

2021 - 2022
Graduate School of Biostudies, Kyoto University
Master's Program in "Global Frontier in Life Science"
Guidelines for International Student Admissions

Philosophy and Admission Policy of the Graduate School of Biostudies

As an advanced discipline that holds the key to the future of humankind, the life sciences today are undergoing a major evolutionary change. In response to this global trend, the Graduate School of Biostudies was founded in 1999 as Japan's first independent graduate school focused on the life sciences with the objective of building a world-class center for research and developing individuals who can lead the life sciences field into the next generation. Our school has engineered a true fusion of cutting-edge areas in several existing fields. By harnessing the common language of "cells, molecules, and genes" that together form the fundamental principles of life, we have developed an integrated understanding of diverse life forms and the environments they help shape, and have launched innovative efforts in research and education that will produce a new set of values for the future and dignity of life.

To meet the diverse expectations of society for advances in the life sciences, which are becoming increasingly sophisticated and complex, our school seeks students from a broad spectrum of backgrounds who share these ideals of our school, who possess basic academic skills and research aptitudes in the life sciences, and who demonstrate a strong sense of ethics and responsibility in their academic research. We especially welcome students who possess a pioneering spirit to help propel the comprehensive and advanced branches of the life sciences, free from preconceptions, while fully appreciating the dignity of life. Accordingly, the Graduate School of Biostudies endeavors to cultivate individuals with the following attributes:

1. Researchers ready to discover, or to shed fresh light on, fundamental principles of life, who will pioneer new areas of the life sciences;
2. Researchers and engineers committed to global environmental conservation and gains in human health, welfare, and well-being, who are ready to make social contributions through roles in public and private research institutions;
3. Educators and working professionals with a broad-based understanding of the varied phenomena of life in general, who are ready to make social contributions through roles in education, industry, the news media, and government;
4. Researchers, educators, engineers, and working professionals who possess strong communication skills that enable them to hold discussions with researchers and others from Japan and around the world in life science-related fields.

The entrance exam will comprise achievement tests that include a written exam to evaluate the applicant's ability to think logically in English, a skill that is required to read and analyze an article published in an international journal; a written exam to assess the applicant's general knowledge of molecular biology, cell biology, biochemistry, and other life science fields; a written exam to assess the applicant's fundamental knowledge as required to pursue his or her intended field of study; and an oral exam to assess the applicant's judgement, thinking ability, communication skills, initiative, and ethical perspective. Admissions decisions will be made based on the applicant's overall performance on these exams.

Please note that applicants are NOT required to be physically present in Japan for the examination.

The academic year starts on October 1, 2021 or April 1, 2022.

I. “Global Frontier in Life Science”

The Graduate School of Biostudies launched “Global Frontier in Life Science”, an educational program for Doctoral and Master’s students, as a part of K.U. PROFILE (Kyoto University Programs for Future International Leaders: <http://www.opir.kyoto-u.ac.jp/kuprofile/e/index.html>). This program, “Global Frontier in Life Science”, is held entirely in English, including the entrance examinations, lectures, experiments, and discussions. Up to ten applicants will be accepted.

II. Division/Laboratories and Enrollment

The Graduate School of Biostudies consists of two divisions, which are made up of 41 laboratories. Details of each laboratory are described on pp. 11-32 of these guidelines and the Graduate School of Biostudies website (<http://www.lif.kyoto-u.ac.jp/>). Applicants can apply for up to two laboratories. **Thus, applicants must contact the lab heads and fully discuss potential research activities and availability before filing the application.**

III-1. Eligibility Requirements for Applicants expecting to start from October 1, 2021

Applicants must match one of the following requirements by September 30, 2021:

1. Individuals with any nationality who have completed (or are expected to complete by September 30, 2021) 16 years of education in foreign countries. This includes individuals who have completed an equivalent of 16 years of education but have less than 16 years due to skipped (advanced) grades.
2. Individuals, other than Japanese nationals, who graduated (or are expected to graduate by September 30, 2021) from a Japanese university.
3. Individuals who have received (or are expected to receive by September 30, 2021), a degree equivalent to a bachelor’s degree by completing a curriculum with a term of enrollment of at least three years (including completion of such a curriculum by studying relevant subjects in Japan via a correspondence course provided by a school in a foreign country and completion of a curriculum at an educational facility that has been accredited as having an approved curriculum under the educational system of said country and is designated by the Minister of Education, Culture, Sports, Science and Technology) at a university or other school in a country other than Japan (only those universities or schools for which the overall conditions of education and research activities have been assessed by a party authorized by the government of said country or an organization concerned, or those corresponding to such entities as designated by the Minister of Education, Culture, Sports, Science and Technology).
4. Individuals, other than Japanese nationals, who are recognized by the Graduate School of Biostudies to have completed an education equivalent to a university degree of Japan and are at least 22 years old by September 30, 2021).
5. Individuals with Japanese nationality who are determined by the Graduate School of Biostudies to have completed an education in foreign countries equivalent to a university degree of Japan or had school education that were mainly given in English, and are at least 22 years old by September 30, 2021).
6. Individuals, other than Japanese nationals, who will be enrolled at least 3 years in a Japanese university by September 30, 2021 and are recognized by the Graduate School of Biostudies as having acquired sufficient credits with excellent academic records.

Those who are applying under requirement 4, 5 or 6 must undergo a preliminary eligibility screening process before applying.

III-2. Eligibility Requirements for Applicants expecting to start from April 1, 2022

Applicants must match one of the following requirements by March 31, 2022:

1. Individuals with any nationality who have completed (or are expected to complete by March 31, 2022) 16 years of education in foreign countries. This includes individuals who have completed an equivalent of 16 years of education but have less than 16 years due to skipped (advanced) grades.
2. Individuals, other than Japanese nationals, who graduated (or are expected to graduate by March 31, 2022) from a Japanese university.
3. Individuals who have received (or are expected to receive by March 31, 2022) a degree equivalent to a bachelor's degree by completing a curriculum with a term of enrollment of at least three years (including completion of such a curriculum by studying relevant subjects in Japan via a correspondence course provided by a school in a foreign country and completion of a curriculum at an educational facility that has been accredited as having an approved curriculum under the educational system of said country and is designated by the Minister of Education, Culture, Sports, Science and Technology) at a university or other school in a country other than Japan (only those universities or schools for which the overall conditions of education and research activities have been assessed by a party authorized by the government of said country or an organization concerned, or those corresponding to such entities as designated by the Minister of Education, Culture, Sports, Science and Technology).
4. Individuals, other than Japanese nationals, who are recognized by the Graduate School of Biostudies to have completed an education equivalent to a university degree of Japan and are at least 22 years old by March 31, 2022.
5. Individuals with Japanese nationality who are determined by the Graduate School of Biostudies to have completed an education in foreign countries equivalent to a university degree of Japan or had school education that were mainly given in English, and are at least 22 years old by March 31, 2022.
6. Individuals, other than Japanese nationals, who will be enrolled at least 3 years in a Japanese university by March 31, 2022 and are recognized by the Graduate School of Biostudies as having acquired sufficient credits with excellent academic records.

Those who are applying under requirement 4, 5 or 6 must undergo a preliminary eligibility screening process before applying.

IV. Eligibility Screening

Applicants filing under eligibility requirement 4, 5 or 6 above are required to contact the Student Affairs Section (Kyomu gakari) of the Graduate School of Biostudies to request that the designated application form for preliminary eligibility screening to be sent at any time, but no later than December 9 (Wed), 2020. Submit the following preliminary eligibility screening documents via email to the Student Affairs Section of the Graduate School of Biostudies (150kyomu@adm.lif.kyoto-u.ac.jp) by JST 5:00 p.m., November 19 (Thu), 2020 at latest. When filing the admission application, applicants cannot in principle apply for any laboratory other than the one or two specified in the documents being submitted for the eligibility screening.

The screening results will be sent by e-mail to the applicants as soon as the decision is made, at latest on December 10 (Thu), 2020.

1. Documents for the Eligibility Screening

When filing under eligibility requirement 4 or 5

(1) Application form for the eligibility screening (designated form)	This form is provided upon request.
(2) Academic transcript	Submit an academic transcript prepared and sealed by the university last attended. (The transcript does not need to be sealed if it is made of a material that prevents photocopying.)
(3) Research progress report (designated form)	Present a brief, objective statement on the progress of the applicant's research in the field of specialization. This form is provided upon request.
(4) Details of previous studies (designated form)	Submit a certificate of research work content prepared and sealed by the institution to which the applicant belongs. This form is provided upon request.
(5) A valid score for GRE General Test or Subject Test (See Note below)	Any scores of the Subject Test are optional. Acceptable test includes: Biology/ Biochemistry, Cell and Molecular/Biology/Chemistry/Physics.
(6) Others	Documents or printed materials that support academic or scientific achievements, if any, such as books, research articles, or academic presentations.

When filing under the eligibility requirement 6

(1) Application form for the eligibility screening (designated form)	This form is provided upon request. (designated form)
(2) Letter of recommendation	Submit a letter of recommendation prepared and sealed by the university in which you are/were enrolled. Note that recommendation letters must be written on the letterhead of the institution to which the recommender belongs and are valid only when the recommender's handwritten signature and full contact addresses (including Email address) are provided.
(3) Academic transcript	Submit an academic transcript prepared and sealed by the university in which you are/were enrolled. (The transcript does not need to be sealed if it is made of a material that prevents photocopying.)
(4) Statement of personal objectives (designated form)	This form is provided upon request.
(5) A valid score for GRE General Test or Subject Test See Note below)	Any scores of the Subject Test are optional. Acceptable test includes: Biology/ Biochemistry, Cell and Molecular/Biology/Chemistry/Physics.

Note

- 1) For applicants who hold a GRE* General Test or Subject Test score for Biology/Biochemistry, Cell and Molecular Biology/Chemistry/Physics, those scores can be provided as supplemental supporting information.

***GRE:** Graduate Record Examination <http://www.ets.org/gre>

Designated Institution (DI) Code: 3814 Kyoto U

- 2) Successful applicants filing under the eligibility requirement 6, expecting to matriculate in April, 2022, must submit an academic transcript for the 2021 academic year to the Student Affairs Section (Kyomu gakari) of the Graduate School of Biostudies by February 24 (Thu), 2022. Otherwise successful applicants whose transcripts demonstrate a failure to meet the admissions standards of the Graduate School of Biostudies may be refused admission.

Successful applicants filing under eligibility requirement 6 must also submit a certificate of withdrawal by March 31 (Thu), 2022; thus, they cannot obtain a bachelor's degree at the university currently attended.

V. Application Fee

Application fee: 10,000 yen

Payment period: From December 1 (Tue) to December 18 (Fri), 2020 JST

Only payments marked as made within this period will be valid; those made outside this period will be invalid. Once received, application fees will not be refundable under any circumstances.

[Payment methods]

1. Payment by Credit Card (only for applicants residing outside Japan).

Applicants residing outside Japan should pay the application fee (10,000 yen) and Service Fee (650 yen). Please access the URL below titled “Examination Settlement Service (EXSS)” and complete the payment process following the instructions provided during the designated payment period. For details, please refer to a separate sheet titled “Payment Methods for Application Fees with Convenience Store or Credit Card”. Note that the Application Completed page must be printed out and submitted along with the other application documents (see section VI below).

EXSS: <https://www3.univ-jp.com/kyoto-u/en/bio/>

2. Payment with Convenience Store (only for applicants residing inside Japan).

Applicants residing inside Japan should pay the application fee (10,000 yen) and Service Fee (650 yen). Please access the URL below titled “Examination Settlement Service (EXSS)” and complete the payment process following the instructions provided during the designated payment period. For details, please refer to a separate sheet titled “Payment Methods for Application Fees with Convenience Store or Credit Card”. Note that the Application Completed page must be printed out and submitted along with the other application documents (see section VI below).

EXSS: <https://www3.univ-jp.com/kyoto-u/en/bio/>

3. Payment by bank transfer (only for applicants residing inside Japan).

Applicants residing inside Japan should pay the application fee (10,000 yen) by bank transfer with the following procedures.

