World Premier International Research Center Initiative (WPI)
FY 2020 WPI Project Progress Report

Host Institution	Kyoto University	Host Institution Head	MINATO Nagahiro
Research Center	Institute for the Advanced Study of Human Biology		
Center Director	SAITOU Mitinori	Administrative Director	OGAWA Tadashi

Common instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2021) situation of your WPI center.
* So as to execute this fiscal year's follow-up review on the "last" center project plan, prepare this report based on it.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.
- Prepare this report within 10-20 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within 2 pages)).

Summary of State of WPI Center Project Progress (write within **2 pages**)

We have continued to strive to establish ASHBi as one of the WPI centers during FY2020, despite the challenging circumstances posed by COVID19 for domestic/international interactions. We have adapted ourselves to these new circumstances, driving our work forward in a seamless manner.

The main building for ASHBi (Building B of the Faculty of Medicine Campus; ~2010 m^2 of working space) has reached a fully functioning state, with six principal investigator (PI) groups (**Alev**, **Amemori**, **Bourque**, **Hiiragi**, **Murakawa**, and **R. Yamamoto**), a Mathematical Science group (**Hiraoka**), a Bioethics and Philosophy group (**Fujita**), a Single-Cell Genome Information Analysis Core (SignAC: **T. Yamamoto**), and an ASHBi Administrative Office (**T. Ogawa**) working in an interactive manner, together with other ASHBi PI groups based at Kyoto University (KU) and Shiga University of Medical Science (SUMS: a domestic satellite of ASHBi). A new space for maintaining cynomolgus monkeys for ASHBi research at the Primate Genome Engineering Core (PRiME: **Tsukiyama**) of SUMS (125 m^2) has also been established.

Over FY2020, the SignAC has constantly provided essential support, supplying next-generation sequences (NGS) for ASHBi research and organizing the **1st ASHBi SignAC Workshop 2021**, to which more than 200 scientists attended. SignAC joined the **"Innovative Support Alliance for Life Science (iSAL)"** at KU, which provides easy access to state-of-the-art equipment to researchers inside/outside of KU (see **4. Making Organizational Reforms**). The PRiME has succeeded in generating three and five knockout monkeys for *NPHP1* (with **Yanagita**) and *DISC1* (with **Isa**), respectively, and they have initiated careful analyses of these knockout animals.

In conjunction with our classification of ASHBi PIs into four groups (Developmental Biology, Genome Informatics, Macaque Genome Engineering, and Basic/Clinical Medicine), we have engaged in discussions on the initiation of **ASHBi Flagship Projects**. We propose the following projects as candidates: **"**Mechanism and *ex vivo*/*in vitro* reconstitution of primate development" (Developmental Biology group), "Establishing an interdisciplinary platform for the integrated analysis of disease-associated gene functions in primates" including "A systematic study of anxiety disorders by an integrative approach that combines functional genomics and neuroscience" (Genome Informatics/Macaque Genome Engineering), "Mechanism and regulation of aging-associated disorders" (Basic/Clinical Medicine group), and "Creating an integrated framework for using human tissues including fetal tissues for human biology research" (**Fujita** and all ASHBi PIs) (see **7. Center's Response to the Results of Last Year's Follow-up, Response 2**).

The representative papers by ASHBi PIs in 2020 in line with the ASHBi's five key themes include "Recapitulating the human segmentation clock with pluripotent stem cells: *Nature*" (**Alev, T. Yamamoto: Themes 1**, **2**, and **4**), "ZGLP1 is a determinant for the oogenic fate in mice: *Science*" (**Saitou, T. Yamamoto: Themes 1**, **2**, and **4**), "Personalized and graph genomes reveal missing signal in epigenomic data: *Genome Biol.*" (**Bourque**: **Themes 1**, **2**, and **3**), "Contribution of the

pulvinar and lateral geniculate nucleus to the control of visually guided saccades in blindsight monkeys: ***J. Neurosci.***" (**Isa: Themes 2** and **3**), "Combined Cohesin–RUNX1 deficiency synergistically perturbs chromatin looping and causes myelodysplastic syndromes: *Cancer Disc.*" (**S. Ogawa: Themes 1** and **2**), "Developmental stages of tertiary lymphoid tissue reflect local injury and inflammation in mouse and human kidneys: *Kidney Int.*" (**Yanagita: Themes 1** and **2**), and "The American public is ready to accept human-animal chimera research: *Stem Cell Rep.*" (**Fujita: Themes 1** and **2**) (see **1. Advancing Research of the Highest Global Level**).

Hiraoka and **Fujita** have actively organized interdisciplinary research. The key ongoing projects by **Hiraoka** include: 1) Resolution of the curse of dimensionality in single-cell RNA sequence data analysis (with **Saitou**, **T. Yamamoto**, manuscript in preparation, patent pending), 2) Trajectory inference by optimal transport theory and a Gaussian mixture model (with **Alev**, **Saitou**), and 3) Topological data analysis of immune cells (with **Ueno**), among others. **Hiraoka** organized the **2nd ASHBi Mathematical Biology Workshop** (Sep 2020). The key ongoing projects by **Fujita** include: 1) Ethics of embryoid research (with **Alev**), 2) Ethics of cerebral organoid research (with **Isa**), and 3) Ethics of using human fetal tissues in research (with **Saitou**).

