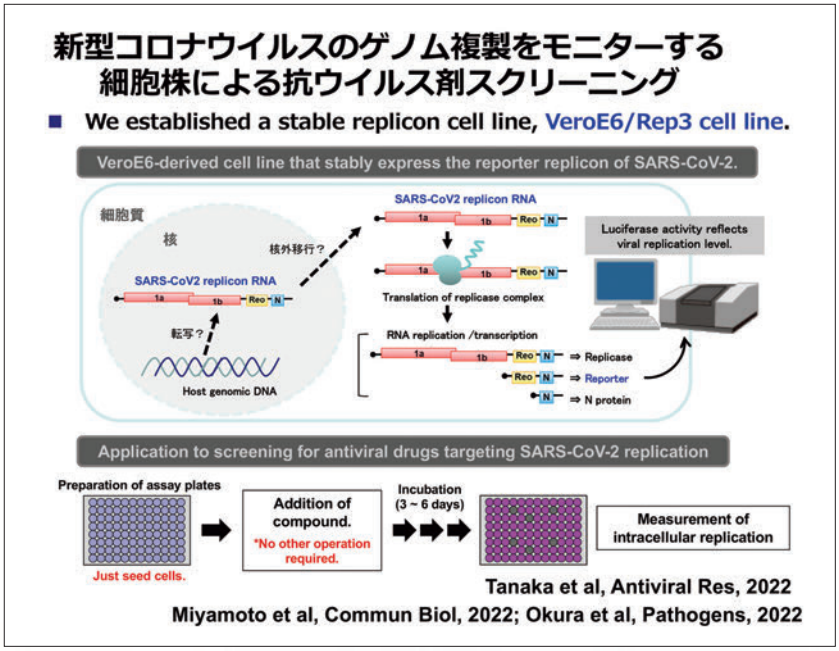

Fig. 1

https://www.med.yamanashi.ac.jp/clinical_basic/microbio/Microbiology_Yamanashi_Uni_Japanese/About_us.html

tiviral compounds against SARS-CoV-1, and no highly effective antiviral compounds have yet been developed. Highly effective antiviral agents are most needed in the early stages of an epidemic, when virulence is high, and are not something that can be developed quickly. In our laboratory, we have already succeeded in producing a replicon system of SARS-CoV-2 that does not produce infectious particles and have established a cell line in which the replicon stably replicates. The replicon cell line will enable large-scale high-throughput screening. To prepare for the emergence of new beta-coronaviruses that are likely to reemerge in the future, we are searching for antiviral agents against pan-beta-coronaviruses.

Development of antivirals against hepatitis B virus

Hepatitis B virus (Hepatitis B virus) enters the human hepatocyte via the receptor NTCP, the viral genome is transported into the nucleus where it becomes cccDNA and initiates stable viral genome replication. sgRNA is transported into the viral capsid and transcribed into relaxed circular DNA by the reverse transcriptase activity of viral polymerase in the nucleocapsid. Current antivirals used in clinical practice are derived from anti-HIV agents as reverse transcriptase inhibitors in origin. Therefore, cccDNA and viral genome inserted into host genome could not be completely eliminated from the patients. Our aims of study are to develop antivirals that target infection steps other than reverse transcription.

Development of HCV-surrogate animal models using rodent hepaciviruses.

Since hepatocarcinogenesis is often observed after elimination of HCV from patients with hepatitis C by antiviral agents, it is needed to elucidate the mechanism of hepatocarcinogenesis by the virus and to develop new therapies. In addition, it is not uncommon for patients to become re-infected after elimination of HCV with antiviral agents. Therefore, it should be necessary to develop vaccines for developing countries and drug users. Experimental animal systems are required for pathogenicity analysis and vaccine development. However, HCV has a very limited host range and is susceptible only to humans and chimpanzees. Human liver chimeric mice, which are susceptible for *in vivo* infection, are available as small experimental animals, but their immunodeficiency makes them unsuitable for pathological and immunological analyses. We are developing experimental animal models using rodent hepaciviruses, which are closely related to HCV and can be used to infect immune-competent rats and mice. These surrogate models will be served as very useful tools for basic research for analysis on hepatitis C pathogenicity and vaccine development against HCV.

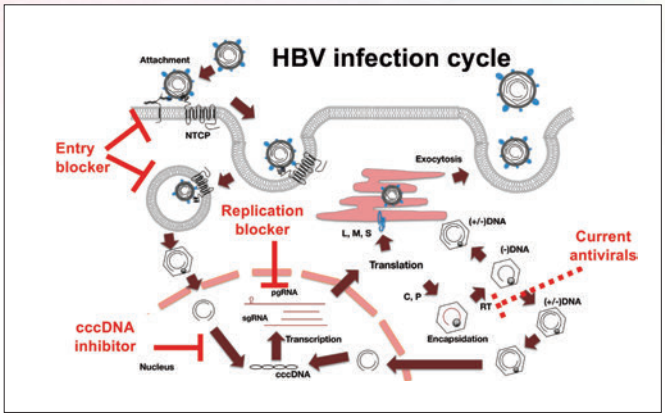

Fig. 2

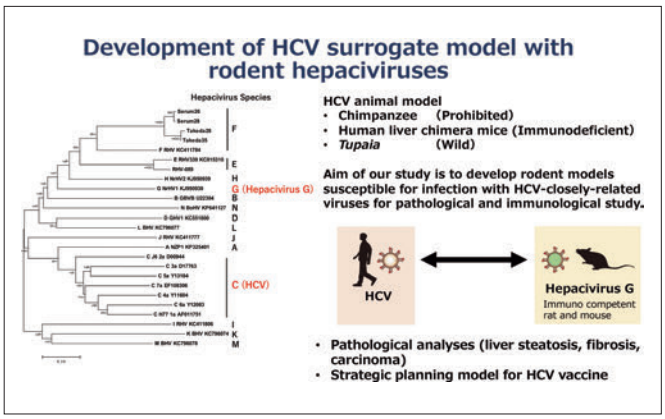

Fig. 3

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Tomohisa TANAKA, D.V.M., Ph.D.

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Professor ····· Kohji MORIISHI, D.V.M., Ph.D.
Associate Professor ····· Tomohisa TANAKA, D.V.M., Ph.D.

Selected Paper (2022.6-2024.9)

1. Kasai K, Yamashita A, Akaike Y, Tanaka T, Matsuura Y, Moriishi K: HCV infection activates proteasome via PA28gamma acetylation and heptamerization to facilitate the degradation of RNF2, a catalytic component of polycomb repressive complex I. mBio, in press, 2024

2. Washizaki A, Murayama A, Murata M, Kiyohara T, Yato K, Yamada N, Aly HH, Tanaka T, Moriishi K, Nishitsuji H, Shimotohno K, Goh Y, Ishii KJ, Yotsuyanagi H, Muramatsu M, Ishii K, Takahashi Y, Suzuki R, Akari H, Kato T: Neutralization of hepatitis B virus with vaccine-escape mutations by hepatitis B vaccine with large-HBs antigen. *Nat Commun*, 13: 5207, 2022

3. Tanaka T, Saito A, Suzuki T, Miyamoto Y, Takayama K, Okamoto T, Moriishi K: Establishment of a stable SARS-CoV-2 replicon system for application in high-throughput screening. *Antiviral Res*, 199: 105268, 2022

Professor Ken-ichiro SEINO, M.D., Ph.D.

Research Project

Basic medical research for cancer and transplantation/regeneration

Outline

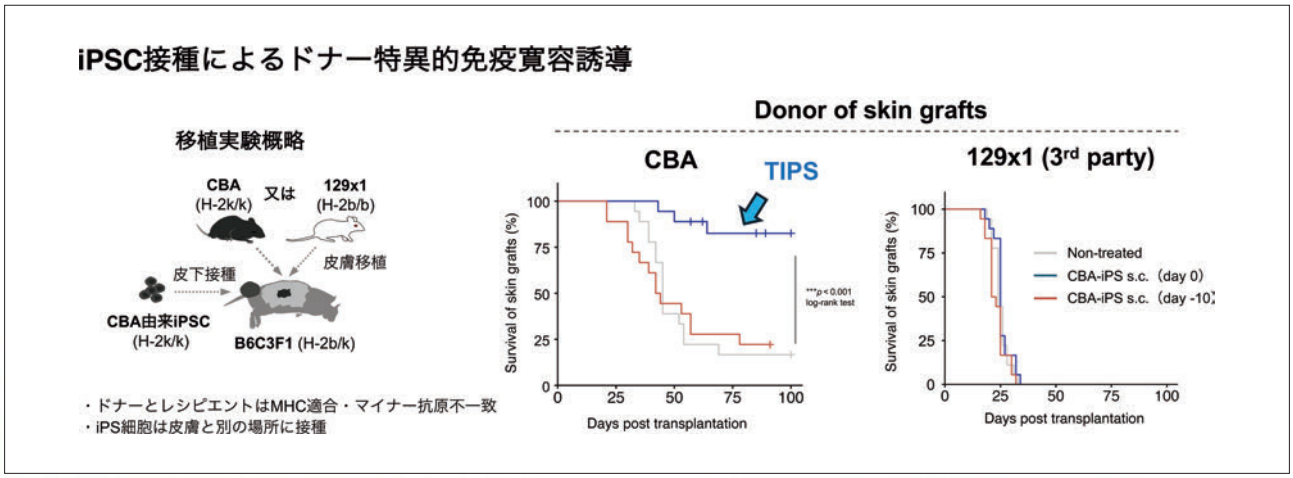
In this laboratory, we are interested in matters related to cancer and organ transplantation, as Dr Seino has a background in gastrointestinal surgery. With regard to cancer, we have been studying cancer immunity, particularly in relation to the tumour microenvironment. With regard to transplantation, pluripotent stem cells have been established in recent years, and we are studying immune regulation in cell transplantation medicine using these cells. In other words, the laboratory conducts basic medical research on cancer and transplantation/regeneration, and conducts research with the aim of discovering new principles and fundamental facts that can lead to new diagnosis and treatment. Among them, we focus on research on immunology, which is an extremely important basic science for both cancer and transplantation, and conduct research on molecules that enhance immune functions important for cancer immunity, on the relationship between cancer stem cells and immune responses, or on the induction of immune tolerance, and on alloimmune control methods using pluripotent stem cells. In recent years, we have also been working on cell therapy (autologous macrophage therapy) for liver cirrhosis, which was developed from our cancer immunology research.

Contents and Result

Development of new immunoregulatory methods using pluripotent stem cells

In recent years, the development of cell transplantation medicine using pluripotent stem cells such as ES cells and iPS cells has been anticipated. On the other hand, the immune response (rejection) that occurs during such transplantation has not received much attention. We are attempting to develop a new method of immune regulation against rejection, utilising the potential of pluripotent stem cells.

Recently, we established an MHC-compatible minor antigen-mismatched transplantation system using mouse skin grafts as a model. Using this model, it has become possible to study in detail the immune response that occurs



Induction of immune regulatory macrophages from pluripotent stem cells and its application

https://seinolab.wixsite.com/seinolab/

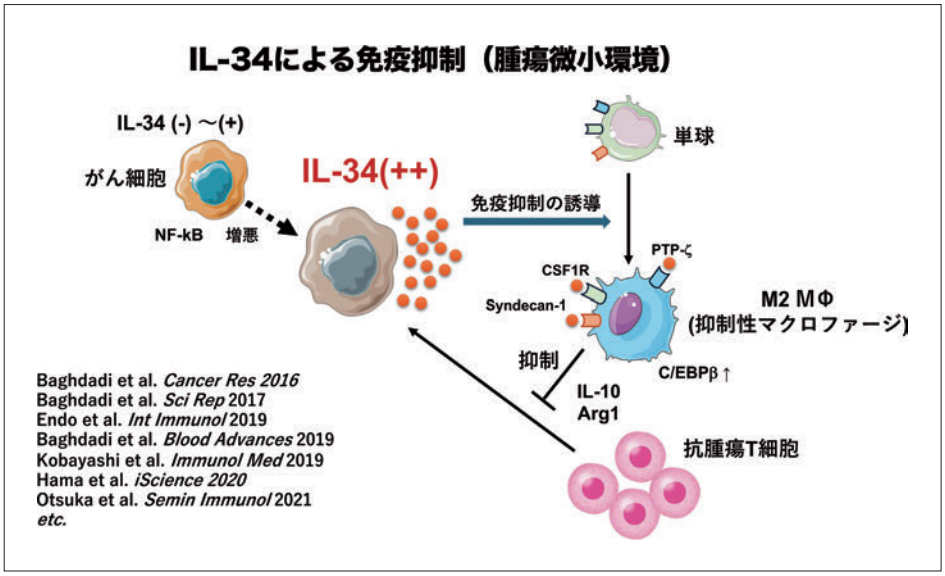
during transplantation from iPS cells and to investigate methods to control this response. Recently, we found that in MHC-compatible minor antigen-mismatched combinations, iPS cells inoculated subcutaneously into allo hosts formed teratomas without being rejected. When skin grafts were performed as a secondary transplantation to hosts in which the teratoma had grown, it was also found that donor-specific immune tolerance was induced. Detailed mechanisms are currently being investigated.

Such studies are important for establishing safe cell transplantation medicine, and we are continuing our research with the aim of establishing more effective methods to control immunity in regenerative medicine.

Treatment of liver cirrhosis by IL-34-induced macrophages

In our previous cancer immunology studies, we found that cancer cells that became resistant to anticancer drugs produced IL-34 and attracted immunosuppressive M2 macrophages to the surrounding area. We also found that MDSCs within the tumour play an important role to induce the resistance to treatment by IL-34. MDSCs within tumours were involved in angiogenesis and immunosuppressive Treg infiltration. Drugs that inhibited these MDSCs were found to partially lift resistance to treatment.