Payment at a bank window in Japan

- (1) **Enter the applicant's name in the appropriate spaces (three spaces) on the Application Fee Payment Request Form (available upon request via regular mail). Take the form to a bank without separating any of its portions (payment through the post office or Japan Post Bank is not available) and make your payment. Please note that payment via the Internet is not accepted.**
- (2) No transfer fee is charged if payment is made at the head office or a branch office of Mitsui Sumitomo Banking Corporation. If payment is made at any other bank, you shall be responsible for the cost of transfer.
- (3) After making your payment, make sure that the bank's receipt seal is stamped on the "Evidence of Application Fee Payment" and the "Application Fee (and Transfer Fee) Receipt" returned from the bank. Paste the "Evidence of Application Fee Payment" (left portion) on the "Form for Affixing Evidence of Application Fee Payment". Please retain the copy of the "Application Fee (and Transfer Fee) Receipt" with revenue stamp attached for your records.

Payment via ATM

Bank Name	Branch	Type of Account	Account No.	Recipient's Name
Mitsui Sumitomo Bank 三井住友銀行	Kyoto 京都支店	Ordinary (<i>futsu</i>) 普通	8089428	Kyoto University 国立大学法人 京都大学

- (1) Enter the applicant's name as the payer in the appropriate space in the ATM so that the university will be able to identify by whom the amount was deposited in the university's account.
- (2) Extra charge for deposit via ATM must be paid by the applicant.
- (3) Submit the receipt of the deposit to be issued with the ATM and make a photocopy of the receipt for yourself.

VI. Application Documents

(1) Admission application form, photograph card, examination card	Use the provided form. Fill in the blanks and paste a photo to each of the two indicated places. Make sure the photos present your full-face and frontal view, without a hat or cap, and are taken within the past three months.
(2) Research achievement (Questions for application screening)	Use the provided form. Fill in the boxes in the designated form. Do not exceed to write expanding the original size of the boxes. The sizes are fixed. Please write in Times New Roman 12 point.
(3) Academic transcript (Original Copy)	Submit an academic transcript prepared and sealed by the university you are currently attending or from which you have graduated.

(4) Graduation certificate or certificate of expected graduation (Original Copy)	Submit a certificate prepared by the university you are currently attending or from which you have graduated.
(5) Recommendation letters	<p><u>At least two</u> letters are required. (Mandatory)</p> <p>Letter of recommendation 1: Written by a faculty member of your current educational institution, who can evaluate your academic performance and potential for success in the Master's program. The letter must be written on the letterhead of the respective institution and must include the recommender's contact information and hand-written signature.</p> <hr/> <p>(Choose at least one, as appropriate)</p> <p>Letter of recommendation 2: Written by the faculty supervisor of the applicant at the university to which you belong or from which you graduated, who can evaluate your research and your potential to become a productive scientist. The letter must be written on the letterhead of the supervisor's institution and must include the supervisor's contact information and hand-written signature.</p> <p>Letter of recommendation 3: If you are employed at a public agency or company at the time of application, submit a letter of recommendation from your immediate supervisor, with his/her hand-written signature. The letter must include your supervisor's contact information and be written on the letterhead of the agency/company to which he/she belongs.</p>
(6) A valid score for GRE General Test and Subject Test	<p>General Test score is required.</p> <p>Any scores of the Subject Test are optional. Acceptable test includes: Biology/Biochemistry, Cell and Molecular/Biology/Chemistry/Physics</p>
(7) A valid score for IELTS or TOEFL	Unnecessary for English-native speakers (Please contact the Student Affairs Section in advance.)
(8) Evidence of application fee payment form	<p>Applicants residing outside Japan: After paying your application fees via internet, the Application Completed page must be printed out and submitted. Applications will not be accepted if payment could not be confirmed.</p> <p>Applicants residing inside Japan: After paying your application fees at a convenience store or a bank window or by an ATM, paste the Evidence of Application Fee Payment with the bank's receipt seal stamped or the receipt issued by the ATM. Applications will not be accepted if no receipt seal is stamped on the Evidence of Application Fee Payment form.</p>
(9) Address for further communication	<p>Use the designated forms.</p> <p>For further communication on the examination results and the enrollment procedures, clearly write your name, address and post code on the designated form.</p>

*If you change your address after applying, you must promptly inform the new address to the Student Affairs Section (Kyomu gakari) of the Graduate School of Biostudies.

VII. Application Procedures

Applicants must prepare a packet of all necessary admission application documents in print and submit it to the postal address indicated on p.9. When sending the packet by post, use registered mail and write clearly “Admission Application Form for the Graduate School of Biostudies Master’s program of Global Frontier in Life Science” on the front of the envelope.

VIII. Application Period

The application period is from December 21 (Mon), 2020 to January 12 (Tue), 2021 JST.

When submitting in person: office hours are 9:00 a.m. – 12:00 p.m. and 1:00 p.m. – 5:00 p.m.

When sending the application documents by post, ensure that the application documents are delivered by January 12 (Tue), 2021.

Note that the admission application form will not be accepted if the application completed page or the Evidence of Payment for Application Fees with the bank’s receipt seal stamped or the receipt issued by the ATM is not pasted on the Form for Affixing Evidence of Payment for Application Fees.

--- Attention -----

1) If you are unable to submit a GRE General Test score or a TOEFL/IELTS score by January 12 (Tue), 2021 due to your local test schedule change concerning the COVID-19 coronavirus epidemic, later submissions will be accepted until January 29 (Fri), 2021.

In this case, please notify the Student Affairs Section of the Graduate School of Biostudies of your situation, no later than January 12 (Tue), 2021.

2) Before enclosing your application documents, please make a scanned copy (pdf) of them and send them to the Student Affairs Section (150kyomu@adm.lif.kyoto-u.ac.jp) via email by January 12 (Tue), 2021 so that the copy can be substituted if your documents sent by post did not arrive in our office by the designated deadline.

IX. Examination Schedule

January 18 (Mon), 2021 ~ January 22 (Fri), 2021	Document Screening Only successful applicants who pass the screening of the admission documents will be able to take the interview (Oral Examination).
January 27 (Wed), 2021	Announcement of successful applicants in document screening

February 1 (Mon), 2021 ~ February 17 (Wed), 2021	Interview (Oral Examination) The interview date and method* will be arranged individually after the decision is made. *e.g. Skype or ZOOM or other protocols
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X. Announcement of Final Successful Applicants

The list of successful applicants is scheduled to be posted on a bulletin board on the 1st floor of the South Campus Research Bldg. (Faculty of Medicine Bldg. G) at approximately 5p.m., February 22 (Mon), 2021. Simultaneously, the same list will be posted on the web site of the Graduate School of Biostudies (<http://www.lif.kyoto-u.ac.jp/e/>). Telephone inquiries about the selection results shall not be accepted.

XI. Admission Fee and Tuition

Admission Fee: 282, 000 yen (tentative)

(The admission fee amount may be revised at the time of enrollment.)

Tuition for the first semester: 267,900 yen (annual tuition: 535,800 yen, tentative)

(The tuition fee amount may be revised at the time of enrollment or later.)

Notes:

- (1) “Master’s Program” at Kyoto University refers to the first two-year program in a doctoral program specified in the Standards for the Establishment of Graduate Schools, and is a term used at Kyoto University.
- (2) Students who have completed the Master's degree in the Graduate School of Biostudies and wish to continue on for the Doctoral Program must nevertheless submit a formal application for the Doctoral Program.
- (3) Others
 - 1) After the application is accepted, no changes are allowed in any of the application items. Furthermore, once received, application fees will not be refundable under any circumstances.
 - 2) **For applicants residing inside Japan:** To request **the Application Fee Payment Request Form**, write your post code, address, and name on a self-addressed 240 mm x 332 mm-sized envelope, and affix 84 yen postage to the self-addressed envelope. Write **“Request for Application Fee Payment Request Form”** on the front of the envelope, place the self-addressed envelope inside, and send it to the address below).
 - 3) The instructions of enrollment procedures will be e-mailed to each successful applicant in late July, 2021 for those who would like to enroll in October, 2021. For those who will enroll in April, 2022, it will be informed in early February, 2022.
 - 4) Applicants with physical disabilities (degree of physical disability as stipulated in the enforcement ordinance of the School Education Law) who require special arrangements for taking examinations or attending courses should immediately contact the Student Affairs Section (Kyomu gakari).

[Handling of Personal Information]

Personal information provided in application documents will be handled in accordance with “Kyoto University’s Rules regarding the Protection of Personal Information.”

< Notice >

From 2021, entrance examinations of the Global Frontier in Life Science will be held in winter instead of summer.

< Where to send your application, and Inquiries >

Student Affairs Section (Kyomu gakari) of the Graduate School of Biostudies,
Kyoto University

Yoshida-Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Phone: +81-75-753-9424 Fax: +81-75-753-9229 E-mail: 150kyomu@adm.lif.kyoto-u.ac.jp

September, 2020

Graduate School of Biostudies, Kyoto University
<http://www.lif.kyoto-u.ac.jp/e/>

Division of Integrated Life Science

1) Laboratory of Chromosome Transmission

PI: NAKASEKO, Yukinobu (Associate Prof.) <nakaseko@lif.kyoto-u.ac.jp>

Outline of the research

Our research is focused on the cell cycle regulation of eukaryotic cells. Using fission yeast as a model system, regulation of chromosome segregation and separation during mitosis has been studied. We are trying to identify individual genes involved in these steps and to elucidate the functional networks of these genes.

Publications

Nakamura, T., Pluskal, T., Nakaseko, Y., and Yanagida, M. Impaired coenzyme A synthesis in fission yeast causes defective mitosis, quiescence-exit failure, histone hypoacetylation and fragile DNA. *Open Biol.* 2, 120117 (2012). doi: 10.1098/rsob.120117.

Irvine, D. V., Goto, D. B., Vaughn, M. W., Nakaseko, Y., McCombie, W. R., Yanagida, M., and Martienssen, R. Mapping epigenetic mutations in fission yeast using whole-genome next-generation sequencing. *Genome Res.* 19, 1077-1083 (2009). doi: 10.1101/gr.089318.108.

Hanyu, Y., Imai, K. K., Kawasaki, Y., Nakamura, T., Nakaseko, Y., Nagao, K., Kokubu, A., Ebe, M., Fujisawa, A., Hayashi, T., Obuse, C., and Yanagida, M. *Schizosaccharomyces pombe* cell division cycle under limited glucose requires Ssp1 kinase, the putative CaMKK, and Sds23, a PP2A-related phosphatase inhibitor. *Genes Cells.* 14, 539-554 (2009). doi: 10.1111/j.1365-2443.2009.01290.x.

Website of the lab: http://www.lif.kyoto-u.ac.jp/e/?post_type=labos&p=135

Key words: chromosome, cell cycle, genetic analysis

2) Laboratory of Gene Biodynamics

PI: SHIRAISHI, Hideaki (Associate Prof.) <siraisi@kuchem.kyoto-u.ac.jp>

Outline of the research

We investigate the growth, morphogenesis, and evolution of photosynthetic microorganisms. We currently focus on developing molecular genetic tools for the analysis and genetic manipulation of the edible alkalophilic cyanobacterium *Arthrospira* (*Spirulina*).