To promote fusion research among young scientists and develop a collaborative atmosphere, we have initiated the "**ASHBi Fusion Research Grant**" projects, and this year, selected 7 applications (5 for math-bio, 1 for ethics-bio, and 1 for bio-bio fusions) for this award. We organized the **2nd ASHBi Retreat** (Feb 2021), in which 7 young researchers from the ASHBi Fusion Research Grant projects gave oral presentations and 36 poster presentations were performed, with 93 participants in highly active discussions (see **2. Generating Fused Disciplines**).

We have been making efforts to increase our international visibility. The International Society for Stem Cell Research (ISSCR) invited ASHBi to join the "**International Circle of Stem Cell Research Institutes and Centers**" in Aug 2020. The European Molecular Biology Organization (EMBO) invited ASHBi to co-organize "**EMBO-Japan Virtual Lectures**," which will be held in Oct 2021. Using the tenure position provided by KU, we initiated an international search to recruit one foreign PI in Oct 2020 and are currently in the final selection process. Upon his/her appointment, the foreign PI ratio in ASHBi will increase to 22.2%, satisfying the WPI standard. We have intensified recruitment of foreign researchers and hired five additional researchers as of Apr 2021, increasing the foreign researcher ratio at ASHBi to 24% in Apr 2021. To further increase the number of foreign researchers, in Feb 2020, we established the "**Foreign Researcher Employment Support Program**," which provides financial support (up to 5 million JPY/year for 3 years) to ASHBi PIs who hire foreign researchers. Using this program, ASHBi plans to recruit 3–5 foreign researchers in FY2021, which will raise the ratio of our foreign researchers to near or beyond the WPI standard of 30%. Furthermore, we are actively recruiting foreign graduate students. As of Apr 2021, there are 11 foreign graduate students in the ASHBi PI labs. To accelerate the recruitment of foreign students, we introduced the "**Financial Support Program for International Graduate Students**" in FY2020, and calls for this program will begin in FY2021. This program provides financial support (up to 150,000 JPY/month) to foreign graduate students by hiring them as research assistants (RA) (see **3. Realizing an International Research Environment** and **6. Others**).

Note that many foreign postdocs and students are having serious difficulties in obtaining visas to work or study in Japan under the COVID19 pandemic, despite their having been formally appointed to the laboratories of ASHBi PIs or having passed admittance examinations for the Graduate Schools of KU during FY2020. We strongly hope an immediate resolution of this situation.

KU has provided two tenured positions to ASHBi, which has greatly helped in new PI recruitment. ASHBi researchers obtained approximately 1 billion JPY in total as external funds in FY2020, allowing ASHBi to sustainably develop itself as a world-level research center. ASHBi has introduced a billing system for services offered by SignAC to secure and expand the functionality of SignAC. A number of seminars to accelerate research activity in KU and other universities/WPI centers have been organized by the Research Acceleration Unit in the ASHBi Administrative Office (see **4. Making Organizational Reforms** and **5. Efforts to Secure the Center's Future Development over the Mid- to Long-term**).

* Describe clearly and concisely the progress being made by the WPI center project from the viewpoints below.
- In addressing the below-listed 1-6 viewpoints, place emphasis on the following:
  (1) Whether research is being carried out at a top world-level (including whether research advances are being made by fusingdisciplines).
  (2) Whether a proactive effort continues to be made to establish itself as a "truly" world premier international research center.
  (3) Whether a steadfast effort is being made to secure the center's future development over the mid- to long-term.

1. Advancing Research of the Highest Global Level

* Among the research results achieved by the center, concretely describe those that are at the world's highest level. In Appendix 1, list the center's research papers published in 2020.
* Regarding the criteria used when evaluating the world level of center, note any updated results using your previous evaluation criteria and methods or any improvements you have made to those criteria and methods.

ASHBi investigates a key concept of human biology with a particular focus on genome regulation and disease modeling, thereby creating a foundation of knowledge for understanding the key biological traits that make us "human" and for developing innovative therapies. Specifically, we perform investigations in line with the following five key themes:

1. Promote the study of human biology, with a focus on genome regulation
2. Clarify the principles defining the species differences and human traits
3. Generate primate models for intractable human diseases
4. Reconstitute key human cell lineages or tissues *in vitro*
5. Contribute to formalizing an international ethics standard for human biology research

Theme 1 is the fundamental theme covering, as a reflection of the PIs' expertise, areas as broad as reproduction, development, growth and aging as well as heredity and evolution.

The **Alev group** published a manuscript entitled "Recapitulating the human segmentation clock with pluripotent stem cells" (*Nature*, **580**, 124–129, 2020) and made a major contribution to a manuscript entitled "Species-specific segmentation clock periods are due to differential biochemical reaction speeds" (*Science*, **369**, 1450–1455, 2020) (relevant to **Themes 1**, **2**, and **4**).