Recently, the immunosuppressive properties of macrophages induced by IL-34 were utilized and applied to the treatment of inflammatory diseases. Cirrhosis is a terminal manifestation of hepatitis, which can be caused by a variety of reasons, and results from a significant increase in fibrosis, rendering healthy liver tissue incapable of functioning. The only fundamental treatment is liver transplantation, but the shortage of donors is a problem in Japan, and it is hoped to develop a treatment to improve the condition before a liver transplant becomes necessary. We induced macrophages from bone marrow cells under IL-34 or IL-34 plus IL-4 conditions. When these macrophages were injected into a mouse model of liver fibrosis, fibrosis was predominantly suppressed. We now try to clarify the mechanism and show that it can be applied to humans.



The pathological role of IL-34

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Staff

Professor ····· Ken-ichiro SEINO, M.D., Ph.D.
Assistant Professor ····· Akihiro MORI, Ph.D.

Selected Paper (2022.6-2024.9)

1. Haruka Wada, Ryo Otsuka, Wilfred T V Germeraad, Tomoki Murata, Toru Kondo, Ken-ichiro Seino. Tumor cell-induced macrophage senescence plays a pivotal role in tumor initiation followed by stable growth in immunocompetent condition., 11: e006677. 06 October 2023. https://doi.org/10.1136/jitc-2023-006677

2. Nabeel Kajihara, Yunqi Ge & Ken-ichiro Seino. Blocking of oestrogen signals improves anti-tumour effect regardless of oestrogen receptor alpha expression in cancer cells. **Br J Cancer**, 129: 935-946, 03 August 2023. https://doi.org/10.1038/s41416-023-02381-0

3. Tomoki Murata, Naoki Hama, Tomoki Kamatani, Akihiro Mori, Ryo Otsuka, Haruka Wada, Ken-ichiro Seino. iPSC-derived hematopoietic stem and progenitor cells induce mixed chimerism and donor-specific allograft tolerance. **Am J Transplantation**, 23(9): 1331-1344, September 2023. https://doi.org/10.1016/j.ajt.2023.05.020

Research Section of Pathophysiology | Division of Genome Biology

Professor Ken-ichi NOMA, Ph.D.

Research Project

Study on 3D genome organization and related diseases

Outline

The eukaryotic genome is organized in the nucleus as a complex 3D genome structure that participates in various nuclear events such as transcriptional regulation, DNA replication, and repair. Disruption in the organization of the genome structure correlates with human diseases, including cancer. Despite the clear importance of 3D genome organization to basic and medical research, the function and mechanism of 3D genome organization remain unclear. Our laboratory employs genomic, genetic, cell biological, and biochemical approaches to study 3D genome organization in fission yeast and human cells. The research projects currently underway are:

Study with the fission yeast model

- Understand how 3D genome organization participates in transcriptional regulation and chromosome dynamics
- Elucidate the molecular mechanisms that form and regulate 3D genome structures throughout the cell cycle
- Uncover proteins and their post-translational modifications involved in 3D genome organization

Research on human senescence

- Determine how 3D genome organization contributes to transcriptional regulation in senescent cells
- Elucidate how 3D genome structure is formed and regulated in senescent cells
- Uncover proteins involved in 3D genome organization in senescent cells

Contents and Result

Elucidation of the 3D genome-organizing mechanism in the fission yeast model

Our laboratory employs fission yeast as a model system to elucidate mechanisms of 3D genome organization. In particular, we are interested in how protein complexes, condensin and cohesin, mediate 3D genome organization. Condensin and cohesin complexes are known to play pivotal roles in mitotic chromosomal compaction and sister-chromatid cohesion, respectively. Using state-of-the-art genomic technologies such as in situ Hi-C and ChIA-PET, we have shown that condensin and cohesin participate in 3D genome organization. Interestingly, condensin and cohesin direct different gene contact networks, although they are distributed at approximately 500 gene loci across the fission yeast genome and often bind to the same gene loci. For instance, condensin organizes 300–500 kb large chromatin domains, while cohesin forms 30–50 kb smaller domains (Figure 1; Kim et al. Nature Genetics 2016; Tanizawa et al. Nature Structural & Molecular Biology 2017).

Mechanistically speaking, we have found that condensin directly interacts with the TATA-box binding protein TBP, a general transcription factor (Iwasaki et al. Mol Cell 2015). TBP recruits condensin onto highly transcribed genes across the genome, and condensin molecules localized at dispersed gene regions, in turn, mediate 3D genome organization. Therefore, our study implies that condensin is the molecular link that connects genome-wide gene expression patterns with 3D genome organization. Since condensin and cohesin are widely conserved among eukaryotes, 3D genome-organizing mechanisms investigated in the fission yeast model are potentially present in higher eukaryotes. Please see the following section for our human study.

Elucidation of 3D genome organization and gene regulation in human senescent cells

In addition to the fission yeast model, our laboratory studies 3D genome organization in human cells. Our current research focuses on understanding how 3D genome structure is formed and regulated in senescent cells. Cellular senescence is defined as a state of stable cell-cycle arrest and serves as an intrinsic defense against abnormal cell proliferation associated with every type of cancer. It is known that senescence is accompanied by reorganization of the 3D genome structure. Senescent processes also involve the global reprogramming of gene expression. Especially genes encoding the senescence-associated secretory phenotype (SASP) factors are highly activated upon senescence; SASP factors include interleukins, chemokines, growth factors, and matrix metalloproteinases. Using the latest genomic method (in

https://www.igm.hokudai.ac.jp/3dgenome/ja/index.html

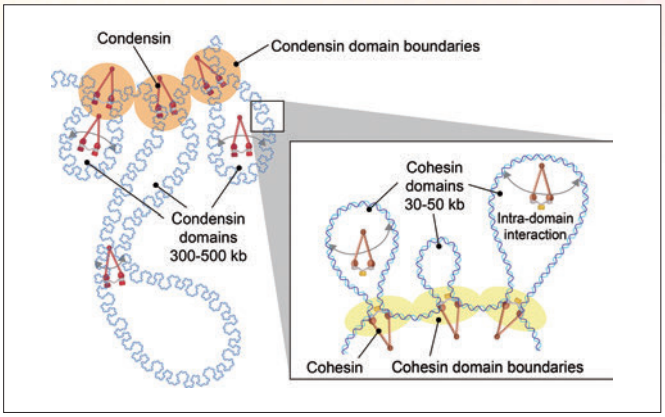

Figure 1. Model of 3D genome organization by condensin and cohesin

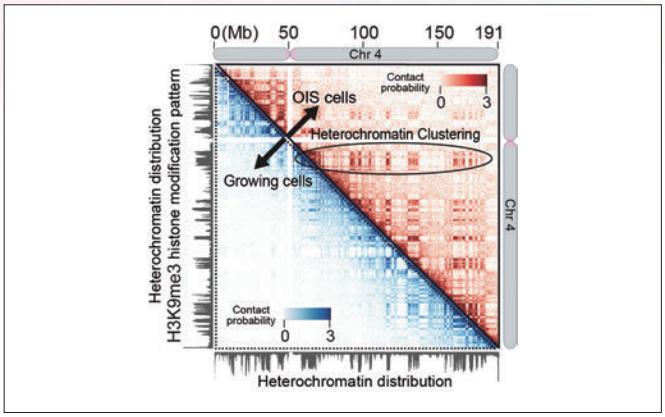

Figure 2. Gene contact maps for human chromosome 4 in OIS (top right) and growing cells (bottom left)

situ Hi-C), we have determined the 3D genome structure in Oncogene-Induced Senescence (OIS) cells. Our genomic study has shown that heterochromatin domains cluster in OIS cells, as previously observed by a microscopic approach (Figure 2). Interestingly, we also found that the key genome-organizing machinery, condensin, participates in senescent processes (Yokoyama et al. Cell Cycle 2015; Iwasaki et al. Nature Communications 2019). Our future project aims to elucidate how condensin concomitantly mediates 3D genome organization and transcriptional regulation in senescent cells.

Elucidating mitotic chromosome architecture using advanced proteomics

Chromosomal condensation is an essential process for the proper segregation of the genome during mitosis and meiosis, and its abnormalities are linked to human diseases such as cancer and hematological disorders. We have employed a mass spectrometric-based proteomics approach to understand how the chromosomal architecture during mitosis is organized by various factors (Ohta et al. Cell 2010; Curr Opin Cell Biol 2011; Mol Cell Proteomics 2016). A classic model proposes that non-histone chromatin proteins act as a structural framework during the formation of mitotic chromosomes. This framework has been suggested to correspond to an insoluble biochemical fraction and referred to as the chromosome scaffold, although how chromosome condensation during mitosis occurs via the formation of the chromosome scaffold remains unclear.

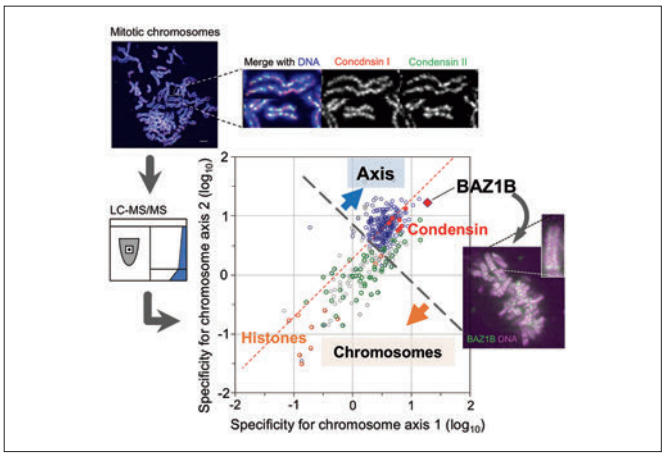

Figure 3. Finding of novel chromosomal axial protein BAZ1B using comprehensive proteomics

Using a quantitative proteomics approach, we recently identified the protein composition of the chromosome scaffold (Ohta et al. Mol Cell Proteomics 2019). Our findings revealed that BAZ1B is among the most abundant proteins in the scaffold fraction and is localized to the chromosomal axis (Figure 3). Knockout experiments of BAZ1B and its homolog BAZ1A result in aberrant chromosomal condensation during mitotic prophase. Our study suggests that BAZ1A and BAZ1B are likely important constituents of the chromosome scaffold required for chromosome condensation around early mitosis. Furthermore, we are expanding our proteomics approach to investigate senescent chromatin. With the dual approach, incorporating genomics and proteomics, we aim to understand the dynamics of genome structure associated with cellular senescence.

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Specially Appointed Assistant Professor	Yik-Lok CHUNG, Ph.D.

Selected Paper (2022.6-2024.9)

1. Tang, M. *et al.* Establishment of dsDNA-dsDNA interactions by the condensin complex. *Mol Cell* 83, 3787-3800.e9 (2023).
2. Wang, X., Fukumoto, T. & Noma, K.-I. Therapeutic strategies targeting cellular senescence for cancer and other diseases. *J Biochem* mvae015 (2024) doi: 10.1093/jb/mvae015.
3. Wang, X. *et al.* Chemo-senolytic therapeutic potential against angiosarcoma. *J Invest Dermatol* S0022-202X(24)00268-9 (2024) doi: 10.1016/j.jid.2024.03.026.

Professor Fumio MOTEGI, Ph.D.

Research Project

Mechanical control of self-organizing biological patterning

Outline

Cells in living organisms originate from a single cell, known as the fertilized egg. The egg undergoes a transition from being 'symmetric' to 'asymmetric,' leading to spatial biases in key physiological processes such as cell division, differentiation, and tissue formation. Although asymmetric patterning in cells and tissues is widely conserved across species, the underlying mechanisms are still poorly understood. Our group aims to uncover the mechanisms that regulate spatial patterning in living organisms, particularly the transition from symmetry to asymmetry in cells and tissues. By using live imaging to observe the dynamic behavior of the nematode *C. elegans* and cultured animal cells, we will elucidate the fundamental principles behind self-organizing biological systems.

Recent findings suggest that cells' ability to sense and respond to mechanical forces plays a crucial role in establishing biological patterns. The interaction between 'cell-derived forces' and 'external forces such as those from the extracellular matrix' creates a heterogeneous mechanical environment within the organism. By studying these complex mechanical interactions *in vivo* and investigating the physiological effects of mechanical forces on cellular processes, we aim to introduce new concepts regarding the role of mechanical forces in biological patterning. Our research will also provide essential insights into the mechanisms underlying various diseases and contribute to the development of preventative strategies. Through this work, we seek to establish a new field of life science that integrates cell and developmental biology with perspectives from mathematics, tissue engineering, and medical sciences.

Contents and Result

Patterning soma-germ dichotomy during embryogenesis

During development, an embryo generates cellular asymmetries by reorganizing the conserved cell polarity regulator, known as PAR protein complexes, from symmetric to asymmetric patterns.

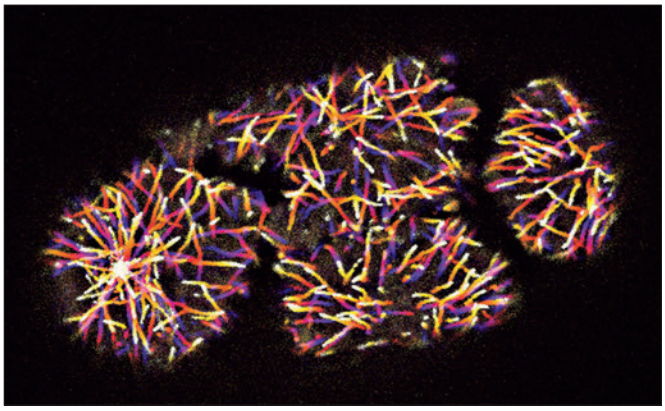

Fig. 1. Dynamics of microtubules in a *C. elegans* early embryo. Colour gradients denote the position of growing microtubule ends over time.