Publications

Tadama, S. and Shiraishi, H. Growth of the edible microalga *Arthrospira platensis* in relation to boron supply. *Int. J. GEOMATE*, 12, 90-95 (2017). doi: 10.21660/2017.30.2580

Shiraishi, H. Cryopreservation of the edible alkalophilic cyanobacterium *Arthrospira platensis*. *Biosci. Biotechnol. Biochem.* 80, 2051-2057 (2016). doi: 10.1080/09168451.2016.1189320

Shiraishi, H. Association of heterotrophic bacteria with aggregated *Arthrospira platensis* exopolysaccharides: implications in the induction of axenic cultures. *Biosci. Biotechnol. Biochem.* 79, 331-341 (2015). doi: 10.1080/09168451.2014.972333

Shiraishi, H. and Tabuse, Y. The *Apl* I restriction-modification system in an edible cyanobacterium, *Arthrospira* (*Spirulina*) *platensis* NIES-39, recognizes the nucleotide sequence 5'-CTGCAG-3'. *Biosci. Biotechnol. Biochem.* 77, 782-788 (2013). doi: 10.1271/bbb.120919

Website of the lab: <http://kuchem.kyoto-u.ac.jp/seika/>

Key words: microbiology, cyanobacteria, spirulina, *Arthrospira platensis*

3) Laboratory of Cell Recognition and Pattern Formation

PI: UEMURA, Tadashi (Prof.) <tauemura@lif.kyoto-u.ac.jp>

Outline of the research

1. Nutri-developmental biology: deciphering regulatory systems of host animals and symbiotic microorganisms that govern nutritional adaptability to ensure animal growth, reproduction, and aging
2. Neuroscience: operating principles of neuronal circuits that evoke selective behavioral outputs in response to nociceptive stimuli
3. Morphogenesis: common principles of epithelial morphogenesis beyond hierarchies of genome, cells and tissues
4. Learning from reproductive parasites: a comprehensive study of “male killing” caused by insect symbionts

We are interested in mechanisms that control animal development and behaviors in response to two categories of environmental inputs: nutrition and sensory stimuli. We are trying to unravel underlying mechanisms of adaptations to nutrient balances using *Drosophila* species. We are also taking interspecies approaches to understand contributions of symbiotic microorganisms to animal growth and reproductive manipulation (“male killing”). By using *Drosophila* somatosensory neurons, we are dissecting operating principles of neuronal circuits that evoke selective behavioral outputs in response to thermal or mechanical nociceptive stimuli. As a related project, we are interested in how genomic information and cells cooperatively build up the entire body of an organism, and trying to understand common principles of epithelial morphogenesis beyond hierarchies of genome, cells and tissues. To conduct these studies, we make full use of molecular, optogenetic, and physiological approaches, imaging, and multi-omics.

Publications (*: Faculties of the lab)

Watanabe, K., Kanaoka, Y., Mizutani, S., Uchiyama, H., Yajima, S., Watada, M., Uemura, T.* and Hattori, Y.* Interspecies comparative analyses reveal distinct carbohydrate-responsive systems among *Drosophila* species. *Cell Reports*, 28: 2594-2607.e7 (2019).

Kondo, T*. and Hayashi, S. Two-step regulation of *trachealess* ensures tight coupling of cell fate with morphogenesis in the *Drosophila* trachea. *eLife*, 8: e45145 (2019).

Harumoto, T*. and Lemaitre, B. Male-killing toxin in a bacterial symbiont of *Drosophila*. *Nature*. 557: 252-255 (2018).

Onodera K., Baba, S., Murakami, A., Uemura, T.*, and Usui, T.* Small conductance Ca^{2+} -activated K^{+} channels induce the firing pause periods during the activation of *Drosophila* nociceptive neurons. *eLife*, 6:e29754 (2017).

Arata, M., Sugimura, S. and Uemura, T.* Difference in Dachsous levels between migrating cells coordinates the direction of collective cell migration. *Dev. Cell*, 42: 479-498 (2017).

Tsuyama, T., Tsubouch, A., Usui, U.*, Imamura, H. and Uemura, T.* Mitochondrial dysfunction induces dendritic loss via eIF2 α phosphorylation. *Journal of Cell Biology*, 216: 815-834 (2017).

Website of the lab: <http://www.cellpattern.lif.kyoto-u.ac.jp/>

Key words: animal development, nutrition, neuroscience, symbiotic microorganisms, morphogenesis, multi-omics, optogenetics

4) Laboratory of Plant Molecular Biology

PI: KOHCHI, Takayuki (Prof.) <tkohchi@lif.kyoto-u.ac.jp>

Outline of the research

1. Photomorphogenesis and environmental regulation of plant development
2. Comparative genomics and molecular genetics with the liverwort, *Marchantia polymorpha*
3. Sex determination and differentiation in plants

Publications

Kato, H., Mutte, S. K., Suzuki, H., Crespo, I., Das, S., Radoeva, T., Fontana, M., Yoshitake, Y., Hainiwa, E., Berg, W., Lindhoud, S., Ishizaki, K., Hohlbein, J., Borst, J. W., Boer, D. R., Nishihama, R., Kohchi, T., and Weijers, D. Design principles of a minimal auxin response system. *Nature Plants* 6: 473-482 (2020). doi: 10.1038/s41477-020-0662-y

Hisanaga, T., Okahashi, K., Yamaoka, S., Kajiwar, T., Nishihama, R., Shimamura, M., Yamato, K. T., Bowman, J. L., Kohchi, T.,* and Nakajima, K.* A cis-acting bidirectional transcription switch controls sexual dimorphism in the liverwort. *EMBO J.*, 38: e100240 (2019). doi: 10.15252/embj.2018100240 *Co-corresponding authors

Yamaoka, S., Nishihama, R., Yoshitake, Y., Ishida, S., Okahashi, K., Bao, H., Nishida, H., Yamaguchi, K., Shigenobu, S., Ishizaki, K., Yamato, K. T., and Kohchi, T. Generative cell specification requires transcription factors evolutionarily conserved in land plants. *Curr. Biol.*, 28: 479-486 (2018). doi: 10.1016/j.cub.2017.12.053

Bowman, J.L., Kohchi, T., Yamato, K.T., *et al.* Insights into land plant evolution garnered from the *Marchantia polymorpha* genome. *Cell*, 171: 287-304 (2017). [dx.doi.org/10.1016/j.cell.2017.09.030](https://doi.org/10.1016/j.cell.2017.09.030)

Inoue, K., Nishihama, R., Kataoka, H., Hosaka, M., Manabe, R., Nomoto, M., Tada, Y., Ishizaki, K. and Kohchi, T. Phytochrome signaling is mediated by PHYTOCHROME INTERACTING FACTOR in the liverwort *Marchantia polymorpha*. *Plant Cell* 28: 1406-1421 (2016). doi: 10.1105/tpc.15.01063

Kubota, A., Kita, S., Ishizaki, K., Nishihama, R., Yamato, K. T. and Kohchi, T. Co-option of a photoperiodic growth-phase transition system during land plant evolution, *Nature Comm.* 5, 3668 (2014). doi: 10.1038/ncomms4668

Website of the lab: <http://www.plantmb.lif.kyoto-u.ac.jp/>

Key words: land plant evolution, light signaling, plant development, sex determination, *Marchantia polymorpha*

5) Laboratory of Molecular and Cellular Biology of Totipotency

PI: NAKANO, Takeshi (Prof.) <nakano.takeshi.6x@kyoto-u.ac.jp>

Outline of the research

1. Plant chemical biology for molecular mechanism of plant growth based on cell regulation and photosynthesis.
2. Signaling network of brassinosteroid that cross talks with the other phytohormones and environmental condition.
3. Application of novel genes to regulate plant growth for useful crop production.

Publications

Nosaki, S., Miyakawa, T., Xu, Y., Nakamura, A., Hirabayashi, K., Asami, T., Nakano, T., Tanokura, M. Structural basis for brassinosteroid response by BIL1/BZR1. *Nature Plants*, 4, 771-776 (2018). doi: 10.1038/s41477-018-0255-1.

Yamagami, A., Saito, C., Nakazawa, M., Fujioka, S., Uemura, T., Matsui, M., Sakuta, M., Osada, H., Nakano, A., Asami, T., Nakano, T. Evolutionarily conserved BIL4 interacts with the brassinosteroid receptor BRI1 and regulates cell elongation. *Scientific Reports* 7(1) Article number 5739 (2017). doi: 10.1038/s41598-017-06016-2.

Taishi Nishimura, Ryo Nagao, Takumi Noguchi, Jon Nield, Fumihiko Sato, Kentaro Ifuku (2016) The N-terminal sequence of the extrinsic PsbP protein modulates the redox potential of Cyt b559 in photosystem II. *Scientific Reports* 6, Article number: 21490 doi:10.1038/srep21490

Shimada, S., Komatsu, T., Yamagami, A., Nakazawa, M., Matsui, M., Kawaide, H., Natsume, M., Osada, H., Asami, T., Nakano, T. Formation and dissociation of BSS1 protein complex regulates plant development via brassinosteroid signaling. *Plant Cell*. 27: 375-90. (2015). doi: 10.1105/tpc.114.131508.

Website of the lab: <http://plantchembio.sun.bindcloud.jp/index.html>

Key words: plant chemical biology, plant growth, phytohormone, brassinosteroid, photosynthesis.

6) Laboratory of Biosignals and Response

PI: NAGAO, Masaya (Prof.) <nagao.masaya.7e@kyoto-u.ac.jp>

Outline of the research

1. Screening for discovery of bioactive natural products.
2. Elucidation of the cellular functions of zinc transporters, ZIPs, and ZnTs

Publications

Fujimoto, S., Tsuji, T., Fujiwara, T., Takeda, T.A., Merriman, C., Fukunaka, A., Nishito, Y., Fu, D., Hoch, E., Sekler, I., Fukue, K., Miyamae, Y., Masuda, S., Nagao, M., Kambe, T. The PP-motif in luminal loop 2 of ZnT transporters plays a pivotal role in TNAP activation. *Biochem J*. 473 (17) 2611-2621 (2016). doi: 10.1042/BCJ20160324

Miyamae, Y., Nishito, Y., Nakai, N., Nagumo, Y., Usui, T., Masuda, S., Kambe, T., Nagao, M. Tetrandrine induces lipid accumulation through blockade of autophagy in a hepatic stellate cell line. *Biochem Biophys Res Commun*. 477, 40-46 (2016). doi: 10.1016/j.bbrc.2016.06.018

Ohtera, A., Miyamae, Y., Yoshida, K., Maejima, K., Akita, T., Kakizuka, A., Irie, K., Masuda, S., Kambe, T., Nagao, M. Identification of a New Type of Covalent PPAR γ Agonist using a Ligand-Linking Strategy. *ACS Chem Biol*. 10, 2794-2804 (2015). doi: 10.1021/acscchembio.5b00628

Hashimoto, A., Ohkura, K., Takahashi, M., Kizu, K., Narita, H., Enomoto, S., Miyamae, Y., Masuda, S., Nagao, M., Irie, K., Ohigashi, H., Andrews, G.K., Kambe, T. Soybean extracts increase cell surface ZIP4 abundance and cellular zinc levels: a potential novel strategy to enhance zinc absorption by ZIP4 targeting. *Biochem J*. 472, 183193 (2015). doi: 10.1042/BJ20150862

Ohtera, A., Miyamae, Y., Nakai, N., Kawachi, A., Kawada, K., Han, J., Isoda, H., Neffati, M., Akita, T., Maejima, K., Masuda, S., Kambe, T., Mori, N., Irie, K., Nagao, M. Identification of 6-octadecynoic acid from a methanol extract of *Marrubium vulgare* L. as a peroxisome proliferator-activated receptor γ agonist. *Biochem Biophys Res Commun*. 440, 204-209 (2013). doi: 10.1016/j.bbrc.2013.09.003

Website of the lab: <http://www.seitaijoho.lif.kyoto-u.ac.jp/>

Key words: bioactive compounds, screening, zinc, transporter

7) Laboratory of Molecular Biology of Bioresponse

PI: KATAYAMA, Takane (Prof.) <takane@lif.kyoto-u.ac.jp>

Outline of the research

Our aim is to decipher the molecular mechanism underlying the symbiotic evolutionary relationship between gut microbes and host, and to develop food-and health-oriented application research. We are also focused on the elucidation of mechanisms of mRNA processing, export, and quality control in the nucleus in human and its industrial applications.

Publications

Sakanaka M, Hansen ME, Gotoh A, Katoh T, Yoshida K, Odamaki T, Yachi H, Sugiyama Y, Kurihara S, Hirose J, Urashima T, Xiao JZ, Kitaoka M, Fukiya S, Yokota A, Lo Leggio L, Abou Hachem M, and Katayama T. Evolutionary adaptation in fucosyllactose uptake systems supports bifidobacteria-infant symbiosis. *Sci. Adv.* 5:eaaw7696, (2019).