In the former study, using iPSC-based technologies, the group succeeded in modelling the human segmentation clock, a biological mechanism underlying the rhythmic and controlled emergence of somites, which give rise to the segmental vertebrate axial skeleton. They observed oscillatory expression of core segmentation clock genes, determined the period of the human segmentation clock to be around 5 hours, and demonstrated the presence of dynamic travelling-wave-like gene expression *in vitro*. They identified and compared oscillatory genes in the human and mouse presomitic mesoderm, which revealed species-specific and shared molecular components and pathways. Using CRISPR–Cas9-based genome editing, they mutated genes responsible for segmentation defects of the vertebrae, such as spondylocostal dysostosis, and revealed gene-specific alterations in oscillation, synchronization or differentiation properties, providing insights into the human segmentation clock as well as diseases associated with human axial skeletogenesis. In the latter study, they showed that the species difference in the oscillation periods of segmentation clocks (mice: 2–3 hours; humans: 5–6 hours) is due to differences in multiple biochemical reactions of *HES7*, the core segmentation clock gene, including degradation and expression delays. Accordingly, they proposed that cell-autonomous differences in biochemical reaction speeds underlie temporal differences in development between species.

The **Saitou group** published manuscripts entitled "ZGLP1 is a determinant for the oogenic fate in mice" (*Science*, **367**, 1089, 2020: doi:10.1126/science.aaw4115) and "Long-term expansion with

germline potential of human primordial germ cell-like cells *in vitro*" (*EMBO J.*, **39**, e104929) (relevant to **Themes 1**, **2**, and **4**).

In the former study, the group showed that ZGLP1, a conserved transcriptional regulator with GATA-like zinc fingers, determines the oogenic fate in mice. ZGLP1 acts downstream of bone morphogenetic protein, but not retinoic acid (RA), and is essential and sufficient for the oogenic program and meiotic entry. Their findings elucidate the mechanism for mammalian oogenic fate determination, providing a foundation for promoting *in vitro* gametogenesis and reproductive medicine. In the latter study, the group showed that human primordial germ cell-like cells (hPGCLCs) derived from hiPSCs can be propagated to at least ~10^6-fold over a period of 4 months with retention of their germline potential. During expansion, however, hPGCLCs maintain an early hPGC-like transcriptome and preserve their genome-wide DNA methylation profiles, most likely due to the retention of maintenance DNA methyltransferase activity. These characteristics contrast starkly with those of mouse PGCLCs (mPGCLCs), which, under an analogous condition, show a limited propagation (up to ~50-fold) and persist only around 1 week, yet undergo cell-autonomous genome-wide DNA demethylation. This study uncovers critical divergences in expansion potential and the mechanism for epigenetic reprogramming between the human and mouse germ cell lineage.

The above works were the result of close collaborations with the **T. Yamamoto group** and **SignAC**.

The **Bourque group** published a manuscript entitled "Personalized and graph genomes reveal missing signal in epigenomic data" (*Genome Biol.*, **21**, 124, 2020) (relevant to **Themes 1** and **2**).

Epigenomic studies that use next-generation sequencing experiments typically rely on the alignment of reads to a reference sequence. However, because of genetic diversity and the diploid nature of human and other primate genomes, the group hypothesized that the use of a generic reference could lead to incorrectly mapped reads and bias downstream results. In this manuscript, they showed that the use of personalized genomes and more advanced graph-genomes allows the recovery of new peaks enriched for indels and SNVs. These altered peaks are more likely to differ between individuals and, as such, could be relevant to the study of various human phenotypes.

The **Isa group** made a major contribution to a manuscript entitled "Selective mesoaccumbal pathway inactivation affects motivation but not reinforcement-based learning in macaques" (*Neuron*, **108**, 568–581, 2020) and published a manuscript entitled "Contribution of the pulvinar and lateral geniculate nucleus to the control of visually guided saccades in blindsight monkeys" (*J. Neurosci.*, doi: 10.1523/JNEUROSCI.2293-20.2020) (relevant to **Themes 2** and **3**).

In the former study, using a cutting-edge double-infection viral vector technique to regulate the activity of critical neural circuits in macaque monkeys, the group showed that, unlike what has been observed in rodents, the mesoaccumbal pathway in primates is critical for high-effort motivation but not for all forms of reinforcement-based learning. In the latter study, using a meticulous model in macaque monkeys, the group investigated the mechanism underlying "blindsight," a phenomenon in which some patients with critical damage to the primary visual cortex (V1) can still respond to visual stimuli presented in their lesion-affected visual field. Their findings support the notion that the pulvinar and lateral geniculate nucleus play key roles in compensating V1 lesioning, and that the visuomotor functions of blindsight monkeys were supported by plastic changes in the visual pathway involving the pulvinar, which emerged after V1 lesioning. During the phylogeny of vertebrate species, the extrageniculate visual pathway is more developed in fish, amphibians, reptiles, birds, and, among mammals, rodents, while the geniculate visual pathway is more developed in primates. The compensatory mechanism of the function of the geniculate pathway by the extrageniculate pathway when the former is damaged, shown in this study, provides novel insight into the relationship

between the two visual pathways existing in vertebrates.