Our group previously demonstrated that the asymmetric patterning of the fertilized *C. elegans* egg relies on cell-autonomous, self-organizing interactions between PAR protein complexes. After the fertilized egg undergoes cell division and reaches the multicellular stage, each blastomere re-establishes its spatial pattern in response to external signals from neighboring cells and the extracellular matrix. How each cell in a developing embryo senses environmental stimuli and reorients the pattern of the cell-autonomous PAR protein interaction network remains unknown.

To explore this question, we are studying *C. elegans* embryogenesis, focusing on the generation of asymmetric patterns in the germ cell progenitor lineage, which undergoes repeated cycles of asymmetric cell divisions during embryogenesis. We found that the germ cell progenitor lineage reverses the orientation of PAR complexes between the second and the third rounds of asymmetric division in response to environmental cues. By employing an approach that combines blastomere manipulation with non-invasive mechanical manipulation, we aim to uncover the mechanisms governing the environmental responsiveness of autonomous PAR protein patterning. This project will provide fundamental insights into the design principles of multicellular patterning during development.

https://www.motegilab.com

Fig. 2. Germline development (upper cells) and oogenesis (lower cells) in C. elegans. Green and red indicate the plasma membrane and germ granules, respectively.

Patterning germ cells to oocytes via cytoplasmic streaming

Sexual reproduction, the process of creating new organisms through the union of two individuals, involves the fusion of an egg and sperm. The quality of the egg is crucial for successful reproduction and is typically well-regulated in a healthy state but declines with age. To ensure egg quality, egg precursors, germ cells, form a unique structure known as a syncytium, which facilitates cytoplasmic transfer between germ cells. A cell that receives cytoplasm from neighbouring cells matures into an egg, while the donor cells undergo apoptosis. Cytoplasmic transfer is driven by hydrodynamic forces, but the dynamic properties of this process remain largely unexplored, leaving its significance in oogenesis unclear.

Our group aims to understand and manipulate cytoplasmic transfer during oogenesis in *C. elegans*. By controlling actin polymerization-dependent hydrodynamic forces in the cytoplasm, we seek to uncover the mechanisms by which these forces regulate germ cell morphogenesis and control egg quality. Our research will also provide insights into how the decline in cytoplasmic transfer and egg quality occurs in response to aging and stress. The comprehensive understanding of cytoplasmic mechanics gained from this project will contribute to advancements in reproductive science, improving the efficiency of egg production and quality maintenance.

Patterning focal adhesion-mediated mechanosensing by microtubules

Cells *in vivo* are exposed to a heterogeneous mechanical environment created by neighboring cells and the extracellular matrix. Many cell types actively sense and respond to a variety of mechanical signals from their surroundings, modulating cell motility and tissue morphogenesis. This process known as mechanosensing depends on integrin-containing transmembrane complexes called focal adhesions, which link the internal actin cytoskeleton to the external environment. The mechanism by which focal adhesions transduce nano-scale environmental information into cellular-scale rearrangements of actin filaments remains unclear.

Our group aims to systematically understand how microtubule-mediated focal adhesion turnover contributes to the mechanosensory function of focal adhesions during cell migration. In previous studies, we found that GEF-H1, an activator of the small GTPase RhoA, plays a critical role in regulating focal adhesion turnover through its interaction with microtubules. Notably, GEF-H1-RhoA activity is closely coupled to the cycles of plasma membrane protrusion and retraction in migrating cells. To artificially manipulate the extracellular mechanical environment, we are currently developing new techniques to create extracellular substrates with gradients of stiffness using microprinting and polymer engineering techniques.

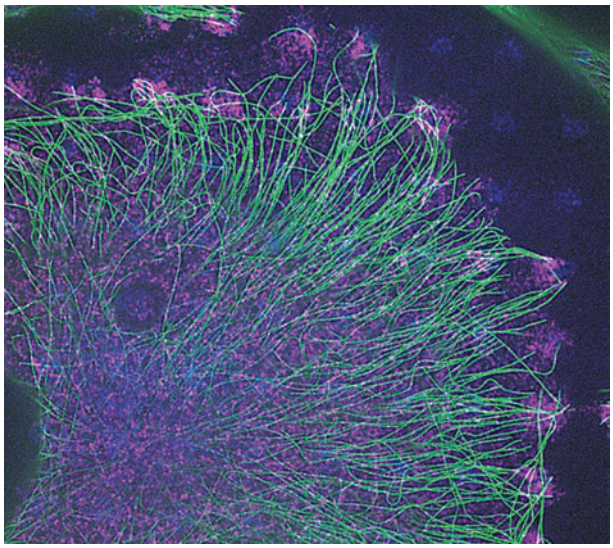

Fig. 3. Focal adhesion (magenta) and microtubules (green) in a migrating HT1080 human fibrosarcoma cell.

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Selected Paper (2022.6-2024.9)

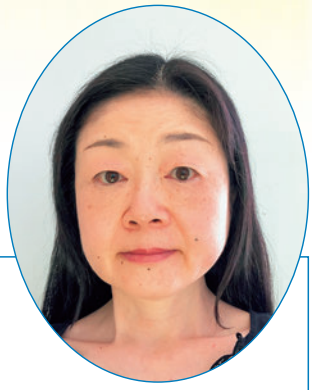
1. Ana M. Pasapera, Sarah M. Heissler, Masumi Eto, Yukako Nishimura, Robert S. Fischer, Hawa R. Thiam, Clare M. Waterman. (2022) MARK2 regulates directed cell migration through modulation of myosin II contractility and focal adhesion organization. Current Biology. doi.org/10.1016/j.cub.2022.04.088

2. Kazunori Yamamoto, Fumio Motegi. (2023) Cell polarity: Adapting the PAR cascade to diverse cellular contexts. Current Biology. doi.org/10.1016/j.cub.2023.08.083

3. Yukimasa Shibata, Yuri Tanaka, Hiroyuki Sasakura, Yuki Morioka, Toshihiro Sassa, Shion Fujii, Kaito Mitsuzumi, Masashi Ikeno, Yukihiko Kubota, Kenji Kimura, Hidenao Toyoda, Kosei Takeuchi & Kiyoji Nishiwaki. (2024) Endogenous chondroitin extends the lifespan and healthspan in C. elegans. Scientific Reports. doi.org/10.1038/s41598-024-55417-7

Research Section of Pathophysiology | Division of Microbial Oncology

Associate Professor **Naoko KAMIYA, Ph.D.**



Research Project

Molecular mechanism underlying *Helicobacter pylori*-mediated gastric carcinogenesis

Outline

It has been well established that chronic infection with *Helicobacter pylori* (*H. pylori*) is associated with atrophic gastritis and peptic ulcer, which can progress to gastric cancer. In 2014, the International Agency for Research on Cancer (IARC), a division of the World Health Organization (WHO), reported that 78% of all gastric cancer cases are estimated to be attributable to chronic *H. pylori* infection. Especially, it has been revealed though epidemiological studies that infection with *H. pylor*i strains carrying *cagA* gene plays an essential role in the development of gastric cancer. The *cagA*-positive *H. pylor*i delivers the *cagA* gene product, the CagA protein, into human gastric epithelial cells via the bacterial type IV secretion system. It has been reported that CagA can interact with a number of host proteins in gastric epithelial cells. Therefore, CagA is thought to deregulate multiple cellular signaling pathway and thereby promote gastric carcinogenesis. However, whole molecular mechanism of CagA-dependent gastric carcinogenesis has not been elucidated. In our division, we are conducting cutting-edge studies to elucidate oncogenic mechanisms of the bacterial CagA protein. These studies will contribute to the foundation for novel methods of prevention and treatment of gastric cancer.

Contents and Result

Deregulation of host cell signaling by *cagA*-positive *H. pylori*

Significant genomic polymorphism is observed in the genome sequence of *H. pylori*. Clinically isolated *H. pylori* strains can be classified into two groups: those that possess the *cagA* gene and those that do not. East Asian countries such as Japan, Korea, and China are known to show the highest incidence of gastric cancer in the world. More than 90–95% of *H. pylori* strains isolated in East Asian countries carry *cagA* gene. In contrast, the proportion of *cagA*-positive strains is 60% of *H. pylori* isolated from around the world, excluding East Asian countries, where the incidence rate of gastric cancer is relatively low. Epidemiological studies have revealed that infection with *cagA*-positive *H. pylor*i strains induce more severe atrophic gastritis and peptic ulcer, and significantly increase the risk of developing gastric cancer compared to *cagA*-negative strains.

The genome of *cagA*-positive *H. pylori* contains a DNA region known as *cag*PAI (*cag* pathogenicity island). The *cag*PAI includes *cagA* and several genes encoding components of a bacterial micro-syringe, termed the type IV secretion system (Figure 1). The *cagA*-positive *H. pylor*i delivers the *cagA* gene product, the CagA protein, into human gastric epithelial cells via the type IV secretion system. Inside the host cells, CagA undergoes tyrosine phosphorylation by host cell kinases. Tyrosine-phosphorylated CagA acquires the ability to bind to and activate the tyrosine phosphatase SHP2. SHP2 functions as a positive signaling molecule that connects growth factor receptors to the Ras-MAPK pathway and is involved in cell prolifera-

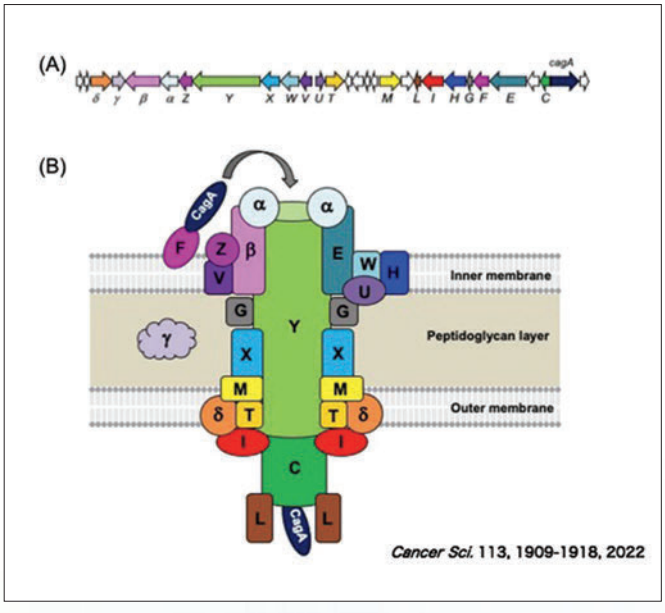


Figure 1. *H. pylori* type IV secretion system and CagA.
(A) Schematic view of the *cag*PAI encoded by the *H. pylori* strain 26695.
(B) A model for assembly of *H. pylori* type IV secretion system.

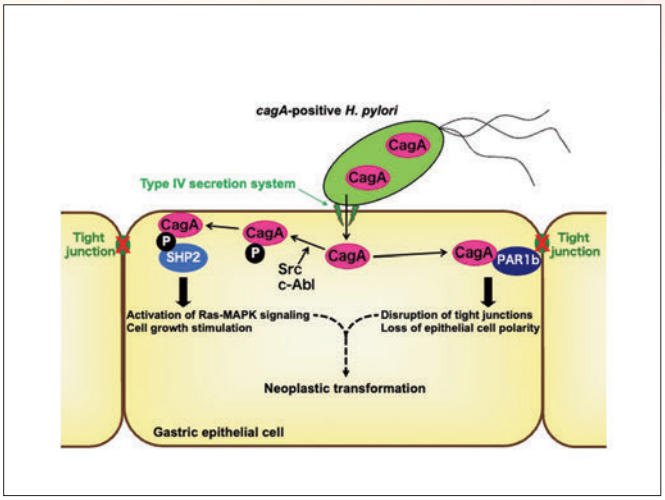


Figure 2. Deregulation of host cell signaling by *H. pylori* CagA.

In human gastric epithelial cells, CagA interacts with SHP2 in a tyrosine phosphorylation-dependent manner, thereby activating its phosphatase activity. On the other hand, CagA interacts with PAR1b in a tyrosine phosphorylation-independent manner, thereby inhibiting its kinase activity.

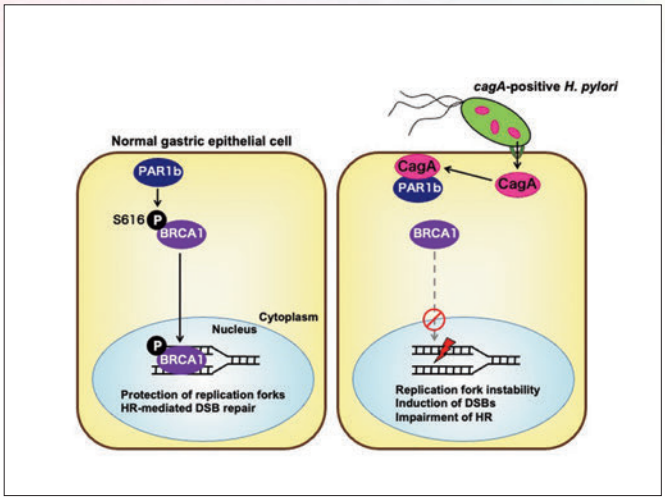


Figure 3. Induction of genome instability by *H. pylori* CagA.

In normal gastric epithelial cells, PAR1b phosphorylates BRCA1 to promote cytoplasmic-to-nuclear translocation of BRCA1. CagA inhibits nuclear translocation of BRCA1 via PAR1b inhibition, thereby inducing genome instability.

tion and cell motility. CagA deregulates cell growth through aberrant activation of SHP2 (Figure 2). On the other hand, CagA binds and inhibits the serine/threonine kinase PAR1b (also known as MARK2) via CM motif in a tyrosine phosphorylation-independent manner. PAR1b has an essential role in establishment and maintenance of epithelial cell polarity. CagA inhibits kinase activity of PAR1b, thereby causing junctional and polarity defects (Figure 2).