Gotoh A, Katoh T, Sakanaka M, Ling Y, Yamada C, Asakuma S, Urashima T, Tomabechei Y, Katayama-Ikegami A, Kurihara S, Yamamoto K, Harata G, He F, Hirose J, Kitaoka M, Okuda S. and Katayama T. Sharing of human milk oligosaccharides degradants within bifidobacterial communities in faecal cultures supplemented with *Bifidobacterium bifidum*. *Sci. Rep.* 8:13958. (2018).

Kurata M, Fujiwara N, Fujita KI, Yamanaka Y, Seno S, Kobayashi H, Miyamae Y, Takahashi N, Shibuya Y and Masuda S. Food-Derived Compounds Apigenin and Luteolin Modulate mRNA Splicing of Introns with Weak Splice Sites. *iScience*, 22, 336-352 (2019).

Okamura M, Yamanaka Y, Shigemoto M, Kitadani Y, Kobayashi Y, Kambe T, Nagao M, Kobayashi I, Okumura K, Masuda S. Depletion of mRNA export regulator DBP5/DDX19, GLE1 or IPPK that is a key enzyme for the production of IP6, resulting in differentially altered cytoplasmic mRNA expression and specific cell defect. *PLoS One*, 13, e0197165, (2018)

Yamada C, Gotoh A, Sakanaka M, Hattie M, Stubbs KA, Katayama-Ikegami A, Hirose J, Kurihara S, Arakawa T, Kitaoka M, Okuda S, Katayama T, and Fushinobu S. Molecular insight into evolution of symbiosis between breastfed infants and a member of the human gut microbiome *Bifidobacterium longum*. *Cell Chem. Biol.* 24:515-524. (2017).

Website of the lab: <http://www.bunshioutou.lif.kyoto-u.ac.jp/index.html>

Key words: gut microbes, symbiosis, coevolution, mRNA, export

8) Laboratory of Plant Developmental Biology

PI: ARAKI, Takashi (Prof.) <taraqui@lif.kyoto-u.ac.jp>

Outline of the research

We are interested in molecular mechanisms underlying plant's responses to environment. Plants have evolved plastic developmental programs with both genetic and epigenetic basis to adapt their sessile mode of life to changing environment. Using an angiosperm, *Arabidopsis thaliana* and a liverwort, *Marchantia polymorpha* as model systems, we have been investigating (1) regulation of growth phase transition (especially, flowering) in response to environmental signals, (2) long-distance systemic signaling in the control of development, (3) sexual reproduction processes (especially, male gametogenesis and fertilization), and (4) origin and evolution of regulatory systems for plastic development.

Publications

Tuzuki, M., Futagami, K., Shimamura, M., Inoue, C., Kunimoto, K., Oogami, T., Tomita, Y., Inoue, K., Kohchi, T., Yamaoka, S., Araki, T., Hamada, T., and Watanabe, Y. An early arising role of microRNA156/529c-*SPL* module in

reproductive development revealed by the liverwort *Marchantia polymorpha*. **Curr. Biol.** 29: 3307-3314., e1-e5 (2019). doi: 10.1016/j.cub.2019.07.084

Hisanaga, T., Yamaoka, S., Kawashima, T., Higo, A., Nakajima, K., Araki, T., Kohchi, T., and Berger, F. Building new insights in plant gametogenesis from an evolutionary perspective. **Nature Plants** 5: 663-669 (2019). doi: 10.1038/s41477-019-0466-0

Inoue, K., Nishihama, R., Araki, T., and Kohchi, T. Reproductive induction is far-red high irradiance response mediated by phytochrome and PHYTOCHROME INTERACTING FACTOR in *Marchantia polymorpha*. **Plant Cell Physiol.** 60: 1136-1145 (2019). doi: 10.1093/pcp/pcz029

Higo, A., Kawashima, T., Borg, M., Zhao, M., López-Vidriero, I., Sakayama, H., Montgomery, S. A., Sekimoto, H., Hackenberg, D., Shimamura, M., Nishiyama, T., Sakakibara, K., Tomita, Y., Togawa, T., Kunimoto, K., Osakabe, A., Suzuki, Y., Yamato, K. T., Ishizaki, K., Nishihama, R., Kohchi, T., Franco-Zorrilla, J. M., Twell, D., Berger, F., and Araki, T. Transcription factor DUO1 generated by neo-functionalization is associated with evolution of sperm differentiation in plants. **Nature Commun.** 9(5283): 1-13 (2018). doi: 10.1038/s41467-018-07228-3

Endo, M., Yoshida, M., Sasaki, Y., Negishi, K., Horikawa, K., Daimon, Y., Kurotani, K.-i., Notaguchi, M., Abe, M., and Araki, T. Reevaluation of florigen transport kinetics with separation of function by mutations that uncouple flowering initiation and long-distance transport. **Plant Cell Physiol.** 59: 1621-1629 (2018). doi: 10.1093/pcp/pcy063

Bowman, J.L., Kohchi, T., Yamato, K.T., Jenkins, J., Shu, S., Ishizaki, K., Yamaoka, S., Nishihama, R., Nakamura, Y., Berger, F., Adam, C., Aki, S.S., Althoff, F., Araki, T., [33 authors omitted] Inoue, K., [64 authors omitted] and Schmutz, J. Insights into land plant evolution garnered from the *Marchantia polymorpha* genome. **Cell** 171: 287-304 (2017). doi: 10.1016/j.cell.2017.09.030

Higo, A., Niwa, M., Yamato, K. T., Yamada, L., Sawada, H., Sakamoto, T., Kurata, T., Shirakawa, M., Endo, M., Shigenobu, S., Ishizaki, K., Nishihama, R., Kohchi, T. and Araki, T. Transcriptional framework of male gametogenesis in the liverwort *Marchantia polymorpha* L. **Plant Cell Physiol.** 57: 325-338 (2016). doi: 10.1093/pcp/pcw005

Website of the lab: <http://www.plantdevbio.lif.kyoto-u.ac.jp/index.html>

Key words: flowering, florigen, sexual reproduction, germ line specification, gametogenesis

9) Laboratory of Plasma Membrane and Nuclear Signaling

PI: YOSHIMURA, Shigehiro (Associate Prof.) <yoshimura@lif.kyoto-u.ac.jp>

Outline of the research

Our laboratory studies how various cellular processes are governed by nano-scale structures and interactions of biomolecules, as well as their macroscopic bulk behavior in cellular environments. We try to integrate such different hierarchies of biomolecular dynamics by using techniques in single-molecule live-cell imaging, biochemistry, biophysics and bioinformatics. Specific research topics include: (1) how endocytic process is orchestrated by membrane-bound proteins, cytoskeletal network and lipid bilayer, (2) how intracellular membrane-less organelle (nuclear pore complex, mitotic chromosome, nucleolus, etc.) are assembled/disassembled by post-translational modifications, and (3) how viral genome and proteins are assembled in a vast host cell-plasm.

Publications

H. Yamazaki, H. Kosako and S.H. Yoshimura (2020) “Quantitative proteomics indicate a strong correlation of mitotic phospho-/dephosphorylation with non-structured regions of substrates.” **Biochim. Biophys. Acta. Proteins Proteom.**, 1868(1): 140295, DOI: 10.1016/j.bbapap.2019.140295.

H.A. Konishi and S.H. Yoshimura (2020) “Interactions between non-structured domains of FG- and non FG-nucleoporins coordinate the ordered assembly of the nuclear pore complex in mitosis. *FASEB J.*, 34(1): 1532-1545, DOI: 10.1096/fj.201901669R.

Yoshida, A., Sakai, N., Uekusa, Y., Imaoka, Y., Itagaki, Y., Suzuki, Y., and Yoshimura, S.H. “Morphological changes of plasma membrane and protein assembly during clathrin-mediated endocytosis” *PLOS Biol.* 16(5): e2004786 (2018). doi: 10.1371/journal.pbio.2004786.

Kumeta, M., Konishi, H.A., Zhang, W., Sakagami, S. and Yoshimura, S.H. “Prolines in the α -helix confer the structural flexibility and functional integrity of importin β .” *J. Cell Sci.*, 131(1): e0188764 (2018). doi: 10.1242/jcs.206326.

Konishi H.A., Asai S., Watanabe T. and Yoshimura S.H. “*In vivo* analysis of protein crowding within the nuclear pore complex in interphase and mitosis” *Sci. Rep.*, 7(1): 5709 (2017). doi: 10.1038/s41598-017-05959-w

Lolodi, O., Yamazaki, H., Otsuka, S., Kumeta, M. and Yoshimura S.H. “Dissecting *in vivo* steady-state dynamics of karyopherin-dependent nuclear transport.” *Mol. Biol. Cell.* 27: 167-176 (2016). doi: 10.1091/mbc.E15-08-0601

Website of the lab: <http://www.chrom.lif.kyoto-u.ac.jp>

Key words: molecular crowding, liquid-liquid phase separation, cytoskeletal dynamics, membrane dynamics, mechanobiology, virus infection, bioinformatics, atomic force microscopy

10) Laboratory of Developmental Neurobiology

PI: KENGAKU, Mineko (Prof.) < kengaku@icems.kyoto-u.ac.jp >

Outline of the research

We study the dynamics and mechanisms of the formation of neural networks in the brain. We also aim to develop live-imaging techniques for observation of molecular signals controlling cell motility in the developing brain.

Publications

Kawabata-Galbraith, K., Fujishima, K., Mizuno, H., Lee, S.J., Uemura, T., Sakimura, K., Mishina, M., Watanabe, N. and Kengaku, M. MTSS1 regulation of actin-nucleating formin DAAM1 in dendritic filopodia determines final dendritic configuration of Purkinje cells. *Cell Rep.* 24(1):95-106. (2018).doi: 10.1016/j.celrep.2018.06.013.

Wu, Y.K., Umeshima, H., Kurisu, J. and Kengaku, M. Nesprins and opposing microtubule motors generate a point force driving directional nuclear motion in migrating neurons. *Development.* 145(5): dev158782. (2018). doi: 10.1242/dev.158782.

Fukumitsu, K., Fujishima, K., Yoshimura, A., Wu, Y.K., Heuser, J. and Kengaku, M. Synergistic action of dendritic mitochondria and creatine kinase maintains ATP homeostasis and actin dynamics in growing neuronal dendrites. *J. Neurosci.* 35(14):5707- 5723 (2015). doi: 10.1523/JNEUROSCI.4115-14.2015.

Fujishima, K., Horie, R., Mochizuki, A. and Kengaku, M. Principles of branch dynamics governing shape characteristics of cerebellar Purkinje cell dendrites. *Development* 139 (18): 3442-3455 (2012). doi: 10.1242/dev. 081315.

Website of the lab: <https://kengaku.icems.kyoto-u.ac.jp/>

Key words: neuronal differentiation, dendrite, cell migration, cortex formation, neural circuit formation

11) Laboratory of Biochemical Cell Dynamics

PI: SUZUKI, Jun (Prof.) <jsuzuki@icems.kyoto-u.ac.jp>

Outline of the research

We are researching on biological phenomenon with our interests by unbiased screening-based identification of key genes regulating it. Currently, we are interested in the phenomenon called phospholipid scrambling, which is involved in variety of biological systems such as removal of unwanted materials in cells, blood coagulation, cell fusion, formation of lipid domain, and so on. Defects of these processes cause various human diseases such as autoimmunity, bleeding disorder, muscle dystrophy, and neuronal diseases. We can classify our research to 3 stages: to explore new fields by identifying the key genes; to develop primary finding; to think how our finding is applicable to medicine or biotechnology. Through all stages, we will conduct the interesting research and enjoy science.

Publication:

Gyobu S, Ishihara K, Suzuki J, Segawa K, and Nagata S. Characterization of the scrambling domain of the TMEM16 family. *Proc Natl Acad Sci USA*. 114: 6274-6279 (2017). doi: 10.1073/pnas.1703391114.