The **S. Ogawa group** published a manuscript entitled "Combined Cohesin–RUNX1 deficiency synergistically perturbs chromatin looping and causes myelodysplastic syndromes" (*Cancer Disc.*, **10**, 836–853, 2020) (relevant to **Themes 1** and **2**).

Using sophisticated conditional-knockout mouse models and genomics technologies, the group demonstrated the critical role of the interplay between STAG2, a cohesin component frequently mutated in myeloid neoplasms, and RUNX1, a master transcription factor of hematopoiesis, in myelodysplastic syndrome (MDS) development. They revealed the contribution of STAG2 and RUNX1 in the regulation of high-order chromatin structures, particularly enhancer–promoter looping, and the link between transcriptional pausing and selective gene dysregulation caused by cohesin deficiency. The group validated that high-pausing genes were down-regulated also in STAG2–Cohesin-mutated primary leukemia samples. Their results highlight a unique STAG2–RUNX1 interplay in gene regulation and provide insights into Cohesin-mutated leukemogenesis.

The **Yanagita group** published manuscripts entitled "Developmental stages of tertiary lymphoid tissue reflect local injury and inflammation in mouse and human kidneys" (*Kidney Int.*, **98**, 448–463, 2020) and "Spatiotemporal ATP dynamics during AKI predict renal prognosis" (*J. Am. Soc. Neph.*, **31**, 2855–2869, 2020) (relevant to **Themes 1** and **2**).

The group has been working on the etiology of critical kidney diseases. In the former study, based on their previous findings that aged mice exhibited multiple tertiary lymphoid tissues (TLTs) after acute kidney injury and that TLTs are associated with sustained kidney injury/inflammation, they analyzed surgically resected kidneys from patients, classified TLTs into three distinct stages, and found that TLT stages reflect local injury/inflammation in human kidneys. In the latter study, using a novel mouse line allowing the visualization of spatiotemporal ATP dynamics at single cell resolution, they revealed ATP dynamics differences among nephron segments, which explain the distinct sensitivities of such segments to ischemic reperfusion injury. They found a strong correlation between ATP recovery in proximal tubules in acute phase and renal fibrosis in chronic phase. Accordingly, cold ischemia enhanced ATP recovery in acute phase and reduced renal fibrosis in chronic phase, providing a proof of concept for renal hypothermia, which has been utilized empirically in kidney transplantation and partial nephrectomy in humans. This study improves our understanding of kidney energy dynamics during kidney injury and repair.

The **Fujita group** published manuscripts entitled "The moral status of human embryo-like structures: potentiality matters? The moral status of human synthetic embryos" (*EMBO Rep.*, **21**, e50984, 2020) and "The American public is ready to accept human-animal chimera research" (*Stem Cell Rep.*, **15**, 804–810, 2020) (relevant to **Theme 5**).

In the former study, the group provided a rationale for the application of the 14-day rule to embryoid structures *in vitro* (see **2. Generating Fused Disciplines**). The latter study was a joint project with the University of Minnesota, where a questionnaire survey was completed by 430 members of the general American public, polling to what extent they approve of human–animal chimeric embryo research. The group found that ~80% of the respondents approved of injecting animal embryos with hiPSCs (Stage 1), ~70% approved of creating chimeric animals containing human organs (Stage 2), and ~60% approved of transplanting these organs into humans (Stage 3). The level of acceptance among regular Americans was higher than that among regular Japanese using the same questionnaire in 2016. In Japan, following the promulgation of new guidelines in 2019, research that goes so far as to create chimeric animals (Stage 2) has been approved. However, NIH suspended the use of federal subsidies for research involving the injection of hPSCs

into animal embryos (Stage 1) in 2015. The group argued that NIH should relax their restrictions, given the permissive attitudes of the American public and the results of other scientific reviews. This work represents an interdisciplinary and international cooperative research that stimulates an international discussion regarding the regulation of human–animal chimeric embryo research.

2. Generating Fused Disciplines

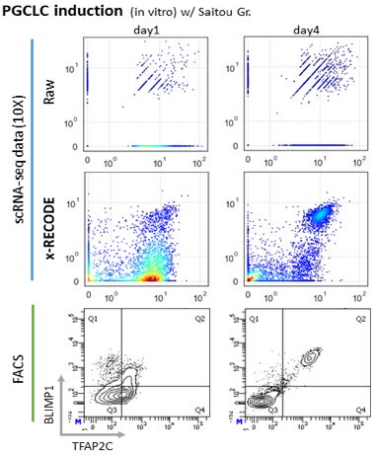
* Describe the content of measures taken by the center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields. If any, describe the interdisciplinary research/fused discipline that have resulted from your efforts to generate fused disciplines. You may refer to the research results described concretely in "1. Advancing Research of the Highest Global Level."

ASHBi has been performing fusion research between mathematics (the **Hiraoka group**) and life sciences, and between humanities/social sciences (the **Fujita group**) and life sciences, and such research has been progressively expanding/maturing. We continue to make intensive efforts to advance fusion research, including our launch of the "**ASHBi Fusion Research Grant,**" **ASHBi Retreat**, and other active collaborations with clinical doctors.