Induction of genome instability by *H. pylori* CagA

H. pylori has been thought to promote neoplastic transformation of gastric epithelial cells via CagA-dependent deregulation of cell signaling such as cell growth. On the other hand, cancer develops due to damage to genes, but the molecular mechanisms by which CagA induces genetic mutations are unclear. In this study, we investigated whether CagA induces DNA damages in the host genome. We found that CagA elicits DNA double-strand breaks (DSB) in the host genome through PAR1b inhibition. While DSB occurs in the nucleus, CagA–PAR1b interaction occurs in the cytoplasm. We focused on the molecules that shuttle between the cytoplasm and the nucleus among the group of molecules involved in DSB regulation. We found that CagA impairs nuclear accumulation of BRCA1 through PAR1b inhibition. *BRCA1* is a tumor suppressor gene that causes hereditary breast cancer and ovarian cancer. It is known that inactivating mutations in BRCA1 can induce the accumulation of genetic mutations (genome instability). We found that PAR1b phosphorylates BRCA1 on Ser616, which is required for cytoplasmic-to-nuclear translocation of BRCA1. Nuclear BRCA1 has an essential function in the protection of stalled replication forks. CagA induces shortage of nuclear BRCA1 and thereby causes DNA replication fork instability that generates DSB (Figure 3).

DSB is one of the most dangerous DNA damages, which may lead to cell death (apoptosis). In addition, there is a possibility that gene mutations may be induced during the repair process even when DSB are repaired. The main repair pathways for DSB are known as homologous recombination (HR) and non-homologous end joining (NHEJ). HR-mediated DSB repair does not cause mutations, whereas NHEJ may cause mutations during DSB repair. Since BRCA1 is also essential in HR-mediated DSB repair, CagA inhibits HR-mediated DSB repair. These results indicate that CagA-induced shortage of nuclear BRCA1 causes replication fork instability leading to DSB that are repaired through error-prone pathways such as NHEJ.

Furthermore, intermittent expression of CagA in cultured human gastric epithelial cells, which mimics CagA delivery in the *H. pylori*-colonized human stomach, induces somatic mutations with Signature 3 (SBS3). Signature 3 is a mutation signature associated with HR repair deficiency, which is particularly detected in cancers with inactivating mutations in the *BRCA1/BRCA2* genes. Genome instability caused by CagA-induced transient BRCAness may promote acquisition of additional driver gene mutations that confer neoplastic transformation.

Staff

Associate Professor ····· Naoko KAMIYA, Ph.D.

Selected Paper (2022.6-2024.9)

1. Murata-Kamiya, N., Hatakeyama, M. *Helicobacter pylori*-induced DNA double-stranded break in the development of gastric cancer. ***Cancer Sci.*** 113, 1909-1918, 2022.

Research Section of Disease Control | Division of Biomedical Oncology

Professor Masahiro SONOSHITA, Ph.D.

Research Project

Elucidating the mechanisms of cancer development to develop novel cancer therapies

Outline

Cancer is currently the leading cause of death in Japan. Despite significant advances in research, effective treatments remain limited. Therefore, our laboratory is dedicated to developing novel cancer therapies by elucidating the fundamental processes of cancer development.

Contents and Result

Establishing novel methods to generate anticancer drugs

Drugs can be one of the effective tools in the fight against cancer. In recent years, targeted therapy, which aims to reduce the side effects of drugs by specifically targeting molecules present in cancer, has been actively studied. However, it has become clear that even approved cancer drugs still have serious side effects.

To address this issue, our laboratory has been employing multiple approaches to drug discovery that complement the concept of targeted therapy. One such approach involves focusing on existing approved drugs and gradually modifying their structures to enhance their anticancer effects while maintaining their pharmacokinetics, such as absorption, distribution, metabolism, and excretion, when administered orally. To this end, we have been using the fruit fly *Drosophila* to model genomic abnormalities in cancer patients. This is because flies offer a convenient research toolkit with many advantages that complement mammalian models. For example, flies have a high degree of conservation of genes and signaling pathways with humans, an abundance of genetic tools for whole-body analyses, and reduced costs for production and breeding. As a drug model, we chose the multi-kinase inhibitor sorafenib, which has strong side effects beside therapeutic benefits in patients.

First, we performed a chemical genetic screening for all kinases in the kinome of medullary thyroid cancer (MTC) model flies and found that inhibition of MNK1, BRAF, and others is an 'undesirable inhibition' causing toxicity for sorafenib. We named these kinases 'anti-targets' to avoid during treatment.

Subsequent computational chemistry predicted an analog of sorafenib that, by increasing the size of a portion of sorafenib, would continue to bind to MTC-causing RET as a desirable target but not to the anti-targets. When we dosed this analog to mice implanted with human MTC, the analog produced significantly improved tumor suppression compared to sorafenib.

Thus, by combining fly genetics with computational chemistry and mammalian experimental systems, our laboratory has succeeded in creating novel leads with reduced toxicity of existing drugs through 'Rational polypharmacology' (Figure 1; Sonoshita & Cagan. *Curr Top Dev Biol* 2017; Sonoshita et al. *Nat Chem Biol* 2018). We expect to apply this method to study also other diseases where drug discovery has been problematic as well.

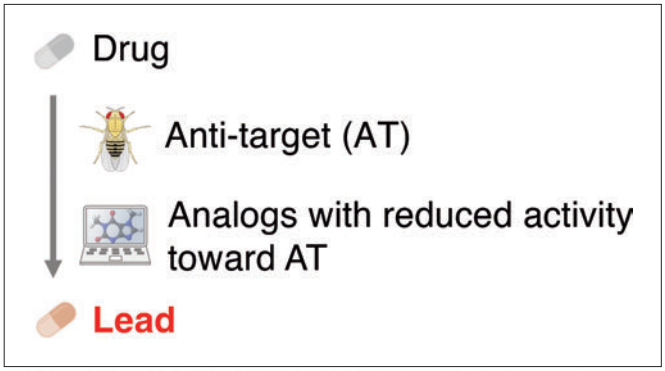


Figure 1: Rational polypharmacology. Based on the anti-targets of existing drugs identified through fly chemical genetic screening, their chemical derivatives are generated using computational chemistry. Their widened therapeutic window is confirmed in mammals, leading to the creation of a new anticancer lead.

https://bmoncology.wixsite.com/mysite

Elucidating the pathogenesis of pancreatic cancer to develop new treatments

Pancreatic cancer represents one of the most difficult cancer types to cure. In the US, the number of deaths due to pancreatic cancer is expected to continue rising, and it is projected to become the second leading cause of cancer death by 2030. However, the development of new drugs to treat pancreatic cancer has been extremely difficult, primarily due to the lack of therapeutic targets and experimental models to efficiently evaluate new drug candidates.

To tackle this problem, we have recently created a novel *Drosophila* model that mimics the genotype of patients with pancreatic cancer. We found that the model flies exhibited tumor phenotypes such as increased cell proliferation and motility, as well as animal lethality. Subsequently, we performed a comprehensive genetic screening using these flies to identify genes and signaling pathways that promote or suppress these phenotypes. In this analysis, we specifically examined the function of kinases, which play a role in relaying, amplifying, and branching signals in various signaling pathways. As a result, we found that these traits were suppressed when the activity of several kinases, including AURK, MEK, and GSK3, was reduced. These results suggest that these kinases are candidates for novel therapeutic targets in pancreatic cancer.

Therefore, we focused on approved drugs and experimental inhibitors of these kinases and administered these compounds to a mouse model xenografted with human pancreatic cancer. Consequently, these compounds markedly inhibited tumor formation in mice. Analysis of clinical specimens also confirmed that pancreatic cancer patients with elevated expression of these kinases exhibited poor prognosis.

These results indicate that it is possible to employ flies to create novel animal models of pancreatic cancer, a typically intractable cancer, and to identify novel therapeutic targets and drug candidates (Figure 2: Jiang et al. *Front Oncol* 2022, Sekiya et al. *Cancer Res* 2023, Fukuda et al. *Cancer Sci* 2024). Based on these findings, our laboratory is currently working on generating model flies that mimic various cancer genotypes, elucidating the mechanisms of these cancers, and creating novel therapeutics using these model flies.

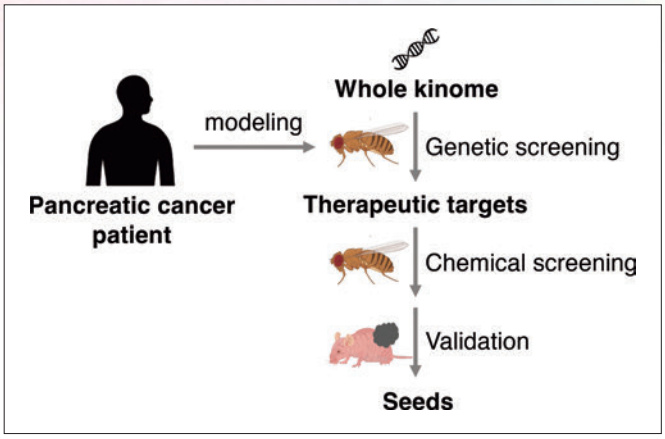


Figure 2: A novel platform to study pancreatic cancer by combining *Drosophila* and mammals in a complementary manner. We generate Drosophila models that mimic the genotype of pancreatic cancer patients and use these flies in a genetic screening to identify novel therapeutic targets. Then, compounds that inhibit these targets are screened out and evaluated for their efficacy in model mice.

Teaching Staff

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Assistant Professor	Ryodai YAMAMURA, Ph.D.

Selected Paper (2022.6-2024.7)

1. Jiang H, Kimura T, Hai H, Yamamura R, **Sonoshita M***. Drosophila as a toolkit to tackle cancer and its metabolism. ***Front Oncol***. 2022 12: 982751.

2. Sekiya S, Fukuda J, Yamamura R, Ooshio T, Satoh Y, Kosuge S, Sato R, Hatanaka KC, Hatanaka Y, Mitsuhashi T, Nakamura T, Matsuno Y, Hirano S, **Sonoshita M***. Drosophila Screening Identifies Dual Inhibition of MEK and AURKB as an Effective Therapy for Pancreatic Ductal Adenocarcinoma. ***Cancer Res***. 2023 83: 2704-2715

3. Fukuda J, Kosuge S, Satoh Y, Sekiya S, Yamamura R, Ooshio T, Hirata T, Sato R, Hatanaka KC, Mitsuhashi T, Nakamura T, Matsuno Y, Hatanaka Y, Hirano S, **Sonoshita M***. Concurrent targeting of GSK3 and MEK as a therapeutic strategy to treat pancreatic ductal adenocarcinoma. ***Cancer Sci***. 2024 115: 1333-1345.

Professor Nobuo N. NODA, Ph.D.

Research Project

1. Research on the molecular mechanism of autophagy
2. Research on biological phenomena regulated by liquid-liquid phase separation
3. Structure-based studies of biomolecular mechanisms

Outline

Autophagy is a major intracellular degradation system and contributes to the health of the organism through the degradation of toxic substances such as damaged mitochondria, denatured proteins, and invasive bacteria. Autophagy performs degradation by sequestering degradation targets into the newly formed double-membrane organelle called autophagosome and transporting them to lysosomes. We are (1) utilizing structural biology techniques to obtain the structure and clues to molecular function of autophagy-related (Atg) proteins, (2) reconstituting and simplifying the various processes of autophagy in vitro to understand the functions, and (3) performing cell-based assays to validate the findings obtained in vitro and to extract physiologically significant functions and phenomena. We are also analyzing the roles of liquid-liquid phase separation, a physical phenomenon that is universally observed in proteins, in the regulation of various biological phenomena, including autophagy, using the methods described in (1) to (3) above.

Contents and Result

Mechanism of autophagosomal membrane shaping by the Atg8 conjugation system

During autophagosome formation, flattened isolation membranes are expanded and transformed into a cup-like morphology, which finally closes into a spherical shape to form autophagosomes. The mechanism driving this sequence of shape changes has not been well understood. We have succeeded for the first time in the world in reconstructing the membrane morphological changes observed during autophagosome formation in vitro by using prolate giant liposomes as a model for the isolation membrane and six purified Atg proteins and ATP. We then showed that the E1, E2, and E3 enzymes responsible for the lipidation of Atg8 possess membrane shaping activity in addition to each enzymatic activity. Furthermore, by using high-speed AFM and solution NMR, we showed that these six protein groups form a dynamic meshwork structure on lipid membranes via weak multivalent interactions and proposed a model in which they act for membrane shaping (Nat Struct Mol Biol 2024).

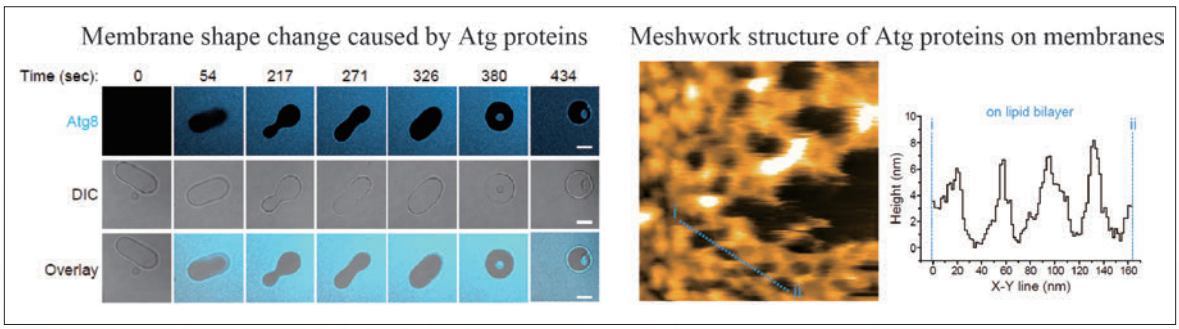

Figure 1: Membrane morphological changes induced by six groups of proteins in the prolate giant liposome (left) and the meshwrok structure on the lipid membrane visualized by high-speed AFM (right).

https://mechanism.igm.hokudai.ac.jp/

Discovery of a novel mitochondrial fission factor and its role in mitophagy

In mitophagy, a process of selective mitochondrial degradation by autophagy, mitochondria are accommodated in autophagosomes by cleavage to a size that fits into the autophagosome, but the molecular mechanism of this process remains unclear. We have studied the function of Atg44, a novel factor involved in mitophagy in yeast, and found that Atg44 localizes to the mitochondrial intermembrane space, overexpression of Atg44 causes mitochondrial fragmentation, and loss of Atg44 causes mitochondrial enlargement. The crystal structure of Atg44 was subsequently determined, which showed that the molecule as a whole has an amphiphilic structure and binds to lipid membranes with curvature using hydrophobic surfaces. Furthermore, in vitro reconstitution experiments showed that Atg44 can bind to lipid membranes by itself and induce membrane fission. These results indicate that Atg44 is a novel mitochondrial fission factor that acts in mitophagy, and we named it mitofissin (Mol Cell 2023).