Suzuki, J., Imanishi, E. and Nagata, S. Exposure of phosphatidylserine by Xk-related protein family members. *J. Biol. Chem.* 289: 30257-30267 (2014). doi: 10.1074/jbc.M114.583419.

Suzuki, J., Denning, D.P., Imanishi, E., Horvitz, H.R. and Nagata, S. Xk-related protein 8 and CED-8 promote phosphatidylserine exposure in apoptotic cells. *Science* 341: 403-406 (2013). doi: 10.1126/science.1236758.

Suzuki, J., Fujii, T., Imao, T., Ishihara, K., Kuba, H. and Nagata, S. Calcium-dependent phospholipid scramblase activity of TMEM16 protein family members. *J. Biol. Chem.* 288: 13305-13316 (2013). doi: 10.1074/jbc.M113.457937.

Suzuki, J., Sims, P.J., Umeda, M. and Nagata, S. Calcium-dependent phospholipid scrambling by TMEM16F. *Nature*, 468:834-838 (2010). doi: 10.1038/nature09583.

Website of the lab: <http://www.suzuki.icems.kyoto-u.ac.jp>

Key words: unbiased screening, gene identification, phospholipid scrambling, phagocytosis, neuron, medicine

12) Laboratory of Multidisciplinary Biology

PI: TANIGUCHI, Yuichi (Prof.) <taniguchi.yuichi.8s@kyoto-u.ac.jp>

Outline of the research

We study on the working principle of the cell as a system comprised of vast numbers of species of bio-molecules such as genome, transcriptome and proteome. We aim at developing technologies with new concepts by integrating knowledge from multiple academic fields including genetics, cell biology, microscopic imaging, chemistry, physics, informatics, large-scale computing and artificial intelligence.

Publications

Kumar, V., Leclerc, S., Taniguchi, Y. “BHi-Cect: A top-down algorithm for identifying the multi-scale hierarchical structure of chromosomes”, *Nucleic Acids Research*, 48, e26 (2020). doi: 10.1093/nar/gkaa004

Ohno, M., Ando, T., Priest, D. G., Kumar, V., Yoshida, Y., Taniguchi, Y. “Sub-nucleosomal genome structure reveals distinct nucleosome folding motifs”, *Cell* 176, 520-534 (2019). doi: 10.1016/j.cell.2018.12.014

Leclerc, S., Arntz, Y., Taniguchi, Y. "Extending single molecule imaging to proteome analysis by quantitation of fluorescent labeling homogeneity in complex protein samples", *Bioconjugate Chemistry* 29, 2541-2549 (2018). doi: 10.1021/acs.bioconjchem.8b00226

Taniguchi, Y., Choi, P. J., Li, G., Chen, H., Hearn, J., Babu, M., Emili, A. & Xie, X. S. "Quantifying E. coli proteome and transcriptome with single-molecule sensitivity in single cells", *Science* 329, 533-538 (2010). doi: 10.1126/science.1188308

Taniguchi, Y., Nishiyama, M., Ishii, Y. & Yanagida, T. "Entropy rectifies the Brownian steps of kinesin", *Nature Chemical Biology* 1, 342-347 (2005). doi: 10.1038/nchembio741

Website of the lab: <https://www.taniguchi.icems.kyoto-u.ac.jp> (To be open soon.)

Key words: multi-omics, microscopic imaging, biophysics, systems medicine, large-scale computing

13) Laboratory of Ultrastructural Virology

PI: NODA, Takeshi (Prof.) <t-noda@infront.kyoto-u.ac.jp>

Outline of the research

Virus infections are accompanied by numerous ultrastructural changes in viral and cellular components. Our laboratory has been investigating the intracellular replication mechanism of influenza, Ebola and Lassa viruses by using virological, molecular biological, and biochemical techniques combining with different microscopic methods such as electron microscopy and high-speed atomic force microscopy. Visualization and characterization of the virus life cycle at the nano-mesoscopic level give us unique knowledge and novel paradigms, which will advance our understanding of molecular basis of the replication mechanism.

Publications

Sugita Y, Matsunami H, Kawaoka Y, Noda T, Wolf M. Cryo-EM structure of the Ebola virus nucleoprotein-RNA complex at 3.6 Å resolution. *Nature* 563:137-140. (2018)

Noda, T., Murakami, S., Nakatsu, S., Imai, H., Muramoto, Y., Shindo, K., Sagara, H. and Kawaoka, Y. Importance of the 1+7 configuration of the ribonucleoprotein complexes for influenza A virus genome packaging. *Nature Communications* 9:54 (2018).

Wan, W., Kolesnikova, L., Clarke, M., Koehler, A., Noda, T., Becker, S., and Briggs, J.A.G. Structure and assembly of the Ebola virus nucleocapsid. *Nature* 551: 394-397 (2017).

Martyushev, A., Nakaoka, S., Sato, K., Noda, T. and Iwami, S. Modelling Ebola virus dynamics: Implications for therapy. *Antiviral Research* 135: 62-73 (2016).

Nakatsu, S., Sagara, H., Sakai, Y. T., Sugaya, N., Noda, T. and Kawaoka, Y. Complete and incomplete genome packaging of influenza A and B viruses. *mBio* 7: e01248-16 (2016).

Website of the lab: <https://www.facebook.com/NodaLab/>

Key words: Influenza virus, Ebola virus, Lassa virus

Division of Systemic Life Science

1) Laboratory of Single-Molecule Cell Biology

PI: WATANABE, Naoki (Prof.) <watanabe.naoki.4v@kyoto-u.ac.jp>

Outline of the research

Why not watch individual protein molecules in action? By using live-cell Single-Molecule Speckle (SiMS) microscopy and our original multi-target super resolution microscopy IRIS, we are trying to bridge the gap between molecular and biological functions to elucidate cellular mechanotransduction, cancer invasion, tissue and neural circuit remodeling and drug resistance mechanisms.

Publications

Yamashiro, S., Taniguchi, D., Tanaka, S., Kiuchi, T., Vavylonis, D. and Watanabe N. Convection-induced biased distribution of actin probes in live cells. *Biophys. J.* 116: 142-150 (2019). doi: 10.1016/j.bpj.2018.11.022

Mizuno, H., Tanaka, K., Yamashiro, S., Narita, A. and Watanabe, N. Helical rotation of diaphanous-related formin mDia1 generates actin filaments resistant to cofilin. *Proc. Natl. Acad. Sci. USA* 115: E5000-E5007 (2018). doi: 10.1073/pnas.1803415115

Kiuchi, T., Higuchi, M., Takamura, A., Maruoka, M. and Watanabe, N. Multitarget super-resolution microscopy with high-density labeling by exchangeable probes. *Nat. Methods* 12: 743-746 (2015). doi: 10.1038/nmeth.3466

Higashida, C., Kiuchi, T., Akiba, Y., Mizuno, H., Maruoka, M., Narumiya, S., Mizuno, K. and Watanabe, N. F- and G-actin homeostasis regulates mechanosensitive actin nucleation by formins. *Nat. Cell Biol.* 15: 395-405 (2013). doi: 10.1038/ncb2693

Mizuno, H., Higashida, C., Yuan, Y., Ishizaki, T., Narumiya, S. and Watanabe, N. Rotational movement of the formin mDia1 along the double helical strand of an actin filament. *Science* 331: 80-83 (2011). doi: 10.1126/science.1197692

Website of the lab: http://www.pharm2.med.kyoto-u.ac.jp/2_index.html

Key words: single-molecule imaging, super-resolution microscopy, cancer therapy

2) Laboratory of Molecular and Cellular Biology

PI: SAKAMAKI, Kazuhiro (Associate Prof.) <sakamaki.kazuhiro.7u@kyoto-u.ac.jp>

Outline of the research

We are interested in the signal transduction mechanisms underlying apoptotic cell death and the biological significance and physiological roles of cell death in organisms. To understand these issues, our main research focuses on the apoptosis executors, caspases, and is to visualize the functional processes of these molecules in cells using live cell imaging and computer simulation. To kill target cells, we are starting up a photo-inducible system, artificially activating caspases. We are also trying to generate appropriate model animals such as mouse, *Xenopus*, and medaka to control the phenomenon of apoptosis in organisms.

Publications

Jaspers, C., Fraune, S., Arnold, A.E., Miller, D.J., Bosch, T., Voolstra, C.R., and Consortium of Australian Academy of Science Boden Research Conference Participants. Resolving structure and function of metaorganisms through a holistic framework combining reductionist and integrative approaches. *Zoology* 133:81-87 (2019). doi: 10.1016/j.zool.2019.02.007.

Moya, A., Sakamaki, K., Mason, B.M., Huisman, L., Forêt, S., Weiss, Y., Bull, T.A., Tomii, K., Imai, K., Hayward, D.C., Ball, E.E., and Miller, D.J. Functional conservation of the apoptotic machinery from coral to man: the diverse and complex Bcl-2 and caspase repertoires of *Acropora millepora*. **BMC Genomics** 17:62 (2016). doi: 10.1186/s12864-015-2355-x.

Sakamaki, K., Ishii, T.M., Sakata, T., Takemoto, K., Takagi, C., Takeuchi, A., Morishita, R., Takahashi, H., Nozawa, A., Shinoda, H., Chiba, K., Sugimoto, H., Saito, A., Tamate, S., Satou, Y., Jung, S.-K., Matsuoka, S., Koyamada, K., Sawasaki, T., Nagai, T. and Ueno, N. Dysregulation of a potassium channel, THIK-1, targeted by caspase-8 accelerates cell shrinkage. **Biochim. Biophys. Acta** 1863: 2766-2783 (2016). doi: 10.1016/j.bbamcr.2016.08.010.

Sakamaki, K., Imai, K., Tomii, K. and Miller, D.J. Evolutionary analyses of caspase-8 and its paralogs: Deep origins of the apoptotic signaling pathways. **BioEssays** 37: 767-776 (2015). doi: 10.1002/bies.201500010.

Kominami, K., Nakabayashi, J., Nagai, T., Tsujimura, Y., Chiba, K., Kimura, H., Miyawaki, A., Sawasaki, T., Yokota, H., Manabe, N. and Sakamaki, K. The molecular mechanism of apoptosis upon caspase-8 activation: quantitative experimental validation of a mathematical model. **Biochim. Biophys. Acta** 1823: 1825–1840 (2012). doi: 10.1016/j.bbamcr.2012.07.003.

Website of the lab: <http://www.mcb.lif.kyoto-u.ac.jp/>

Key words: apoptosis, caspase, cell death, computer simulation, live imaging, optogenetics

3) Laboratory of Immunobiology

PI: TAKAHARA, Kazuhiko (Associate Prof.) <ktakahar@zoo.zool.kyoto-u.ac.jp>

Outline of the research

We focus on dendritic cells, macrophages, and their antigen receptor lectins that recognize polysaccharides on pathogens. We are also interested in immunosuppressive mechanisms of pathogens. Based on these studies, we would like to develop new methods to control immune system.