Fusion between mathematics and life sciences

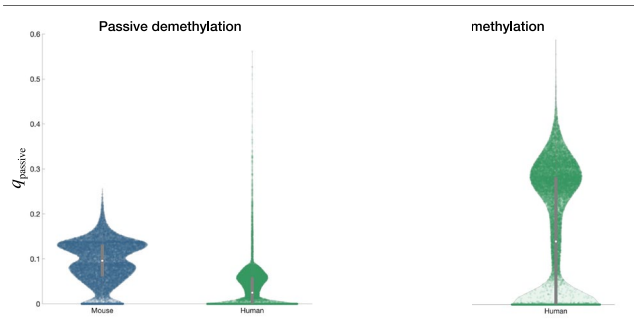
1. Resolution of the curse of dimensionality in single-cell RNA sequence data analysis (with the Saitou group & T. Yamamoto group)

Single-cell RNA sequence (scRNA-seq) data contain rich biological information. However, due to the problem known as the "curse of dimensionality," this information cannot be extracted properly by conventional data analysis methods (e.g., tSNE, MDS, PCA, etc.). To circumvent the curse of dimensionality, last year, based on high-dimensional statistics, we proposed a noise reduction method called RECODE (resolution of the curse of dimensionality). This year, RECODE has been upgraded for denoising UMI-based scRNA-seq data (extended RECODE: xRECODE). xRECODE outperformed representative imputation methods in reproducing true gene expression distributions [Figure: a result of xRECODE applied to 10X Chromium scRNA-seq data during hPGCLC induction] (manuscript in preparation, patent pending).

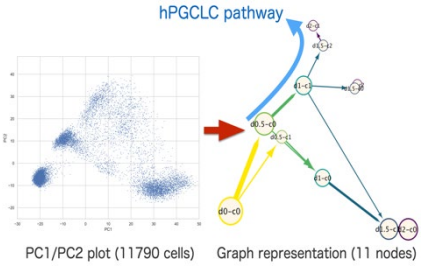


2. Inference and prediction of dynamic epigenetic modifications (with the Saitou group)

Epigenetic modifications, such as DNA methylation and histone modifications, play fundamental roles in regulating gene expression and genome structure. This project aims to develop a method for inferring the kinetics of genome-wide DNA demethylation during germ-cell development. We have constructed two mathematical models with several parameters for methylation/demethylation rates estimated from genome-wide DNA methylation profiles in m/hPGCLCs. We found differences in demethylation kinetics in m/hPGCLCs, suggesting that hPGCLCs may involve more active demethylation than mPGCLCs (Figure: estimated passive and active demethylation rates in m/hPGCLCs). We are planning to perform experiments to verify our prediction and to further improve the accuracy of our models. This study may lead to discovery of a distinct mechanism for genome-wide DNA demethylation between mice and humans.

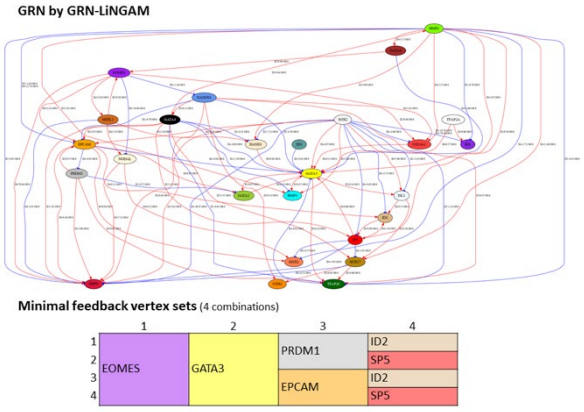


3. Trajectory inference by optimal transport theory and the Gaussian mixture model (with the Alev group & Saitou group)



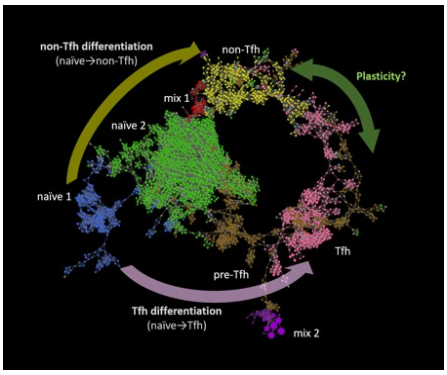
This project aims to develop a novel method for inferring cell differentiation trajectories based on scRNA-seq data. We have developed a method combining the Gaussian mixture model (GMM) with optimal transport (OT) theory. GMM is used for clustering and estimating probability distributions of scRNA seq data, while OT enables time-tracking study of these probability distributions, including interpolations, future predictions, and ancestor searches in scRNA seq data. We first applied the GMM-OT to the scRNA-seq data for hPGCLC specification, identifying clearly branching pathways and genes that appear to contribute to the cell-fate branching (Figure: a graph representation for hPGCLC specification). We will analyze the function of such genes as well as extend the GMM-OT to other cell differentiation processes.

4. Inference of gene regulatory networks by causal discovery (with the Saitou group, S. Shimizu (Shiga Univ.) & K. Mischaikow (Rutgers Univ.))