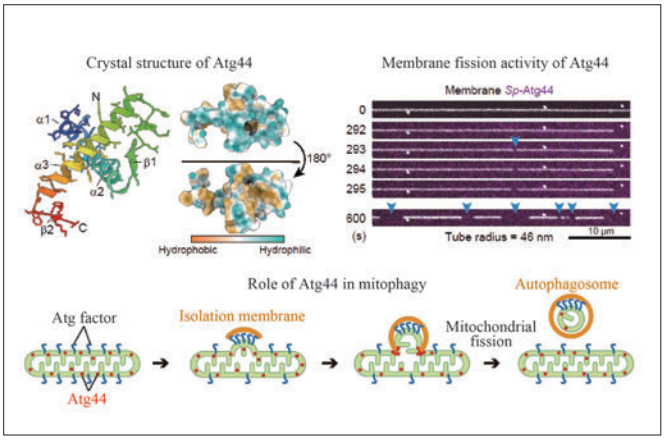

Figure 2: Crystal structure of Atg44 (top left) and membrane fission activity observed in vitro (top right), role of Atg44 in mitophagy (bottom)

Application of AlphaFold prediction of protein complex structures for elucidation of life phenomena

Proteins are responsible for all life phenomena, and they express their functions by forming specific three-dimensional structures and complexes with other biomolecules in a specific manner. Therefore, it is important to elucidate the three-dimensional structure of protein complexes in order to understand life phenomena in general, but it has taken a great deal of time and effort to experimentally elucidate the structures. Using AlphaFold, a highly accurate AI-based structure prediction program, we predicted the structure of the Atg29–Atg31–Atg38 complex, which is involved in autophagy, and clarified the mechanism by which these factors work from the predicted structure (J Cell Biol 2023). Furthermore, we also predicted the structure of the UFL1–UFBP1–CDK5RAP3–UFC1 complex, which is responsible for protein quality control, and succeeded in clarifying the working basis of this complex for the translation quality control mechanism RQC and ER-selective autophagy (Sci Adv 2023; Mol Cell 2024).

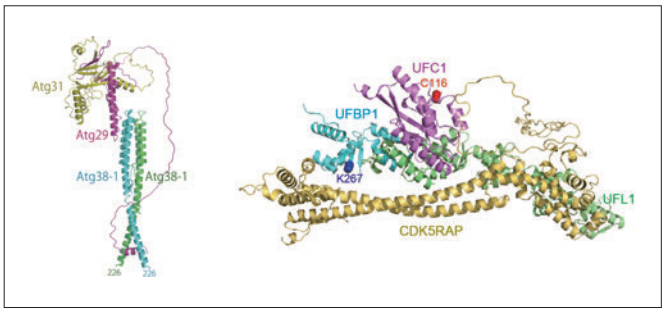

Figure 3: AlphaFold predicted structures of the Atg29-Atg31-Atg38 complex (left) and the UFL1-UFBP1-CDK5RAP3-UFC1 complex (right)

Teaching Staff

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Specially Appointed Assistant Professor	Yuta OGASAWARA, Ph.D.
Specially Appointed Assistant Professor	Eigo TAKEDA, Ph.D.

Selected Paper (2022.6-2024.9)

1. Fukuda, T., Furukawa, K., Maruyama, T., Yamashita, S., Noshiro, D., Song, C., Ogasawara, Y., Okuyama, K., Alam, J. M., Hayatsu, M., Saigusa, T., Inoue, K., Ikeda, K., Takai, A., Chen, L., Lahiri, V., Okada, Y., Shibata, S., Murata, K., Klionsky, D. J., *Noda, N. N. and *Kanki, T. The mitochondrial intermembrane space protein mitofissin drives mitochondrial fission required for mitophagy. ***Mol. Cell*** 83, 2045-2058 (2023). DOI: 10.1016/j.molcel.2023.04.022

2. Alam, J. M., Maruyama, T., Noshiro, D., Kakuta, C., Kotani, T., Nakatogawa, H. and *Noda, N. N. Complete set of the Atg8-E1-E2-E3 conjugation machinery forms an interaction web that mediates membrane shaping. ***Nat. Struct. Mol. Biol.*** 84, 156-169 (2024). DOI: 10.1038/s41594-023-01132-2

3. *Komatsu, M., *Inada, T. and *Noda, N. N. The UFM1 system: Working principles, cellular functions, and pathophysiology. ***Mol. Cell*** 84, 156-169 (2024). DOI: 10.1016/j.molcel.2023.11.034.

Frontier Research Unit | Laboratory of Molecular Cellular Biology

Associate Professor **Tomohiko OKAZAKI, Ph.D.**

Research Project

Understanding the cell fate determination by post-translational modifications and inter-organelle communications, and the interactions between immune and nervous systems

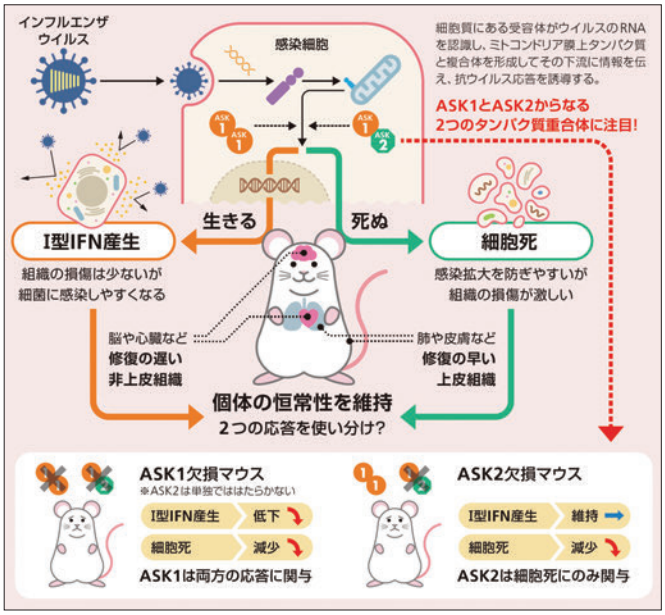
Outline

Our research goal is to understand how cells integrate numerous external and internal signals into meaningful biological outputs by focusing on (1) post-translational modifications and logistics of proteins, or (2) inter-organelle communications. In addition, we are also studying (3) the interactions between immune and nervous systems and (4) neuroethology using Drosophila. Through these studies, we wish to discover the sophisticated systems of living organisms for surviving in a complex world.

Contents and Result

Host defense mechanisms against pathogen infection

When mammalian cells get infected with viruses, they activate the innate immune system as a first-line defense mechanism before activating the adaptive counterpart. The RIG-I-like receptor family, which detects virus-derived RNA within infected cells, and its adaptor molecule IPS-1/MAVS play central roles in this innate immune system. IPS-1 is mainly localized on the mitochondrial outer membrane and has been known to trigger host defense mechanisms including type I interferon (IFN) production and cell death (apoptosis). Type I IFN inhibits viral replication within infected cells, and apoptosis of infected cells altruistically prevents viral propagation to surrounding cells. Although both strategies appear to be effective means of suppressing viral replication, ironically they can also be harmful to the host organism in some instances. Therefore, it is reasonable to assume that host cells may regulate use of the two mechanisms to optimize the benefit to the organism in a context dependent manner and efficiently remove the infecting virus. However, it remained unclear whether such differential regulation exists within infected cells and, if it does, how it is controlled. Our laboratory has identified novel modifications and binding molecules of IPS-1 to address this question.



Protein carboxylation

Protein functions are regulated not only by its amino acid sequence but also by various post-translational modifications. Among them, protein carboxylation is a rare but unique post-translational modification in which a carboxyl group are added to glutamate and aspartate residues by a γ-carboxylase GGCX in a vitamin K (VK) dependent manner. To date, about 20 substrates have been identi-

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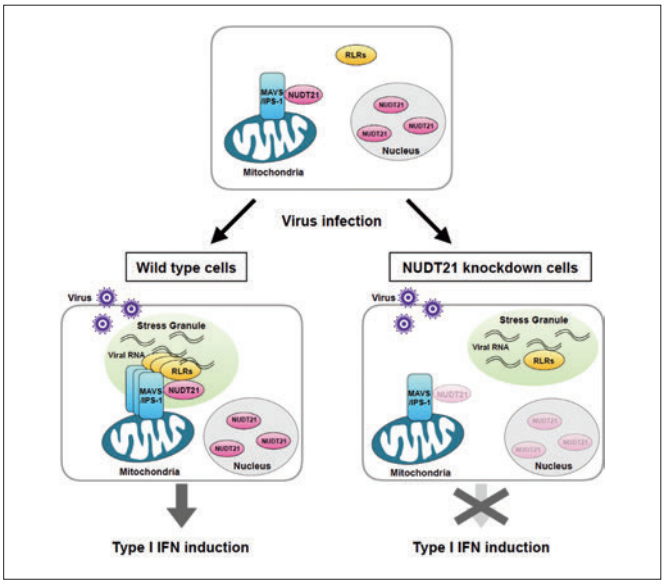
fied as GGCX substrates, which regulate limited physiological processes including blood coagulation and bone formation. We are now examining whether this protein carboxylation plays any role in the regulation of immune systems.

Inter-organelle communications

Although organelles have been long assumed to perform their unique functions by their own organizations, recent studies have discovered functional coordination between them through inter-organelle communications, which is being addressed worldwide as new paradigm shift. We have discovered novel interactions between mitochondria and peroxisomes, and between mitochondria and stress granules, and found that these interactions may play important roles in cell physiology (Tanaka et al., Journal of Cell Science, 2019; Aoyama et al., Journal of Immunology, 2021). We are further investigating the role of these inter-organelle communications.



The interactions between immune and nervous systems in health and disease

The central nervous system has long been thought as an immune-privileged site having no direct communication and interaction with the immune system at least under health conditions, due to its functional importance and the structural features of the blood-brain barrier. However, recent studies have revealed (rediscovered) the presence of lymphatic vessels (pathways for immune cells) in the brain, and also the presence of various immune cells in the adult brain through scRNA-seq analysis. Furthermore, it has been also shown that immunodeficient mice, which lack both T cells and B cells, exhibited various behavioral abnormalities, indicating that immune cells play crucial role in the formation of neural circuits and the brain function. We are currently investigating which and how immune cells contribute to the pathogenesis (or alleviation) of viral infections in the brain, neurodegenerative diseases, and psychiatric disorders such as autism and schizophrenia.

Teaching Staff

Assistant Professor
Nao MORIMOTO, Ph.D.

Staff

Associate Professor ····· Tomohiko OKAZAKI, Ph.D.
Assistant Professor ····· Nao MORIMOTO, Ph.D.

Selected Paper (2022.6-2024.9)

1. Aoyama-Ishiwatari S, Okazaki T*, Iemura S, Natsume T, Okada Y, Gotoh Y. NUDT21 links mitochondrial IPS-1 to RLR-containing stress granules and activates host antiviral defense. ***Journal of Immunology***. (2021), DOI: https://doi.org/10.4049/jimmunol.2000306 (*Corresponding Author)

2. Onda M, Takeuchi R, Isobe K, Suzuki T, Masaki Y, Morimoto N, Osakada F. Temporally multiplexed dual-plane imaging of neural activity with four-dimensional precision. ***Neuroscience Research***. (2021), https://doi.org/10.1016/j.neures.2021.02.001

Endowed Department | Division of Synbiotics

Professor **Tadaaki MIYAZAKI, Ph.D.**

Research Project

We screened lactic acid bacteria (probiotics) that have preventive effects and symptom improvement effects on allergies and viral infections, beauty effects, and sleep induction effects, and lactic acid bacteria-derived substances that their increase functionality, and determined their effectiveness and mechanism. This research will lead to the development of functional foods and drug discovery.

Outline

We will explore probiotics, prebiotics, and synbiotics that have preventive and therapeutic effects on infectious diseases, allergies, inflammatory diseases, and evaluate their effects through experiments on cells and animals, and instrumental analysis. We used hay fever model mice to verify the effect on the improvement of symptoms of hay fever, the mechanism of action, and their synergistic effects, and aim the development of effective synbiotics for the treatment of hay fever, which is one of the important health issues. We also evaluated the cytokine induction by new lactic acid bacteria and investigated their effectiveness to prevent influenza A virus infection. Based on the results, it can be expected to have an effect on suppressing the proliferation of influenza viruses, as well as preventing and improving atopic dermatitis, hay fever, and autoimmune diseases, as clarified. Furthermore, we measured the concentration of soy isoflavone glycosides in soy milk fermented with lactic acid bacteria using LC-MS/MS, and searched for femcare lactic acid bacteria strains that can balance female hormones by utilizing probiotics. Through these studies, our laboratory aims to apply probiotics, prebiotics, and synbiotics to prevention and treatment of diseases, and to contribute to the mental and physical health of women.