Publications

Cui G., Shimba A., Ma G, Takahara K., Tani-ichi S., Zhu Y., Asahi T., Abe A., Miyachi H., Kitano S., Hara T., Yasunaga J., Suwanai H., Yamada H., Matsuoka M., Ueki K., Yoshikai Y, and Ikuta K. IL-7R-dependent Phosphatidylinositol-3 Kinase Competes with STAT5 Signal to Modulate T Cell Development and Homeostasis. **J. Immunol.** 204, 844–857. (2020). doi: 10.4049/jimmunol.1900456

Goji, T., Takahara, K., Negishi, M. and Katoh, H. Cystine uptake through the cystine/glutamate antiporter xCT triggers glioblastoma cell death under glucose deprivation. **J. Biol. Chem.** 292, 19721-19732. (2017). doi: 10.1074/jbc.M117.814392

Ishiguro, T.*, Fukawa, T.*, Akaki, K., Nagaoka, K., Takeda, T., Iwakura, Y., Inaba, K., and Takahara, K. Absence of DCIR1 reduces the mortality rate of endotoxemic hepatitis in mice. **Eur. J. Immunol.** 47, 704-712. (*equal contribution) (2017). doi: 10.1002/eji.201646814

Taneo, J., Adachi, T, Yoshida, A., Takeyasu, K., Takahara, K.* and Inaba, K. Amyloid β oligomers induce interleukin-1 β production in primary microglia in a cathepsin B- and reactive oxygen species-dependent manner. **Biochem. Biophys. Res. Commun.** 458, 561-567. (*corresponding author) (2015). doi: 10.1016/j.bbrc.2015.02.006

Tokieda, S., Komori, M., Ishiguro, Iwakura, Y., Takahara, K.* and Inaba, K. Dendritic cell immunoreceptor 1 alters neutrophil responses in the development of experimental colitis. *BMC Immunol.* 16, 64. (*corresponding author) (2015). doi: 10.1186/s12865-015-0129-5

Adachi, T., Takahara, K., Taneo, J., Uchiyama, Y. and Inaba, K. Particle size of latex beads dictates IL-1 β production mechanism. *Plos One* 8, e68499. (2013). doi: 10.1371/journal.pone.0068499

Takahara, K., Arita, T., Tokieda, S., Shibata, N., Okawa, Y., Tateno, H., Hirabayashi, J. and Inaba, K. Difference in fine specificity to polysaccharides of *C. albicans* mannoprotein between mouse SIGNR1 and human DC-SIGN. *Infect. Immun.* 89, 1699-1706. (2012). doi: 10.1128/IAI.06308-11

Website of the lab: <http://zoo.zool.kyoto-u.ac.jp/imm/>

Key words: lectin, immune modulation, polysaccharide, disease models, dendritic cells

4) Laboratory of Molecular Cell Biology and Development (Collaboration lab in RIKEN, Kobe)

PI (1): KITAJIMA, Tomoya (Prof.) <tomoya.kitajima@riken.jp>

Outline of the research

We are interested in how chromosomes behave in time and space to archive correct chromosome segregation during meiosis and mitosis in mammalian oocytes and zygotes. Taking advantage of our live imaging technology, we conduct comprehensive quantitative analysis of the chromosome dynamics.

Publications

Yoshida, S., Nishiyama, S., Lister, L., Hashimoto, S., Mishina, T., Courtois, A., Kyogoku, H., Abe, T., Shiraishi, A., Choudhary, M., Nakaoka, Y., Herbert, M. and Kitajima, T.S. Prc1-rich kinetochores are required for error-free acentrosomal spindle bipolarization during meiosis I in mouse oocytes. *Nature Communications* 11: 2652 (2020). doi: 10.1038/s41467-020-16488-y

Ding, Y., Kaido, M., Llano, E., Pendas, A.M., and Kitajima, T.S. The post-anaphase SUMO pathway ensures the maintenance of centromeric cohesion through meiosis I-II transition in mammalian oocytes. *Current Biology* 28(10), 1661–1669 (2018). doi: 10.1016/j.cub.2018.04.019.

Kyogoku, H., & Kitajima, T. S. Large cytoplasm is linked to the error-prone nature of oocytes. *Developmental Cell*, 41(3), 287–298 (2017). doi:10.1016/j.devcel.2017.04.009.

Sakakibara, Y., Hashimoto, S., Nakaoka, H., Kouznetsova, A., Höög, C., and Kitajima, T.S. Bivalent separation into univalents precedes age-related meiosis I errors in oocytes. *Nature Communications*, 6, 7550 (2015). doi: 10.1038/ncomms8550

Yoshida, S., Kaido, M., and Kitajima, T.S. Inherent instability of correct kinetochore-microtubule attachments during meiosis I in oocytes. *Developmental Cell*, 33, 589–602 (2015). doi: 10.1016/j.devcel.2015.04.020

Website of the lab: http://chromosegr.riken.jp/index_en.html

Key words: chromosome, meiosis, oocyte, zygote

PI (2): TAKASATO, Minoru (Associate Prof.) <minoru.takasato@riken.jp>

Outline of the research

Utilizing our unique technology that generates kidney organoids from human pluripotent stem cells, we are focusing particularly on uncovering the developmental mechanisms of human mesoderm kidney and the bladder. By precisely recapitulating the developmental processes of human urinary tract in the directed differentiation of human pluripotent stem cells, we are also aiming for the ultimate goal of generating a three-dimensional whole urinary tract that is functional and can be transplanted into patients.

Publications

Phipson, B., Er, P.X., Combes, A.N., Forbes, T.A., Howden, S.E., Zappia, L., Yen, H.-J., Lawlor, K.T., Hale, L.J., Sun, J., Wolvetang, E., Takasato, M., Oshlack, A., Little, M.H., Evaluation of variability in human kidney organoids. *Nat. Methods* 16, 79–87 (2019). doi: 10.1038/s41592-018-0253-2

M. Takasato, P. X. Er, H. S. Chiu, M. H. Little, Generation of kidney organoids from human pluripotent stem cells. *Nat. Protoc.* 11, 1681–1692 (2016). doi: 10.1038/nprot.2016.098

M. Takasato *et al.*, Kidney organoids from human iPS cells contain multiple lineages and model human nephrogenesis. *Nature*. 526, 564–8 (2015). doi: 10.1038/nature15695

M. Takasato, M. H. Little, The origin of the mammalian kidney: implications for recreating the kidney in vitro. *Development*. 142, 1937–1947 (2015). doi: 10.1242/dev.104802

M. Takasato *et al.*, Directing human embryonic stem cell differentiation towards a renal lineage generates a selforganizing kidney. *Nat. Cell Biol.* 16, 118–26 (2014). doi: 10.1038/ncb2894

Website of the lab: <https://www.bdr.riken.jp/en/research/labs/takasato-m/index.html>

Key words: kidney organoid, directed differentiation, pluripotent stem cell, human development

5) Laboratory of Molecular Neurobiology

PI: KIMURA, Ikuo (Prof.) <ikimura@cc.tuat.ac.jp >

Outline of the research

1. Dietary signaling via nutrient-sensing receptors and metabolic syndrome
2. Non-genomic effects via sex steroid hormone receptors and neurological disorder

Publications

Kimura I*, Miyamoto J, Ohue-Kitano R, Watanabe K, Yamada T, Onuki M, Aoki R, Isobe Y, Kashihara D, Inoue D, Inaba A, Takamura Y, Taira S, Kumaki S, Watanabe M, Ito M, Nakagawa F, Irie J, Kakuta H, Shinohara M, Iwatsuki K, Tsujimoto G, Ohno H, Arita M, Itoh H, Hase K. Maternal gut microbiota in pregnancy influences offspring metabolic phenotype in mice. *Science*. 367, eaaw8429 (2020).

Kimura I*, Ichimura A, Ohue-Kitano R, Igarashi M. Free Fatty Acid Receptors in Health and Disease. *Physiol Rev*. 100, 171-210 (2020).

Miyamoto J, Ohue-Kitano R, Mukoyama H, Nishida A, Watanabe K, Igarashi M, Irie J, Tsujimoto G, Satoh-Asahara N, Itoh H, Kimura I*. Ketone body receptor GPR43 regulates lipid metabolism under ketogenic condition. *Proc Natl Acad Sci U S A*. 116, 23813-23821 (2019).

Miyamoto J, Igarashi M, Watanabe K, Karaki SI, Mukoyama H, Kishino S, Li X, Ichimura A, Irie J, Sugimoto Y, Mizutani T, Sugawara T, Ogawa J, Drucker DJ, Arita M, Itoh H, Kimura I*. Gut microbiota confers host resistance to obesity by metabolizing dietary polyunsaturated fatty acids. *Nature Commun*. 10, 4007 (2019).

Website of the lab: <http://www.negishi.lif.kyoto-u.ac.jp/j/toppu.html>

Key words: Endocrinology, GPCR, Fatty Acid, Steroid Hormone, Energy Metabolism

6) Laboratory of Genetics

PI: IGAKI, Tatsushi (Prof.) <igaki@lif.kyoto-u.ac.jp>

Outline of the research

Our research focuses on the molecular basis of cell-cell communication that governs tissue growth, homeostasis, and cancer. We take advantage of the powerful genetics of *Drosophila*.

Research subjects:

1. Mechanism of cell competition
2. Genetic basis of tissue growth regulation
3. Molecular basis of tumor progression and metastasis

Publications

Sanaki, Y., Nagata, R., Kizawa, D., Leopold, P., and Igaki, T. Hyperinsulinemia drives epithelial tumorigenesis by abrogating cell competition. *Dev Cell* 53: 379-389 (2020)

Nagata, R., Nakamura, M., Sanaki, Y., and Igaki, T. Cell competition is driven by autophagy. *Dev Cell* 51: 99-112 (2019)

Yamamoto, M., Ohsawa, S., Kunimasa, K., and Igaki, T. The ligand Sas and its receptor PTP10D drive tumorsuppressive cell competition. *Nature* 542: 246-250 (2017).

Vaughen, J. and Igaki, T. Slit-Robo repulsive signaling excludes tumorigenic cells from epithelia. *Dev Cell* 39: 683-695 (2016)

Nakamura, M., Ohsawa, S. and Igaki, T. Mitochondrial defects trigger proliferation of neighbouring cells via a senescence-associated secretory phenotype in *Drosophila*. *Nat Commun* 5: 5264 (2014).

Ohsawa, S., Sato, Y., Enomoto, M., Nakamura, M., Betsumiya, A. and Igaki, T. Mitochondrial defect drives nonautonomous tumor progression through Hippo signaling in *Drosophila*. *Nature* 490: 547-551 (2012).

Website of the lab: <http://www.lif.kyoto-u.ac.jp/genetics/english/>

Key words: cell-cell communication, cancer, development, cell competition, *Drosophila*

7) Laboratory of Functional Biology

PI: KAKIZUKA, Akira (Prof.) <kakizuka@lif.kyoto-u.ac.jp>

Outline of the research

Using animal models of human diseases, such as neurodegenerations, cancers, and obesity-related diseases, and using metabolic imaging techniques, we aim to elucidate molecular bases of such diseases and develop new strategies to cure or prevent them.

Publications

Ide Y, Horie T, Saito N, Watanabe S, Otani C, Miyasaka Y, Kuwabara Y, Nishino T, Nakao T, Nishiga M, Nishi H, Nakashima Y, Nakazeki F, Koyama S, Kimura M, Tsuji S, Rodriguez RR, Xu S, Yamasaki T, Watanabe T, Yamamoto M, Yanagita M, Kimura T, Kakizuka A, Ono K. Cardioprotective Effects of VCP Modulator KUS121 in Murine and Porcine Models of Myocardial Infarction. *JACC Basic Transl Sci.* 28;4(6):701-714. (2019). doi: 10.1016/j.jacbts.2019.06.001.

Sugiyama Y, Shudo T, Hosokawa S, Watanabe A, Nakano M, Kakizuka A. Emodin, as a mitochondrial uncoupler, induces strong decreases in adenosine triphosphate (ATP) levels and proliferation of B16F10 cells, owing to their poor glycolytic reserve. *Genes Cells.* 24(8):569-584. (2019). doi: 10.1111/gtc.12712.

Alfaqaan S, Yoshida T, Imamura H, Tsukano C, Takemoto Y, Kakizuka A. PPAR α -Mediated Positive-Feedback Loop Contributes to Cold Exposure Memory. *Sci Rep.* 14;9(1):4538. (2019). doi: 10.1038/s41598-019-40633-3.

Nakano M, Imamura H, Sasaoka N, Yamamoto M, Uemura N, Shudo T, Fuchigami T, Takahashi R, and Kakizuka A. ATP Maintenance via Two Types of ATP Regulators Mitigates Pathological Phenotypes in Mouse Models of Parkinson's Disease. *EBioMedicine.* 22:225-241 (2017). doi: 10.1016/j.ebiom.2017.07.024.