This project develops a mathematical and statistical method to infer gene regulatory networks (GRNs) for describing relationships of transcription regulations among genes from scRNA-seq data. In 2018 and 2019, we developed a novel GRN inference method called GRN-LiNGAM, an extension of the LiNGAM (causal discovery method) combined with DSGRN, for describing the underlying dynamical system of gene regulations. This year, we tackled the development and application of mathematical analysis methods (e.g., feedback vertex set analysis and Boolean dynamics) to dynamical system models obtained by GRN-LiNGAM. We identified genes with potential importance during hPGCLC specification (Figure: an inferred gene regulatory network and its minimal feedback vertex sets). We will perform an integrative analysis with GMM-OT and GRN-LiNGAM to fully understand the hPGCLC specification mechanism and extend the strategy to other systems.

5. Topological data analysis (TDA) of immune cells (with the Ueno group)



This project aims to clarify the structure of immune cell differentiations by applying TDA to scRNA-seq data. We applied Mapper, a powerful TDA method that extracts precise topological structures in high-dimensional data. This year, we have succeeded in describing detailed topological structures of immune cell differentiations involving naïve T cells, Th cells, and Tfh cells—to name only a few—by combining RECODE and Mapper. In particular, we discovered a loop structure implying plasticity between Th and Tfh cells in human samples *in vivo* (Figure: loop structure in the Mapper graph implying plasticity).

Challenges leading to the creation of new mathematical theories

To create fusion between mathematics and life sciences, the **Hiraoka group** has not only explored novel applications of existing mathematical methodologies to data obtained from life sciences, but

also developed new mathematical concepts, theorems and descriptors. Many such endeavors have proved valuable to the fields of both mathematics and life sciences. A key finding is the notion that high-dimensional data with noise—such as scRNA-seq data—possesses intrinsic mathematical structures that can cause improper biological conclusions when analyzed by conventional statistical methods, leading the group to formulate RECODE/xRECODE.

Accordingly, the group is aiming to create a new mathematics field involving "data representation theory," the goal of which will be to comprehensively understand mathematical structures (both static and dynamic) underlying large and complex data and to develop precise and informative descriptors tailored to respective specific analyses. Mathematics is a language of nature, and the rise of data science poses a new challenge to mathematics: to develop a new and descriptive vernacular appropriate for rapidly increasing the size and complexity of data acquired in modern life sciences. Thus, the group will endeavor to establish data representation theory in ASHBi.

Fusion between humanities/social sciences and life sciences

1. Ethics of embryoid research (with the Alev group)

As part of an ASHBi Fusion Research Grant Project, Sawai, Okui, **Alev**, and others have closely examined ethical issues associated with embryoid research, which has seen significant advancement in recent years. The group published a portion of these investigations (*EMBO Rep.*, **21**, e50984, 2020), in which they argued that the 14-day rule (human embryos are not allowed to develop beyond 14 days post-fertilization or beyond the formation of the primitive streak *in vitro*) should be applied to embryoid structures if they contain elements that can mature into fetuses or humans (elements such as blastoids, ETX-embryoids, micropatterned stem-cell cultures, and epiblast-amniotic sac structures), whereas when embryo-like structures do not contain such elements, the studies should be subject to the restrictions placed on research involving human somatic cells.

Moreover, the group regularly invite leading experts in the field to share their perspectives and insights. This year, they hosted five internationally renowned researchers, two life-science researchers, two experts on philosophy and ethics, and one expert on regulation.

Date	Lecturer's Name	Presentation Title
10/9	Dr. Alexandre Erler, Chinese University of Hong Kong, China	Germline genome editing, the scientific community, and democratic governance
11/26	Dr. Nicholas Rivron, IMBA, Austria	The ethics of embryo models formed solely from stem cells
12/11	Dr. Benjamin Hurlbut, Arizona State University, USA	Taking responsibility: Governing research at the edges of human life
12/23	Dr. John Crowley, UNESCO, France	Ethics beyond shared understanding: exponential approaches to radical innovation
2/4	Dr. Martin Pera, The Jackson Laboratory, USA	Human pluripotent stem cells and the human embryo

2. Ethics of cerebral organoid research (with the Isa group and others)

In collaboration with **Isa** and other scientists, philosophers, and ethicists from both inside and outside Japan, the group categorized the issues incumbent upon research and clinical applications involving cerebral organoids into three categories (*in vitro* studies, *in vivo* studies in animals and humans, and issues around research regulation) and is continuing discussion to prepare a manuscript. Furthermore, as part of an ongoing effort to revise the ISSCR Guidelines, **Fujita** participated in a Working Group to investigate the issues around organoid and chimeric animals research, and gave a lecture at the ISSCR 2020 Virtual event's Ethics Focus Session (the session was very well attended, with a total of 908 attendees), contributing to the ASHBi's mission "to formalize an international ethics standard for human biology research."