Contents and Result

Evaluation of cytokine induction by novel lactic acid bacteria and determination of preventive effect on influenza A virus infection

Cytokine inducibility of blue rose-derived lactic acid bacteria BRKS-6 was evaluated using mouse-derived spleen cells. BRKS-6 was found to have no ability to induce the inflammatory cytokine IL-17, but to have the ability to induce the anti-inflammatory cytokine IL-27. Therefore, it was suggested that BRKS-6 is effective in the prevention and treatment of diseases that require immunosuppressive effects, such as atopic dermatitis, hay fever, and autoimmune diseases.

In addition, Enterococcus faecium PTA-5844 WR (Ef-WR), a lactic acid bacterium that has the ability to activate immunity, was shown the antiviral activity against influenza A virus (IAV), and preventive oral administration of Ef-WR is recommended. It was proven to be effective in alleviating the symptoms of mice infected with IAV. Weight loss due to viral infection was suppressed by Ef-WR administration. Furthermore, virus titers in bronchoalveolar lavage fluid tended to be lower with Ef-WR administration on day 5 after IAV infection. Ef-WR administration reduced the expression of inflammatory cytokines in IAV-infected lungs. Furthermore, the expression of antiviral-related genes and antioxidant genes in lung tissue was increased by Ef-WR administration. These findings suggest that administration of Ef-WR is effective in preventing IAV infection and alleviating symptoms in mice by enhancing the expression of antiviral and antioxidant genes by suppressing the virus replication.

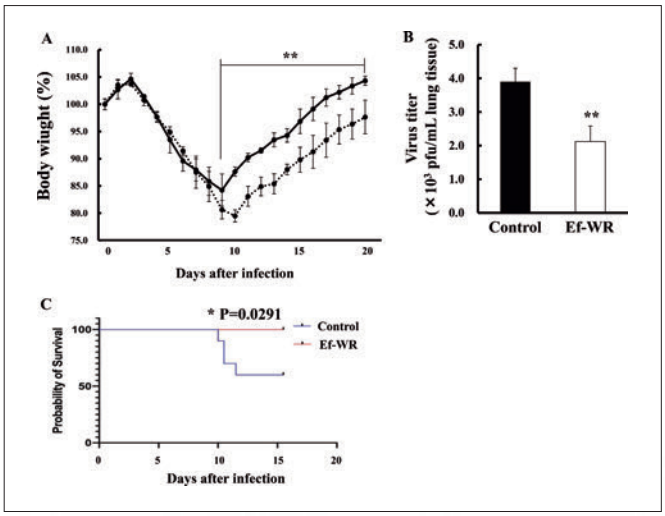


Figure 1

http://www.igm.hokudai.ac.jp/pbi/

Effects of new synbiotics to improve the symptoms in hay fever model mice

In order to verify the effects of new synbiotics, we orally administered plant lactic acid bacteria and rosmarinic acid, which is abundant in plants of the Lamiaceae family, to cedar pollinosis model mice, either alone or at the same time, to investigate their effect on improving symptoms of hay fever and its mechanism. As a pollen allergy model mouse, 5-week-old BALB/c male mice were intraperitoneally administered three times with Cryj1 and Al(OH)3, which are cedar pollen antigens, as primary sensitization, and then sequentially with Cryj1 as secondary sensitization. Hay fever was caused by intranasal administration for 10 days. Sneezing and nose-scratching behavior, which are symptoms of hay fever, were alleviated in the co-administered group compared to the single-administered group. The amount of histamine in the serum was significantly decreased in the group administered with lactic acid bacteria alone and the group administered simultaneously. Compared to the single administration group, in the coadministration group, the amount of Cryj1-specific IgE in the serum was significantly decreased, and the mRNA expression of IL-10, IFN-γ, and Foxp3 in the spleen, which is the central tissue of immune response, was significantly decreased. Simultaneous administration of these new synbiotics and rosmarinic acid was shown to effectively alleviate symptoms of hay fever.

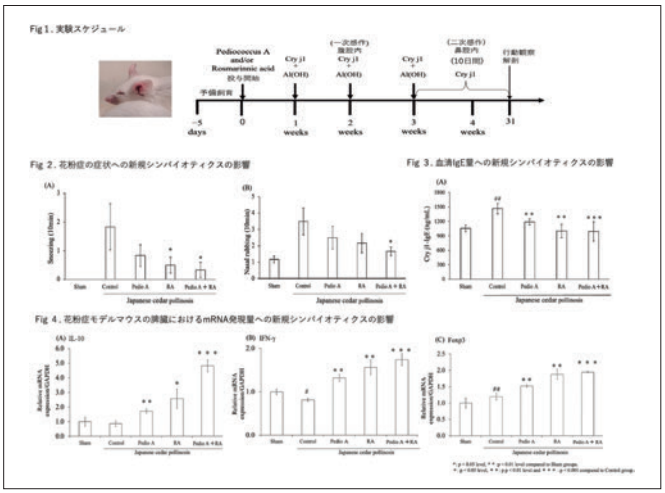


Figure 2

Teaching Staff

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Specially Appointed Assistant Professor
Keiko TADA, Ph.D.

Staff

Professor ····· Tadaaki MIYAZAKI, Ph.D.
Professor ····· Koichi SATO
Specially Appointed Assistant Professor ····· Keiko TADA, Ph.D.

[Patent application]

Composition of lactic acid bacteria and daidzein effective against allergies that suppresses the mRNA expression level of IgE receptor α (Invention notification number: P2023-078)

Allergy suppressant containing lactic acid bacterium *Pediococcus sp. KB1* and rosmarinic acid as active ingredients (invention notification number: P2024-117)

Selection of lactic acid bacteria for the development of Femtech products

We selected lactic acid bacteria that have a high ability to efficiently convert isoflavone glycosides in soybean foods into aglycones in the human body in order to alleviate symptoms peculiar to women such as depression, irritability, and anxiety caused by hormonal imbalance. In order to confirm the aglyconization ability of each lactic acid bacteria in soy milk products, daidzein, genistein, daidzin, and genistin were quantified, and freeze-dried samples of methanol-extracted soy milk and soy milk fermentation liquid were subjected to LC-MS/MS. As a result of comparing the concentrations of daidzein and genistein, the daidzein concentration increased by lactic acid bacteria strain A was average 23.2 times higher than that of soy milk, and the genistein concentration increased by 31.8 times, and when the three lactic acid bacteria strains were compared, the daidzein concentration was increased the most by lactic acid bacteria strain A. By lactic acid bacteria strain B, the concentration of daidzein was 10.0 times higher and that of genistein was 11.4 times higher than that in soy milk, and by the lactic acid bacteria strain C, daidzein was 2.04 times higher and genistein was 2.53 times higher. This is presumed that lactic acid bacteria assimilated daidzin and genistin in soymilk, resulting in an increase of the aglycone concentration after fermentation, and it was revealed that lactic acid bacteria strain A had the strongest aglycone production ability.

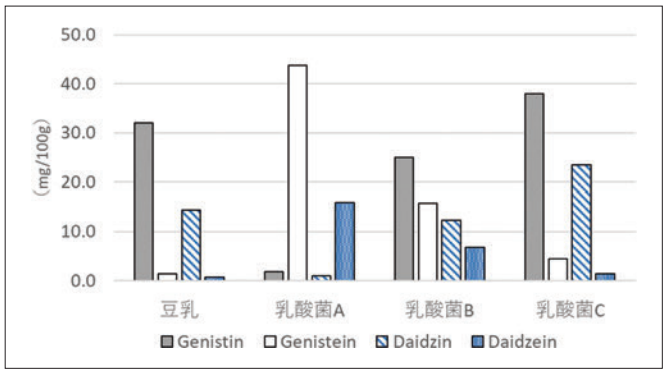

Figure 3

Selected Paper (2022.6-2024.9)

1. Kazunobu Baba, Akina Oomori, Tadaaki Miyazaki, Preventive effect of Enterococcus faecalis and β-glucan on the onset and exacerbation of symptoms of atopic dermatitis in mice. Allergy and Immunology 2023, Volume 7, Issue 3: 183-194. Doi: 10.3934/Allergy.2023013

2. Tadaaki Miyazaki, Koichi Sato, Takashi Shimada, Jun Nishihira, Shigetaka Kurimoto, Toyoyo Katsuyama, Clinical study to verify the effects of Ganoderma lucidum to activate NK cell -A placebo-controlled, randomized, double-blind, parallel-group comparative study-. Japanese Pharmacology and Therapeutics, Vol.50, Issue 4, 535-550, 2022

3. Tadaaki Miyazaki, Prevention and treatment of infectious diseases and cancer through regulating the immune system by β-glucan Jpn J Med Pharm Sci Vol. 80, 6, 631-633, 2023

Attached Facility | Laboratory of Animal Experimentation

Director (Professor) **Kenichiro SEINO, M.D., Ph.D.**

Research Project

Promotion of humane care and use of experimental animals in high-quality research Studies on the viral pathogenesis

Outline

This laboratory was established in April 2000 as a shared facility of the Institute for Genetic Medicine, with the aim of conducting animal experiments with high accuracy and reproducibility. Its predecessor was the Laboratory of Animal Experimentation of Institute of Immunological Science which was established in 1976. In April 2008, a completely renovated facility was opened, and service of reproductive technology has started. All animal experiments conducted at this facility must be properly conducted from the viewpoint of scientific and animal welfare according to the National University Corporation Hokkaido University Provisions on Animal Experiments. Currently, inbred and genetically engineered mice are used in the facility. In addition to a general animal room, the facility has a BSL3/ABSL3 room, anti-cancer drug use laboratory, a laboratory for reproductive technology for mice, a quarantine room, etc. Furthermore, as devices registered in the Hokkaido University Open Facility, we have a non-invasive High-sensitivity in vivo imaging of fluorescence and bioluminescence system (IVIS Spectrum), an X-ray CT scanner for small animals, and an X-ray irradiation device.

Contents and Result

Promotion of humane care and use of experimental animals in high-quality research

To conduct high-quality animal experiments, following facilities were installed.

Microbiological control of laboratory animals is an important issue for safe and appropriate animal experimentations. Our ultimate goal is to elucidate how infection with an infectious disease manifests pathogenicity in vivo and leads to pathological conditions such as lethal hemorrhagic fever and carcinogenesis. For this purpose, we have been conducting research on highly pathogenic viruses, such as COVID-19, hantavirus, and severe fever with thrombocytopenia syndrome virus, in our BSL3 facility.

(1) We reported pathogenic changes of novel mutant strains of COVID-19 using a hamster model.

(2) To clarify the current situation of hantavirus infection in Sri Lanka, we developed a diagnostic method suitable for the endemic virus, conducted an epidemiological survey, and showed that hantavirus infection is a risk for the development of chronic kidney disease of unknown cause, which is a national problem in Sri Lanka.

(3) We developed and reported a mouse model of hemorrhagic fever with renal syndrome (HFRS) caused by hantavirus. In general, infectious diseases carried by rodent hosts can be tolerated asymptomatically and without symptoms in laboratory mice. However, by intravenously administering KHFV5 which is a virus strain isolated from the blood of an HFRS case, they succeeded in reproducing the hepatitis and hemorrhage in the kidney medulla that are characteristic of HFRS cases. It is believed that the symptoms were reproduced by artificially inducing viremia with a high titer of hantavirus. A comparison was also made with the KHF4 strain, which does not exhibit kidney hemorrhage with single mutation near the transmembrane region involved in cell entry, and that the highly virulent strain had high viral load in the lungs at the early stage of infection. It was suggested that the CTLs ultimately induced may not be directed toward eliminating the virus, but rather may be leading to increased inflammation and bleeding, and this model is believed to be useful for developing treatments and evaluating vaccines.

http://www.igm.hokudai.ac.jp/lae/index-j.html

Fig. 1. Equipment in the facility 1

A: Air conditioning systems. B: Double-door barrier autoclaves. C: SPF animal room. D: Biosafety level 3 room (BSL3/ABSL3) for animals experimentally infected with highly virulent microbes.

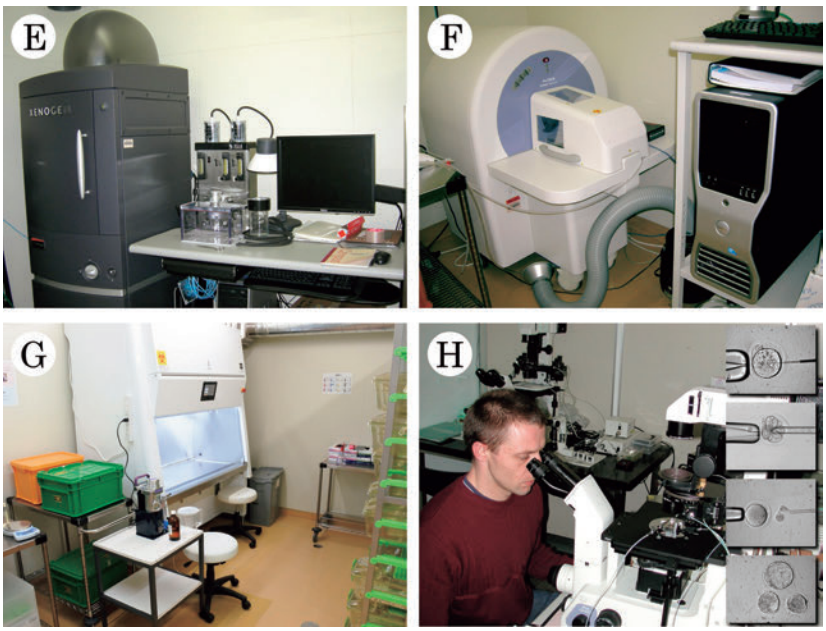

Fig. 2. Equipment in the facility 2

E: IVIS® Imaging Systems. F: X-ray μCT. G: Anti-cancer drug use room. H: Germ cell manipulation room for generate genetically engineered mice.