Yoshida T, Kakizuka A, Imamura H. BTeam, a novel BRET-based biosensor for the accurate quantification of ATP concentration within living cells. *Sci Rep.* 7:44873 (2017). doi: 10.1038/srep44873.

Website of the lab: <http://www.funcbiol.lif.kyoto-u.ac.jp/>

Key words: drug development, neurodegenerative diseases, cancer, obesity, ATP, FRET biosensor

8) Laboratory of Chromosome Function and Inheritance

PI: CARLTON, Peter (Associate Prof.) <carlton.petermark.3v@kyoto-u.ac.jp>

Outline of the research

We study how chromosomes, the carriers of genetic information, are correctly maintained and passed on through generations. Combining molecular genetic approaches with advanced microscopy and quantitative imaging, we focus on mechanisms of chromosome pairing, recombination, and segregation in meiosis in the nematode *C. elegans*.

Publications

Sato-Carlton, A., Nakamura-Tabuchi, C., Chartrand, S.K., Uchino, T., and Carlton, P.M. Phosphorylation of the synaptonemal complex protein SYP-1 promotes meiotic chromosome segregation. *J. Cell Biol.* 217, 555–570. (2017). doi: 10.1083/jcb.201707161

Kafer, G.R., X. Li, T. Horii, I. Suetake, S. Tajima, I. Hatada, and P.M. Carlton. 5-Hydroxymethylcytosine Marks Sites of DNA Damage and Promotes Genome Stability. *Cell Rep.* 14:1283–1292. (2016). doi:10.1016/j.celrep.2016.01.035.

Sato-Carlton, A., X. Li, O. Crawley, S. Testori, E. Martinez-Perez, A. Sugimoto, and P.M. Carlton. Protein phosphatase 4 promotes chromosome pairing and synapsis, and contributes to maintaining crossover competence with increasing age. *PLoS Genet.* 10:e1004638. (2014). doi:10.1371/journal.pgen.1004638.

Mishima, Y., C.D. Jayasinghe, K. Lu, J. Otani, M. Shirakawa, T. Kawakami, H. Kimura, H. Hojo, P. Carlton, S. Tajima, and I. Suetake. Nucleosome compaction facilitates HP1 γ binding to methylated H3K9. *Nucleic Acids Res.* 43:10200–10212. (2015). doi:10.1093/nar/gkv841.

Kafer, G.R., P.M. Carlton, and S.A. Lehnert. The histone variant H2A.Z is dynamically expressed in the developing mouse placenta and in differentiating trophoblast stem cells. *Placenta*. 36:1325–1328. (2015). doi:10.1016/j.placenta.2015.08.018.

Schermelleh, L., P.M. Carlton, S. Haase, L. Shao, L. Winoto, P. Kner, B. Burke, C.M. Cardoso, D.A. Agard, M.G. Gustafsson, H. Leonhardt, and J.W. Sedat. Subdiffraction Multicolor Imaging of the Nuclear Periphery with 3D Structured Illumination Microscopy. *Science*. 320:1332–1336. (2008). doi:10.1126/science.1156947.

Website of the lab: <https://www.carltonlab.org/>

Key words: Meiosis, Chromosome segregation, *C. elegans*, super-resolution microscopy

9) Laboratory of Bioimaging and Cell Signaling

PI: MATSUDA, Michiyuki (Prof.) < matsudam@lif.kyoto-u.ac.jp >

Outline of the research

The current aim of our research is to decipher the mechanism underlying cell-to-cell communication. For this purpose, we are visualizing the activities of signaling molecules by using probes based on the principle of Förster resonance energy transfer (FRET). The FRET biosensors are extremely powerful to visualize the spatiotemporal regulation of signal transduction networks within cells and to analyze the activities of individual cells within tissues. We are also developing a series of optogenetic tools to activate molecules of interest within the tissues of live mice. Our laboratory is in charge of the core facility of fluorescence live imaging of Kyoto University.

Publications

Kinjo, T., Terai, K., Horita, S., Nomura, N., Sumiyama, K., Togashi, K., Iwata, S., and Matsuda, M. FRET-assisted photoactivation of flavoproteins for in vivo two-photon optogenetics. *Nat Methods*. 16, 1029-1036, (2019)

Muta, Y., Fujita, Y., Sumiyama, K., Sakurai, A., Taketo, M. M., Chiba, T., Seno, H., Aoki, K., Matsuda, M. & Imajo, M. Composite regulation of ERK activity dynamics underlying tumour-specific traits in the intestine. *Nat. Commun.* 9, 2174, (2018).

Konagaya, Y., Terai, K., Hirao, Y., Takakura, K., Imajo, M., Kamioka, Y., Sasaoka, N., Kakizuka, A., Sumiyama, K., Asano, T. & Matsuda, M. A Highly Sensitive FRET Biosensor for AMPK Exhibits Heterogeneous AMPK Responses among Cells and Organs. *Cell Rep.* 21, 2628-2638, (2017).

Website of the lab: <http://www.fret.lif.kyoto-u.ac.jp/e-phogemon/index.htm>

Key words: multiphoton fluorescence microscopy, biosensors, optogenetics, transgenic mouse

10) Laboratory of Theoretical Biology

PI: HONDA, Naoki (Associate Prof.) < honda.naoki.4v@kyoto-u.ac.jp >

Outline of the research

Our laboratory aims to elucidate the theoretical logic of dynamic living systems. By developing and simulating mathematical models, we are trying to understand mechanisms underlying phenomena in a bottom-up manner. We are also utilizing machine learning to extract hidden rules of dynamic, complicated phenomena from experimental quantitative data in a top-down manner. By means of these theoretical approaches, we are studying neuronal wiring in the brain, emotional neural dynamics, noise-resistant embryonic development, mechano-chemical mechanisms of

collective cell migration, cytoskeleton-based cellular morphogenesis, identification of intracellular information processing, and animal behavioral strategies.

Publications

Honda N*, Akiyama R, Sari DWK, Ishii S, Bessho Y and Matsui T: Noise-resistant developmental reproducibility in vertebrate somite formation. *PLoS Computational Biology* 15(2): e1006579 (2019)

Yamaguchi S, Honda N*, Ikeda M, Tsukada Y, Nakano S, Mori I and Ishii S: Identification of animal behavioral strategies by inverse reinforcement learning. *PLoS Computational Biology* 14(5): e1006122 (2018)

Honda N*: Revisiting chemoaffinity theory: Chemotactic implementation of topographic axonal projection *PLoS Computational Biology* 13(8), e1005702 (2017)

Li Y, Nakae K, Ishii S and Honda N*: Uncertainty-dependent extinction of fear memory in an amygdala-mPFC neural circuit model. *PLoS Computational Biology* 12(9), e1005099 (2016)

Yamao M, Honda N (Co-first), Kunida K, Aoki K, Matsuda M and Ishii S Distinct predictive performance of Rac1 and Cdc42 in cell migration. *Scientific Reports* 5, 17527 (2015)

Website of the lab: <https://sites.google.com/view/theoretical-biology/>

Key words: Mathematical model, Computer simulation, Machine learning, Data-driven modeling, Data analysis

11) Laboratory of Brain Development and Regeneration

PI: IMAYOSHI, Itaru (Prof.) <imayoshi.itaru.2n@kyoto-u.ac.jp>

Outline of the research

We aim to understand the cellular and molecular mechanism of the growth and fate-determination of neural stem cells in the developing and adult mammalian brain. We are also interested in the functional significance of postnatal/adult neurogenesis on higher brain functions, such as spatial learning/memory and olfactory-related behaviors. Our lab has expertise in the optical regulation of gene expression and neuronal activity, genetic manipulation of neural development and plasticity, and long-term monitoring of neural circuit plasticity in vivo with the two-photon microscope and brain endoscope.

Publications

Yamada, M., Nagasaki, C.S., Suzuki, Y., Hirano, Y. and *Imayoshi, I. (2020) Optimization of light-inducible Gal4/UAS gene expression system in mammalian cells. *iScience* in press

*Imayoshi, I., Tabuchi, S., Matsumoto, M., Kitano, S., Miyachi, H., *Kageyama, R. and Yamanaka, A. (2020) Light-induced silencing of neural activity in Rosa26 knock-in and BAC transgenic mice conditionally expressing the microbial halorhodopsin eNpHR3. *Sci Rep.*, 10(1):3191. doi: 10.1038/s41598-020-59984-3.

Yamada, M., Nagasaki, C.S., Ozawa, T. and *Imayoshi, I. (2020) Light-mediated control of gene expression in mammalian cells. *Neurosci Res.*, 152:66-77. doi: 10.1016/j.neures.2019.12.018.

Sueda, R., *Imayoshi, I. (equal contribution), Harima, Y., and *Kageyama, R. High Hes1 expression and resultant Ascl1 suppression regulate quiescent versus active neural stem cells in the adult mouse brain. *Genes Dev*, 33, 511-523 (2019).

Yamada, M., Suzuki, Y., Nagasaki, S., Okuno, H. and *Imayoshi, I. Light-inducible Tet-gene expression system in mammalian cells. *Cell Reports*, 25, 487-500 (2018)

*Suzuki, Y. and *Imayoshi, I. Network analysis of exploratory behaviors of mice in a spatial learning and memory task. *PLoS One* Jul 10;12(7):e0180789 (2017). doi: 10.1371/journal.pone.0180789.

*Imayoshi, I. and *Kageyama, R. bHLH Factors in Self-Renewal, Multipotency, and Fate Choice of Neural Progenitor Cells. *Neuron* 82: 9-23 (2014).

Sakamoto, M., Ieki, N., Miyoshi, G., Mochimaru, D., Miyachi, H., Imura, T., Yamaguchi, M., Fishell, G., Mori, K., Kageyama, R. and *Imayoshi, I. Continuous postnatal neurogenesis contributes to formation of the olfactory bulb neural circuits and flexible olfactory associative learning. *The Journal of Neuroscience* 34: 5788-5799 (2014).

I*mayoshi, I., Isomura, A. (equal contribution), Harima, Y., Kawaguchi, K., Kori, H., Miyachi, H., Fujiwara, T.K., Ishidate, F. and *Kageyama, R. Oscillatory control of factors determining multipotency and fate in mouse neural progenitors. *Science* 342: 1203-1208 (2013).

Imayoshi, I., Sakamoto, M., Ohtsuka, T., Takao, K., Miyakawa, T., Yamaguchi, M., Mori, K., Ikeda, T., Itohara, S. and *Kageyama, R. Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. *Nature Neuroscience* 11: 1153-1161 (2008).

Website of the lab: <https://brainnetworks.iimdfree.com>

Key words: Neural stem cells, Neurogenesis, Optogenetics, Hippocampus, Olfactory bulb

12) Laboratory of Genome Maintenance

PI: MATSUMOTO, Tomohiro (Prof.) <tmatsumo@house.rbc.kyoto-u.ac.jp>

Outline of the research

The spindle checkpoint is a unique negative feedback that converts/amplifies a physical signal sensed by kinetochores (attachment of the spindle and/or tension), and regulates the timing of sister chromatid separation for equal chromosome segregation. Mad2, a signal carrier of this feedback, plays a vital role in the spindle checkpoint. It is specifically localized at unattached kinetochores that are the origin of the checkpoint signal. Mad2 targets CDC20 and inhibits its activity to promote sister chromatid separation. We study Mad2, a central player of the spindle checkpoint, to reveal mechanisms which regulate the activity of Mad2.

Publications

Kitagawa T., Ishii K., Takeda K. and Matsumoto T. The 19S proteasome subunit Rpt3 regulates distribution of CENP-A by associating with centromeric chromatin. *Nat Commun.* (2014). doi: 10.1038/ncomms4597.

Horikoshi Y, Habu T and Matsumoto T. An E2 enzyme Ubc11 is required for ubiquitination of Slp1/Cdc20 and spindle checkpoint silencing in fission yeast. *Cell Cycle*. 12:961-71 (2013).

Ito D, Saito Y and Matsumoto T. Centromere-tethered Mps1 pombe homolog (Mph1) kinase is a sufficient marker for recruitment of the spindle checkpoint protein Bub1, but not Mad1. *Proc Natl Acad Sci U S A*. 109:209-14 (2012).