3. Ethics of using human fetal tissues in research (with the Saitou group and others)
With **Saitou**, **Takashima** (Center for iPS Cell Research and Application: CiRA), and other Japanese philosophers, ethicists, and legal scholars, the group has examined ethical issues related to the use of human fetal tissues in research. Ultimately, the group aims to create guidelines for conducting fetal tissue studies, compile reports that form an academic basis for such studies, and clarify the items necessary for explanatory documents to donors. This year, they investigated the present regulatory situation, the history of these studies in Japan and abroad (USA, UK, Germany, and France), and identified general principles for conducting human fetal tissue studies in an ethical way. The main principles included: (1) the separation of abortion decisions and tissue donation decisions, ensuring the former precede the latter; (2) the separation of abortion doctors and researchers, and (3) the placement of coordinators to support decision-making. Furthermore, the absence of Japanese legislation directly applicable to the use of human cells and tissues in research, and the fact that Japanese law does not clarify whether dead fetuses younger than 12 weeks old are humans or objects, were all raised as obstacles to the creation of consistent guidelines.

4. Other activities
The group hosted a lecture by Mr. Tetsuro Nagaoka (part-time lecturer, Kyoto University)—who specializes in the philosophy of Kitaro Nishida—entitled 'The Profundity of "Life" from the Perspective of Nishida's Philosophy' (Jan 2021). While the approaches of scientists and philosophers differ, given that both share a common goal of defining the nature of humanity and life itself, it is vital and timely to promote cross-disciplinary discussion and mutual exchange of ideas on such key topics.

ASHBi Fusion Research Grant
To promote fusion research among young scientists, to develop a collaborative atmosphere for generating intellectual inspiration across different fields, and to further advance the collaborative power of fusion research in ASHBi, this year, we initiated the "ASHBi Fusion Research Grant" project.

Accordingly, each project must form a research team consisting of researchers from different fields (math-bio, ethics-bio, and bio-bio). The supporting period is 1–3 years and the funding is up to 3 million yen per year for each project. To train young researchers in performing fusion research, the Fusion Research Grant project leaders should be non-PIs, i.e., postdocs, Assistant Professors, etc. Since most young researchers are not yet familiar with fusion research, we have paid close attention to and offered active support for their training: we have set up a committee consisting of PIs from each major discipline —Eiraku (biology), Fujita (ethics), and Hiraoka (math)— for examining the progress of and giving feedback to the Fusion research teams, and we have also organized two workshops in which the teams present their work to all ASHBi members. This year, we selected 7 applications (5 for math-bio, 1 for ethics-bio, and 1 for bio-bio fusions) to award this grant. We believe that this project will promote fusion research in ASHBi and the training of young researchers.

Selected Research Projects of FY2020

Category	Representative	Project Title
Math-Bio	Yusuke Seto	Mathematical modelling and experimental modulation of the dynamics of human osteogenesis
	Yusuke Imoto	Identification of multi-resolution cell differentiation dynamics from scRNA-seq data via mathematical data analysis and interactive visualization system
	Kumiko Yoshioka-Kobayashi	Characterization of gene regulatory networks in human and non-human in vitro segmentation clocks
	Taro Tsujimura	Topological approaches for integrative 3D epigenomics
	Sohei Tasaki	Inference of genome-wide DNA demethylation kinetics by dynamic model fitting Research

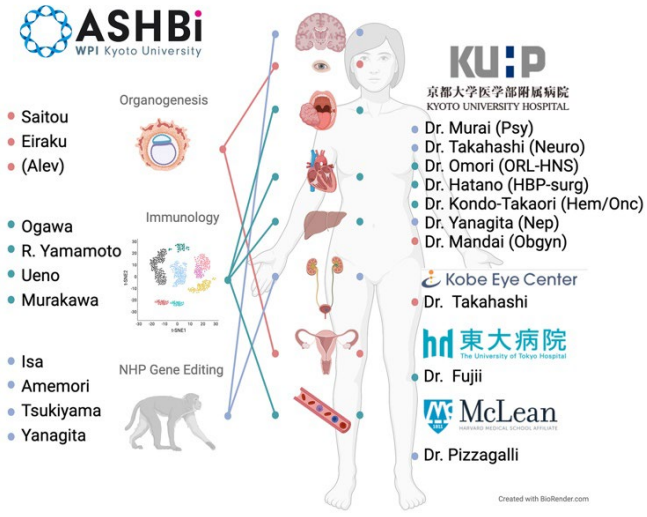
Ethics-Bio	Tsutomu Sawai	Examining ethics and governance in developmental biology
Bio-Bio	Xun Chen	Deciphering evolutionary differences of germline transposable element dynamics

ASHBi Retreat 2021

For promoting collaborative research and creating a good working atmosphere, we organized the second ASHBi Retreat (Feb 2021). Due to COVID19, the event was held via online systems (Zoom and SpatialChat). The retreat consisted of two parts: a fusion research workshop in the morning and a poster session in the afternoon. In the workshop, 7 young researchers from all fusion research grant projects gave presentations and explained their research's progress and future scope. It was an extremely valuable occasion for young researchers to share the expected and unexpected difficulties encountered in fusion research with all ASHBi members, and to receive their constructive criticisms and advice for moving the research forward. In the poster session, we had in total 36 poster presentations (1–3 posters from each PI group). Although the session was held online, the environment was as exciting as—or more exciting than—a face-to-face format, due to the extensive preparation by the ASHBi Office staff in setting up multiple online poster presentation rooms, across which participants could move and attend different poster sessions seamlessly. After the poster session, we also organized a networking session by SpatialChat, where researchers and students deepened their discussions and sharpened the inspirations they experienced during the retreat. In total, 93 researchers and students participated in the retreat. See https://ashbi.kyoto-u.ac.jp/events/ashbi-retreat-2021_report/ for the event report.