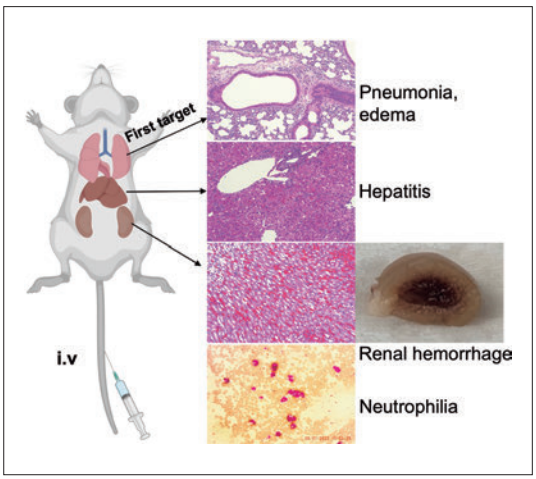

Fig. 3. Establishment of hemorrhagic fever with renal syndrome model

Teaching Staff

Associate Professor
Kumiko YOSHIMATSU, D.V.M., Ph.D.

Staff

Director (Professor) ····· Kenichiro SEINO, M.D., Ph.D.
Associate Professor ····· Kumiko YOSHIMATSU, D.V.M., Ph.D.

Selected Paper (2022.6-2024.9)

1. Tamura T, Irie T, Deguchi S, Yajima H, Tsuda M, Nasser H, Mizuma K, Plianchaisuk A, Suzuki S, Uriu K, Begum MM, Shimizu R, Jonathan M, Suzuki R, Kondo T, Ito H, Kamiyama A, Yoshimatsu K, Shofa M, Hashimoto R, Anraku Y, Kimura KT, Kita S, Sasaki J, Sasaki-Tabata K, Maenaka K, Nao N, Wang L, Oda Y, Genotype to Phenotype Japan C, Ikeda T, Saito A, Matsuno K, Ito J, Tanaka S, Sato K, Hashiguchi T, Takayama K, Fukuhara T. Virological characteristics of the SARS-CoV-2 Omicron XBB.1.5 variant. Nat Commun. 2024; 15(1): 1176. Epub 20240208. February 2024

2. Gamage CD, Nanayakkara S, Sarathkumara YD, Muthusinghe DS, Shimizu K, Arikawa J, Lokupathirage SMW, Nanayakkara N, Gunarathne L, Chandrajith R, Harada KH, Koizumi A, Yoshimatsu K. Hantavirus infection as a risk factor for chronic kidney disease of unknown aetiology (CKDu) and its prevalence in endemic areas of Sri Lanka since 2010 according to a retrospective serological analysis. J Med Microbiol. 2022; 71(12). December 2022

3. Wei Z, Shimizu K, Nishigami K, Tsuda Y, Sarathukumara Y, Muthusinghe DS, Gamage CD, Granathne L, Lokupathirage SMW, Nanayakkara N, Arikawa J, Kikuchi F, Tanaka-Taya K, Suzuki M, Morikawa S, Arai S, Yoshimatsu K. Pathological Studies on Hantaan Virus-Infected Mice Simulating Severe Hemorrhagic Fever with Renal Syndrome. Viruses. 2022; 14(10). Epub 20221013. Octorber 2022

Attached Facility

Center for Infectious Cancer Research (CICR)

PI, Professor **Masahiro SONOSHITA, Ph.D.**

Research Project

(1) Joint Usage/Collaborative Research Management and Supporting
(2) Research related to Infectious Cancers

Outline

The Institute for Genetic Medicine (IGM), Hokkaido University, was named "The Core Research Institute of Excellence for Advanced Research on Infectious Cancer Caused by Persistent Infection of Bacteria and Viruses" by MEXT in 2012. Part of the IGM's mandate is to promote collaboration on cancer-related infections, including funding for travel and research expenses. The Center for Infectious Cancer Research (CICR) was established to support the IGM and performs its own research on cancer-related infections. The CICR has two aims: (A) to manage joint usage/collaborative research projects and symposia at the IGM, and (B) to elucidate the mechanisms of cancer development and malignant transformation caused by infection and to establish new treatments and preventative methods. Details of its activities are as follows.

(I) Management of joint usage/collaborative research projects and symposia: Joint research projects are the core of IGM activities and are of two types: (i) general joint research projects, in which researchers visit from out side of IGM and carry out research using the CICR's advanced research equipment; and (ii) early period of joint research projects, in which researchers located out side of IGM apply for expenses to send research materials and preliminary data. For these joint research projects, the CICR has available a LSM980 super-resolution confocal microscope, Ultramicroscope II sheet-type microscope, Keyence fluorescence microscope, multiplex CODEX spatial analysis system, next-generation sequencer, BD Rhapsody single-cell analysis system, SeqGeq single-cell RNA seq analysis software, a laser microdissecter, and Strand NGS RNA seq data analysis software. In addition, the CICR supports research meetings, symposia, etc. Regarding joint research symposia, the CICR organizes them every year including and pays for the travel and accommodation expenses of the speakers. It also organizes the IGM-sponsored Infectious Cancer Research Symposium, which consists of special lectures by leading researchers.

(II) Support for the operation of liaison laboratories: From 2017, the CICR has established five virtual laboratories, called 'liaison laboratories', which study the four stages of infection-induced cancer: pathogen infection, carcinogenesis, immune response and inflammation induction, as well as develop new technologies for curing the infectious cancers. The heads of each lab are IGM scientists: Professor Akinori Takaoka (pathogen infection), Professor Toru Kondo (carcinogenesis), Professor Kenichiro. Seino (immune response), Professor Masaaki Murakami (inflammation induction), and Professor Kenichi Noma (new technology development). With regard to the development of new technologies, a next-generation sequencer was introduced in 2020, and the genome analysis room GATCHA was established in 2024 to carry out genome analysis and gene expression analysis as a commissioned business in the future.

(III) Support for young researchers: IGM provides travel support to young researchers for overseas conferences on infectious cancer through donations from its former director, Ichiro Azuma, and also manages the operation of the Hokkaido University Interdepartmental Symposium. The CICR manages both of these initiatives.

(IV) The CICR assists public health laboratories in IGM that carry out PCR testing for SARS-CoV-2 through the provision of funding and staff.

(V) Research on infectious cancer and related research: The main members of the CICR are Specially Appointed Professor Masanori Hatakeyama, Professor Koji Moriishi

https://www.igm.hokudai.ac.jp/vec/

and Associate Professor Naoko Kamiya, who are all investigating infectious cancer. In addition, the CICR is conducting research projects on cervical cancer in collaboration with the Department of Obstetrics and Gynecology at Hokkaido University Hospital and cytokine storm research on SARS-CoV-2.

Contents and Result

Gene expression analysis of human papillomavirus (HPV) infectious cancers to identify preventive and therapeutic targets

According to the World Health Organization, about 570,000 people worldwide were diagnosed with cervical cancer in 2018, of which about 310,000 died. Moreover, about 99% of cervical cancer is an infectious cancer caused by high-risk HPV. There is a vaccine for high-risk HPV. It has been reported that infection with high-risk HPV has been suppressed and the incidence of cervical cancer has decreased worldwide by the vaccination. In Japan, however, the vaccination rate is low due to the problem of adverse reactions, thus the incidence of cervical cancer caused by HPV infection has not been suppressed. Furthermore, in addition to the vaccination coverage problem, high malignancy, poor response to treatment, and poor prognosis are clinical problems in Japan.

The histological type is one of the factors involved in the grade of cervical cancer and the choice of treatment, but differential diagnosis is difficult in some cases due to the lack of diagnostic markers. This project is joint research with the Department of Obstetrics and Gynecology, Graduate School of Medicine, Hokkaido University, and Department of Surgical Pathology, Hokkaido University Hospital. We are analyzing gene expression profiles of cervical cancer specimens by RNA sequencing to identify diagnostic and prognostic markers and therapeutic targets for HPV-positive cervical cancer. We have analyzed 18 biopsy specimens and 10 pathology specimens already and extracted highly expressed genes as candidate diagnostic markers in each tissue type.

We will evaluate the usefulness of these candidate factors as diagnostic markers by immunostaining cancer tissues. In addition, the correlation between gene expression profiles, histological type, cancer stage, response to treatment, and prognosis will be analyzed.

A cluster analysis showed gene expressions tended to form clusters in a tissue type-dependent manner most likely via HPV infection. Squamous cell carcinoma, the most common histological type of cervical cancer, was classified into two different clusters, showing a tendency to be associated with prognosis of the degree of its malignancy (Figure 1).

In the future, the number of specimens will be increased, and a correlation analysis with clinical information will be conducted.

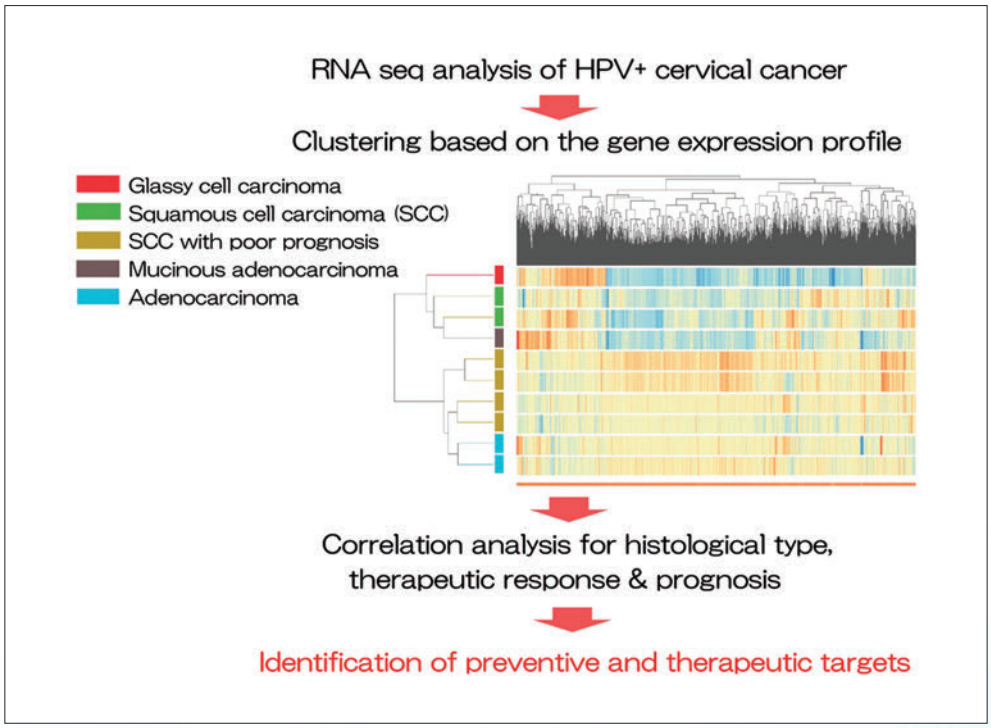

Fig. 1. Transcriptome analysis of HPV+ cervical cancer for identification of preventive and therapeutic targets

Research on the mechanism of gastric carcinogenesis by *H. pylori*.

H. pylori is a Gram-negative rod that lives in the gastric mucosa of humans. It has been estimated that about half of the world's total population is infected with it. *H. pylori* can be divided into two strains: those that carry the *cagA* gene and those that do not, and chronic infection with *cagA*-positive *H. pylori* is a known risk factor for gastric cancer. Gastric cancer is the fourth leading cause of site-specific cancer mortality worldwide, with a particularly high incidence in East Asia including Japan. Genetic factors are also risk factors for gastric cancer, but no risk assessment of gastric cancer that integrates *H. pylori* infection and genetic factors has been studied. We performed the world's largest genomic analysis of Japanese gastric cancer patients and non-cancer controls. The results revealed that nine genes, including the *BRCA1* and *BRCA2* genes, which are known to be associated with hereditary breast, ovarian cancer and other risks, are associated with gastric cancer risk. Furthermore, an integrated analysis of pathological variants of these nine gastric cancer-related genes and *H. pylori* infection revealed that the risk of gastric cancer is significantly increased when the carrier of pathological variants of a group of genes involved in homologous recombination repair (*ATM, BRCA1, BRCA2, PALB2*) is also infected with *H. pylori* (Figure 2).

Additionally, we showed that the effect of gastric cancer prevention by eradication of *H. pylori* is more pronounced in carriers of pathological variants of the gene cluster involved in homologous recombination repair. The results of this study are expected to contribute to the construction of genomic medicine for gastric cancer, including the improvement of gastric cancer diagnosis, the development of treatment methods targeting causative genes, and more appropriate preventive measures against gastric cancer.

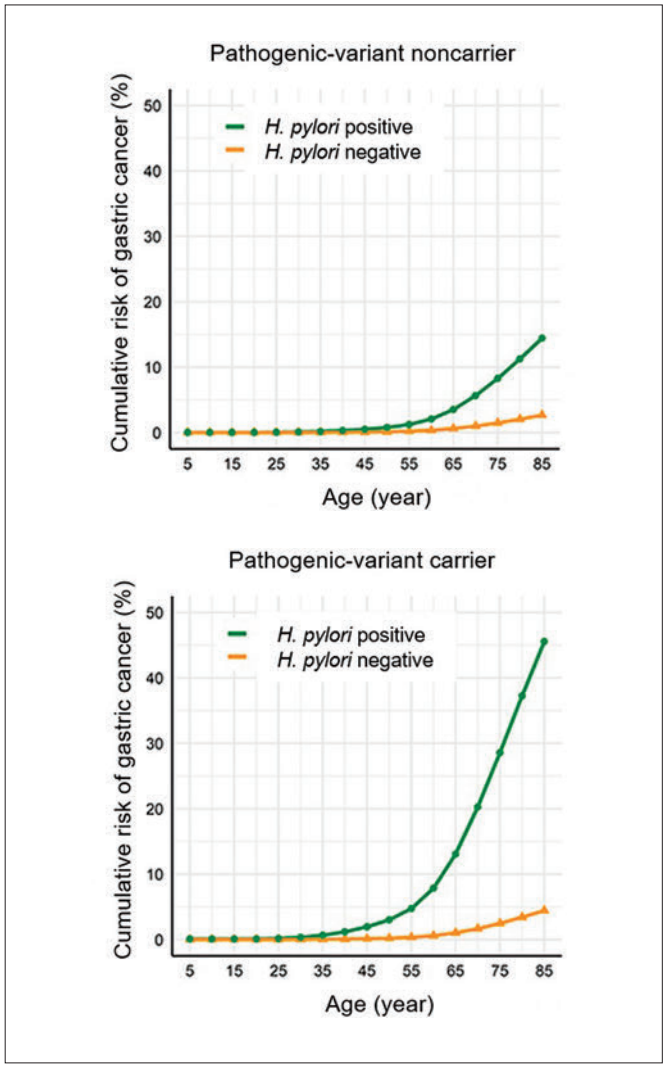

Fig. 2. Cumulative risk of gastric cancer according to pathogenic-variant carrier status

Teaching Staff

Professor
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Professor
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Professor
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Associate Professor
Naoko KAMIYA, Ph.D.