Website of the lab: http://house.rbc.kyoto-u.ac.jp/radiation_system/

Key words: chromosome, mitosis, centromere

13) Laboratory of Cancer Cell Biology

PI: HARADA, Hiroshi (Prof.) < harada.hiroshi.5e@kyoto-u.ac.jp >

Outline of the research

Cells maintain their functions and morphology by exploiting a suitable adaptive response system to diverse and complex tissue microenvironments. Several lines of evidence have suggested that hypoxic, acidic and nutrient-depleted microenvironments exist in solid tumors and induce malignant phenotypes and chemo/radioresistance of cancer cells. We aim to elucidate molecular mechanisms underlying both cellular adaptive responses to the tumor-specific microenvironments and malignant progression of cancer cells.

Publications:

Koyasu, S., Kobayashi, M., Goto, Y., Hiraoka, M., and *Harada, H. Regulatory mechanisms of hypoxia-inducible factor 1 activity: Two decades of knowledge. *Cancer Science*. 109:560-571. 2018.

Kobayashi, M., Morinibu, A., Koyasu, S., Goto, Y., Hiraoka, M., *Harada, H. A circadian clock gene, PER2, activates HIF-1 as an effector molecule for recruitment of HIF-1α to promoter regions of its downstream genes. *FEBS J*. 284:3804-3816. 2017.

Goto, Y., Zeng, L., Yeom, C. J., Zhu, Y., Morinibu, A., Shinomiya, K., Kobayashi, M., Hirota, K., Itasaka, S., Yoshimura, M., Tanimoto, K., Torii, M., Sowa, T., Menju, T., Sonobe, M., Kakeya, H., Toi, M., Date, H., Hammond E. M., Hiraoka, M. *Harada, H. UCHL1 provides diagnostic and antimetastatic strategies due to its deubiquitinating effect on HIF-1α. *Nature Commun.* 6: 6153 (2015). doi: 10.1038/ncomms7153

Zeng, L., Morinibu, A., Kobayashi, M., Zhu, Y., Wang, X., Goto, Y., Yeom, C. J., Zhao, T., Hirota, K., Shinomiya, K., Itasaka, S., Yoshimura, M., Guo, G., Hammond, E. M., Hiraoka, M. *Harada, H. Aberrant IDH3α expression promotes malignant tumor growth by inducing HIF-1-mediated metabolic reprogramming and angiogenesis. *Oncogene* 34: 4758-4766. (2015). doi: 10.1038/onc.2014.411

*Harada, H., Inoue, M., Itasaka, S., Hirota, K., Morinibu, A., Shinomiya, K., Zeng, L., Ou, G., Zhu, Y., Yoshimura, M., McKenna, W. G., Muschel, R. J. Hiraoka, M. Cancer cells that survive radiation therapy acquire HIF-1 activity and translocate towards tumour blood vessels. *Nature Commun.* 3: 783 (2012). doi:10.1038/ncomms3314.

Website of the lab: http://www.rbc.kyoto-u.ac.jp/cancer_biology/

Key words: cancer, tumor microenvironments, hypoxia, chemo/radioresistance

14) Laboratory of Laboratory of Chromatin Regulatory Network

PI: IKURA, Tsuyoshi (Associate Prof.) < ikurat@house.rbc.kyoto-u.ac.jp >

Outline of the research

The eukaryotic genome is tightly packed into the chromatin, a hierarchically organized complex of DNA, histone and nonhistone proteins. This packing represents a common obstacle for the metabolic processes of DNA including transcription, replication, recombination, and DNA repair. Current evidence indicates that chromatin reorganization involving histone modification, histone variant exchange, histone eviction and ATP-dependent chromatin remodeling play an integral role in DNA repair and DNA damage response. However, it remains unclear how such chromatin reorganization is coupled with the initiation of DNA repair process and/or activation of checkpoint machinery after DNA damage. We are now investigating the following issues:

1. The molecular mechanisms by which the TIP60 histone acetylase complex regulates histone H2AX exchange induced by ionizing radiation.

2. The cross-talk between the histone signaling network regulated by histone H2AX exchange and DNA damage response pathways.

Publications

Ikura, M., Furuya, K., Fukuto, A., Matsuda, R., Adachi, J., Matsuda, T., Kakizuka A., Ikura, T. Coordinated regulation of TIP60 and PARP-1 in damaged chromatin dynamics. *Mol Cell Biol.* 36:1595-1607 (2016). doi: 10.1128/MCB.01085-15.

Ikura, M., Furuya, K., Matsuda, S., Matsuda, R., Shima, H., Adachi, J., Matsuda, T., Shiraki, T., Ikura, T. Acetylation of histone H2AX at Lys 5 by the TIP60 histone acetyltransferase complex is essential for the dynamic binding of NBS1 to damaged chromatin. *Mol Cell Biol.* 35: 4147-4157 (2015). doi: 10.1128/MCB.00757-15.

Ikura T., Tashiro, S., Kakino, A., Shima, H., Jacob, N., Amunugama, R., Yoder, K., Izumi, S., Kuraoka, I., Tanaka, K., Kimura, H., Ikura M., Nishikubo, S., Ito, T., Muto, A., Miyagawa K., Takeda, S., Fishel, R., Igarashi, K., *Kamiya, K. DNA damage-dependent acetylation and ubiquitination of H2AX enhances chromatin dynamics. *Mol Cell Biol.* 27:7028-7040 (2007). doi:10.1128/MCB.00579-07

Ikura, T., Ogryzko, V V., Grigoriev, M., Groisman, R., Wang, J., Horikoshi, M., Scully, R., Qin, J., Nakatani, Y Involvement of the TIP60 Histone Acetylase Complex in DNA repair and apoptosis. *Cell.* 102:463-473 (2000). doi.org/10.1016/S0092-8674 (00)00051-9

Website of the lab: <http://house.rbc.kyoto-u.ac.jp/mutagenesis2/index1>

Key words: chromatin dynamics, histone acetyltransferase, histone variant, DNA damage response

15) Laboratory of RNA Viruses

PI: TOMONAGA, Keizo (Prof.) <tomonaga@infront.kyoto-u.ac.jp>

Outline of the research

The main purpose of our research is to investigate the molecular mechanisms underlying the replication and pathogenesis of animal-derived RNA viruses. Analysis of the endogenization of RNA viruses and its role on host-virus co-evolution is also focused on this laboratory.

Publications

Yanai M et al., ADAR2 is involved in self and nonself recognition of Borna disease virus genomic RNA in the nucleus. *J Virol* 94(6):e01513-19 (2020) doi: 10.1128/JVI.01513-19

Kojima S et al., Splicing-dependent subcellular targeting of Borna disease virus nucleoprotein isoforms. *J Virol* 93(5) e01621-1618 (2019) doi: 10.1128/JVI.01621-18.

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Fujino K et al., Inhibition of Borna disease virus replication by an endogenous bornavirus-like element in the ground squirrel genome. *Proc Natl Acad Sci USA* 111:13175-13180 (2014). doi: 10.1073/pnas.1407046111

Matsumoto, Y., Hayashi, Y., Omori, H., Honda, T., Daito, T., Horie, M., Ikuta, K., Fujino, K., Nakamura, S., Schneider, U., Chase, J., Yoshimori, T., Schwemmle, M. and Tomonaga, K. Bornavirus closely associates and segregates with host chromosomes to ensure persistent intranuclear infection. *Cell Host Microbe* 11:492-503 (2012). doi: 10.1016/j.chom.2012.04.009

Horie, M., Honda, T., Suzuki, Y., Kobayashi, Y., Daito, T., Oshida, T., Ikuta, K., Jern, P., Gojobori T., Coffin, J. M. and Tomonaga, K. Endogenous non-retroviral RNA virus elements in mammalian genomes. *Nature* 463:84-87 (2010). doi: 10.1038/nature08695

Website of the lab: <https://t.rnavirus.virus.kyoto-u.ac.jp/>

Key words: bornavirus, endogenous viruses, RNA virus vector

16) Laboratory of Cell Division and Differentiation

PI: TOYOSHIMA, Fumiko (Prof.) <ftoyoshi@infront.kyoto-u.ac.jp>

Outline of the research

Balance between self-renewal and differentiation of stem cells is essential for tissue homeostasis. Biased stem cell self-renewal or differentiation leads to changes in tissue organization. Our group studies on the mechanisms of symmetric/asymmetric stem cell division, stem cell differentiation, stem cell plasticity, and cell lineage-commitment in tissue homeostasis and regeneration. We are interested in how tissue stem cells adapt to physiological changes of the body throughout life stages, such as pregnancy, obesity and aging.

Publications

Ichijo, R., Kobayashi, H., Yoneda, S., Iizuka, Y., Kubo, H., Matsumura, S., Kitano, S., Miyachi, H., Honda, T., and Toyoshima, F. Tbx3-dependent amplifying stem cell progeny drives interfollicular epidermal expansion during pregnancy and regeneration. *Nat. Commun.* 8: 508 (2017). doi:10.1038/s41467-017-00433-7

Matsumura, S., Kojidani, T., Kamioka, Y., Uchida, S., Haraguchi, T., Kimura, A., and Toyoshima, F. Interphase adhesion geometry is transmitted to an internal regulator for spindle orientation via caveolin-1. *Nat. Commun.* 7:11857 (2016). doi: 10.1038/ncomms11858

Iwano, S., Satou, A., Matsumura, S., Sugiyama, N., Ishihama, Y., and Toyoshima, F. PCTK1 regulates integrin-dependent spindle orientation via PKA regulatory subunit KAP0 and myosin X. *Mol. Cell. Biol.* 35, 1197-1208 (2015).

Matsumura S., Hamasaki M., Yamamoto T., Ebisuya M., Sato M., Nishida E. and Toyoshima F. ABL1 regulates spindle orientation in adherent cells and mammalian skin. *Nat. Commun.* 3:626 (2012). doi: 10.1038/ncomms 1634

Website of the lab: <https://www2.infront.kyoto-u.ac.jp/Toyoshima-HP/index-En.html>

Key words: oriented cell division, stem cells, tissue homeostasis

17) Laboratory of Cellular and Molecular Biomechanics

PI: ADACHI, Taiji (Prof.) <adachi@infront.kyoto-u.ac.jp>

Outline of the research

We aim to clarify the mechanisms by which cells sense mechanical stimuli and regulate their activities in tissue adaptation, regeneration and stem cell differentiation in morphogenesis. Based on multiscale biomechanics, our group is involved in the integrated biomechanics and mechanobiology researches of modeling and simulation combined with experiments, focusing on mechano-biochemical couplings in the system dynamics.

Publications

Kameo, Y., Miya, Y., Hayashi, M., Nakashima, T., Adachi, T. In silico experiments of bone remodelling explores metabolic diseases and their drug treatment. *Sci. Adv.*, 6-10: eaax0938 (2020). doi: 10.1126/sciadv.aax0938

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Ando, Y., Okeyo, K. O., Adachi, T. Modulation of adhesion microenvironment using mesh substrates triggers self-organization and primordial germ cell-like differentiation in mouse ES cells. *APL Bioeng*, 3: 016102 (2019). doi: 10.1063/1.5072761

Maki, K., Han, S. W., Hirano, Y., Yonemura, S., Hakoshima, T., Adachi, T. Real-time TIRF observation of vinculin recruitment to stretched α -catenin by AFM. *Sci Rep*, 8: 1575 (2018). doi: 10.1038/s41598-018-20115-8

Okuda S., Takata, N., Hasegawa, Y., Kawada, M., Inoue, Y., Adachi, T., Sasai, Y., Eiraku, M. Strain-triggered mechanical feedback in self-organizing optic cup morphogenesis. *Sci. Adv.* 4-11: eaau1354 (2018). doi: 10.1126/sciadv.aau1354

Website of the lab: <https://www2.infront.kyoto-u.ac.jp/bf05/index-e.html>

Key words: biomechanics, mechanobiology, adaptation, morphogenesis, modeling and simulation