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PI, Professor	Masahiro SONOSHITA, Ph.D.
Professor	Masanori HATAKEYAMA, M.D., Ph.D.
Professor	Masaaki MURAKAMI, D.V.M., Ph.D.
Professor	Kohji MORIISHI, D.V.M., Ph.D.
Associate Professor	Naoko KAMIYA, Ph.D.
Associate Professor	Kumiko YOSHIMATSU, D.V.M., Ph.D.

Selected Paper (2022.6-2024.9)

1. *Helicobacter pylori*, Homologous-Recombination Genes, and Gastric Cancer.
Usui, Y., Taniyama, Y., Endo, M., Koyanagi, Y.N., Kasugai, Y., Oze, I., Ito, H., Imoto, I., Tanaka, T., Tajika, M., Niwa, Y., Iwasaki, Y., Aoi, T., Hakozaki, N., Takata, S., Suzuki, K., Terao, C., Hatakeyama, M., Hirata, M., Sugano, K., Yoshida, T., Kamatani, Y., Nakagawa, H., Matsuda, K., Murakami, Y., Spurdle, AB., Matsuo, K., Momozawa, Y.
New Eng. J. Med. 388(13): 1181-1190 (2023)

2. Diet-mediated constitutive induction of novel IL-4+ ILC2 cells maintains intestinal homeostasis in mice.
Cui, W., Nagano, Y., Morita, S., Tanoue, T., Yamane, Ishikawa, K., Sato, T., H., Kubo, M., Hori, S., Taniguchi, T., Hatakeyama, M., Atarashi, K. and Honda, K.
J. Exp. Med. 2(5): 684-700 (2023)

3. The *Helicobacter pylori* CagA oncoprotein disrupts Wnt/PCP signaling and promotes hyperproliferation of pyloric gland base cells.
Takahashi-Kanemitsu, A., Lu, M., Knight, C.T., Yamamoto, T., Hayashi, T., Mii, Y., Ooki, T., Kikuchi, I., Kikuchi, A., Barker, N., Susaki, E.A., Taira, M., Hatakeyama, M.
Sci. Signal. 16(794): eabp9020 (2023)

Education Activities

Academic staffs of Institute for Genetic Medicine, Hokkaido University are in charge of education for Graduate School of Medicine, Graduate School of Science, Graduate School of Chemical Sciences and Engineering, Graduate School of Life Science or Graduate School of Infectious Diseases. Students can take Master Course and Doctor Course of Graduate School of Medicine, Doctor Course of Graduate School of Science, Master Course and Doctor Course of Graduate School of Chemical Sciences and Engineering, Master Course and Doctor Course of Graduate School of Life Science and Doctoral Course of Graduate School of Infectious Diseases.

Data as of FY2024

Course Title	Degree Program	Instructor
Basic Principles of Medicine Stem Cell Biology	M	KONDO Toru, SON Youlee, OIKAWA Naoto
Principles of Medicine Stem Cell Biology	D	KONDO Toru, SON Youlee, OIKAWA Naoto
Master's Thesis Research in Medical Sciences Department of Stem Cell Biology	M	KONDO Toru, SON Youlee, OIKAWA Naoto
Dissertation Research in Medical Sciences Department of Stem Cell Biology	D	KONDO Toru, SON Youlee, OIKAWA Naoto
Basic Principles of Medicine Molecular Neuroimmunology	M	MURAKAMI Masaaki, HOJYO Shintaro, HASHIMOTO Shigeru
Principles of Medicine Molecular Neuroimmunology	D	MURAKAMI Masaaki, HOJYO Shintaro, HASHIMOTO Shigeru
Master's Thesis Research in Medical Sciences Department of Molecular Neuroimmunology	M	MURAKAMI Masaaki, HOJYO Shintaro, HASHIMOTO Shigeru
Dissertation Research in Medical Sciences Department of Molecular Neuroimmunology	D	MURAKAMI Masaaki, HOJYO Shintaro, HASHIMOTO Shigeru
Basic Principles of Medicine Biomedical Oncology	M	SONOSHITA Masahiro, OSHIO Takako, YAMAMURA Ryodai
Principles of Medicine Biomedical Oncology	D	SONOSHITA Masahiro, OSHIO Takako, YAMAMURA Ryodai
Master's Thesis Research in Medical Sciences Department of Biomedical Oncology	M	SONOSHITA Masahiro, OSHIO Takako, YAMAMURA Ryodai
Dissertation Research in Medical Sciences Department of Biomedical Oncology	D	SONOSHITA Masahiro, OSHIO Takako, YAMAMURA Ryodai
Basic Principles of Medicine Immunobiology	M	SEINO Kenichiro, WADA Haruka, MORI Akihiro
Principles of Medicine Immunobiology	D	SEINO Kenichiro, WADA Haruka, MORI Akihiro
Master's Thesis Research in Medical Sciences Department of Immunobiology	M	SEINO Kenichiro, WADA Haruka, MORI Akihiro
Dissertation Research in Medical Sciences Department of Immunobiology	D	SEINO Kenichiro, WADA Haruka, MORI Akihiro
Basic Principles of Medicine Biological Molecular Mechanisms	M	NODA Nobuo, FUJIOKA Yuko, NOSHIRO Daisuke
Principles of Medicine Biological Molecular Mechanisms	D	NODA Nobuo, FUJIOKA Yuko, NOSHIRO Daisuke
Master's Thesis Research in Medical Sciences Department of Biological Molecular Mechanisms	M	NODA Nobuo, FUJIOKA Yuko, NOSHIRO Daisuke
Dissertation Research in Medical Sciences Department of Biological Molecular Mechanisms	D	NODA Nobuo, FUJIOKA Yuko, NOSHIRO Daisuke
Pharmaceutical Science	M	OHTA Shinya, OKAZAKI Tomohiko, KAMIYA Naoko
Advanced Lecture on Zoonosis Control	D	YOSHIMATSU Kumiko
Advanced and Comprehensive Studies on Zoonosis Control	D	YOSHIMATSU Kumiko
Research Ethics Seminar	D	YOSHIMATSU Kumiko
Biochemistry A (II)	M	MOTEGI Fumio, TAKAOKA Akinori
Introduction to Basic Biological Chemistry	M	MOTEGI Fumio, TAKAOKA Akinori
Modern Trends in Chemical Sciences and Engineering II (Introduction to Basic Biological Chemistry)	D	MOTEGI Fumio, TAKAOKA Akinori
Research in Life Science	M	OKAZAKI Tomohiko
Seminar in Life Science I	M	OKAZAKI Tomohiko
Seminar in Life Science II	M	OKAZAKI Tomohiko
Laboratory Exercises in Life Science	M	OKAZAKI Tomohiko

Campus Map of Hokkaido University

Map of Sapporo Campus

University Organization

- 1 Administration Bureau
- 2 Office of Diversity, Equity, and Inclusion
- 3 Hokkaido University Hospital
- 4 Dental Clinical Division of Hokkaido University Hospital
- 5 Office of Admissions
- 6 Institute for the Advancement of Higher Education
- 7 Institute for the Advancement of Graduate Education

Graduate Schools, Faculties and Schools

- 1 Graduate School of Humanities and Human Sciences
- 2 Graduate School of Law
- 3 Graduate School of Economics and Business
- 4 Graduate School of Education
- 5 Graduate School of International Media, Communication, and Tourism Studies
- 6 Graduate School of Public Policy
- 7 Graduate School of Medicine
- 8 Graduate School of Biomedical Science and Engineering
- 9 Graduate School of Dental Medicine
- 10 Graduate School of Veterinary Medicine
- 11 Graduate School of Infectious Diseases
- 12 Graduate School of Health Sciences
- 13 Graduate School of Information Science and Technology
- 14 Graduate School of Environmental Science
- 15 Graduate School of Science
- 16 Graduate School of Agriculture
- 17 Graduate School of Global Food Resources
- 18 Graduate School of Life Science
- 19 Graduate School of Engineering
- 20 Graduate School of Chemical Sciences and Engineering
- 21 Faculty of Pharmaceutical Sciences
- 22 Faculty of Advanced Life Science

Note: The Graduate School of Fisheries Sciences is located at Hakodate Campus

Research Institutes & Centers

- 1 Center for Ainu and Indigenous Studies
- 2 Hokkaido University Press
- 3 Hokkaido University Archives
- 4 Slavic–Eurasian Research Center
- 5 Center for Experimental Research in Social Sciences
- 6 Information Initiative Center North/South Bldgs.
- 7 Archaeological Research Center
- 8 Center for Environmental and Health Sciences
- 9 Field Science Center for Northern Biosphere
- 10 Research Center for Integrated Quantum Electronics
- 11 Proton Beam Therapy Center
- 12 Research and Education Center for Brain Science
- 13 Institute for Genetic Medicine
- 14 Central Institute of Isotope Science
- 15 Frontier Research in Applied Sciences Bldg.
- 16 Center for Language Learning
- 17 Center for Advanced Tourism Studies
- 18 The Open University of Japan; Hokkaido Study Center
- 19 Health Care Center
- 20 Education and Research Center for Mathematical and Data Science
- 21 Center for Natural Hazards Research
- 22 Center for Human Nature, Artificial Intelligence, and Neuroscience (CHAIN)
- 23 Center for Advanced Human Resource Education and Development, Institute for the Advancement of Graduate Education

Research Institutes/Centers (North Campus Area)

- 1 Creative Research Institution (CRIS)
- 2 Institute for the Promotion of Business-Regional Collaboration (Center for Innovation and Business Promotion, Startup Creation Department, University-Industry Global Development Office)
- 3 Hokkaido Collaboration Center
- 4 Social and Regional Emergence Department, Institute for the Promotion of Business-Regional Collaboration
- 5 Platform for Research on Biofunctional Molecules (PRBM)
- 6 Frontier Research Center for Advanced Material and Life Science
- 7 Arctic Research Center
- 8 Institute for Catalysis
- 9 Research Institute for Electronic Science
- 10 Green Nanotechnology Research Center
- 11 Research Center of Mathematics for Social Creativity
- 12 International Institute for Zoonosis Control
- 13 Institute of Low Temperature Science
- 14 Veterinary Teaching Hospital
- 15 Institute for Vaccine Research and Development (IVReD)
- 16 Institute for Chemical Reaction Design and Discovery (WPI-ICReDD)

Facilities

- 1 Conference Hall
- 2 Clark Memorial Student Center
- 3 Career Center
- 4 Centennial Hall
- 5 Furukawa Hall
- 6 Humanities and Social Sciences Classroom Building
- 7 "Kodomo No Sono" Child Care Center
- 8 Open Innovation Hub "ENREISO"
- 9 Experiment Farm
- 10 Student Services
- 11 Multimedia Education Building
- 12 Gym
- 13 Enyu Gakusha Community Hall
- 14 Sports Training Center
- 15 "Tomoni" Child Care Center
- 16 Student Communication Station
- 17 School of Medicine Centennial Hall

Libraries

- 1 Central Library
- 2 North Library

Dorms

- 1 Hokkaido University International House Kita 8 (Kita 8 Nishi 11)
- 2 Keiteki-Ryo Student Dormitory (Kita 18 Nishi 13)
- 3 Hokkaido University International House Kita 23 (Kita 23 Nishi 13)
- 4 Foreign Scholars' Accommodation (Kita 24 Nishi 12)

Tourist Spots

- 1 Sakushukotoni River
- 2 Central Lawn
- 3 Bust of Dr. William S. Clark
- 4 Elm Grove
- 5 Former School of Agriculture Library
- 6 The Hokkaido University Museum
- 7 Monument to First Artificial Snow Crystal
- 8 Ono Pond
- 9 Monument in Honor of Dr. Inazo Nitobe
- 10 Flowering Tree Garden
- 11 Poplar Avenue
- 12 Gingko Avenue
- 13 Heisei Poplar Avenue
- 14 Site of Old Village
- 15 The Second Farm (Model Barn)
- 16 Botanic Garden

Cafeterias/Restaurants/Stores

- 1 Information Center "Elm Forest Shop"
- 1 Hokkaido University (HU) Co-op
- 2 Clark Cafeteria
- 3 Chuo Cafeteria, HU Co-op
- 4 Seicomart
- 5 Restaurant NORTH KITCHEN
- 6 Hokubu Cafeteria, HU Co-op
- 7 Restaurant Poplar
- 8 Hokudai Marche Café and Labo
- 9 7-Eleven, Hokkaido University School of Engineering store

Information Center "Elm Forest Shop"

The University Information Center is located just inside the main gates of Sapporo Campus. Visitors can browse information regarding campus events as well as enjoy refreshments on the outdoor patio. The Center also carries original Hokkaido University merchandise.

Opening hours:
8:30–17:00

Closed:
December 29–January 3

Institute for Genetic Medicine, Hokaido University 2024-2025

December 2024

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URL : https://www.igm.hokudai.ac.jp/

Institute for Genetic Medicine, Hokkaido University

HOKKAIDO UNIVERSITY
Institute for Genetic Medicine
2024-2025