Active collaborations with clinical doctors

ASHBi PIs have been actively collaborating with clinical doctors to obtain samples from human subjects and to investigate the etiology of critical diseases/promote human biology (see the Figure and attached Table for details). This includes collaborations of:



The **S. Ogawa group** with **Prof. Kondo-Takaori** of the Department of Hematology and Oncology (KU Hospital) and many other clinical doctors, to investigate, among other topics, the mechanism of hematological malignancies; the **Ueno group** with **Prof. Hatano** of the Department of Hepato-Biliary-Pancreatic Surgery (KU Hospital), **Prof. Mandai** of the Department of Gynecology and Obstetrics (KU Hospital), **Prof. Omori** of the Department of Otolaryngology, Head and Neck Surgery (KU Hospital), and many other clinical doctors, to promote human immunology; the **Murakawa group** with **Prof. Yanagita** of the Department of Nephrology (KU Hospital: ASHBi PI), **Prof. Kondo-Takaori** of the Department of Hematology and Oncology (KU Hospital), and many other clinical doctors, to investigate disease-associated enhancers; the **Isa group** with **Prof. Takahashi** of the Department of Neurology (KU Hospital: ASHBi PI), **Prof. Murai** of the Department of Psychiatry (KU Hospital), and many other clinical doctors, to investigate the phenotype of *DISC1* KO monkeys; the **Eiraku group** with **Prof. Takahashi** (Kobe Eye Center) to promote translational research on the hiPSC-derived neural retina; the **Saitou group** with **Prof. Mandai** of the Department of Gynecology and Obstetrics (KU Hospital) to promote human *in vitro* oogenesis research.

In addition, the **Fujita group** has been involved in the Act on the Safety of Regenerative Medicine. The group participated in the MHLW (Ministry of Health, Labour and Welfare)'s consignment project

"Study to Improve the Quality of Screening at the Certified Regenerative Medical Committee (PI: Morikuni Tobita, Juntendo University)," in which they surveyed how CCRMs evaluate regenerative medicine "treatment" and contributed to legal revisions of these applications.

3. Realizing an International Research Environment

* Describe what's been accomplished in the efforts to raise the center's recognition as a genuine globally visible research institute, along with innovative efforts proactively being taken in accordance with the development stage of the center, including the following points, for example:
- Efforts being developed based on the analysis of number and state of world-leading, frontline researchers (in Appendix 2); exchanges with overseas entities (in Appendix 4); number and state of visiting researchers (in Appendix 5)
- Proactive efforts to raise the level of the center's international recognition
- Efforts to make the center into one that attracts excellent young researchers from around the world (such as efforts fostering young researchers and contributing to advancing their career paths)

ASHBi as a globally visible research institute

We have been making efforts to increase our international visibility. As a result of our exertion, ASHBi has been invited to join several world leading research communities as a top Japanese representative.

One example is our relationship with the International Society for Stem Cell Research (ISSCR), which is the largest society in the world dedicated to the advancement of stem cell research. ISSCR invited ASHBi to join the "**International Circle of Stem Cell Research Institutes and Centers**" in Aug 2020. This circle consists of 19 leading institutes/centers in the world on stem cell research and includes the Gladstone Institutes, Boston Children's Hospital, and Penn IRM. ASHBi was one of the first organizations invited to join this growing circle, an indication of our global status in the field.

Circle of stem cell research institutes/centers

ASHBi was also invited by EMBO (the European Molecular Biology Organization), an organization of more than 1800 researchers that promotes excellence in the life sciences in Europe and beyond, to co-organize "**EMBO-Japan Virtual Lectures**". This collaborative activity was proposed to ASHBi Director Saitou directly by EMBO Director Maria Leptin and is more evidence of our global status.

Internationalization of ASHBi PIs (Recruiting a foreign PI)

In FY2020, we recruited three new PIs and one co-PI (Appendix 2a). Moreover, using the new tenured professor/associate professor position provided by KU, we started an international call to recruit one foreign PI in Oct 2020 and are currently in the selection process. This new foreign PI is scheduled to join ASHBi in FY2021 and after his/her appointment, the ratio of foreign PIs in ASHBi will increase to more than 20% (22.2% = 4/18), satisfying the WPI standard.

New PIs/co-PIs who joined ASHBi in FY2020 and FY2021

Year	Name	Position	Former affiliation
FY2020	**Ryo Yamamoto**	PI, Associate Professor	Stanford U, USA
	Kenichi Amemori	PI, Associate Professor	Kyoto U (PRI), Japan
	Yasuhiro Murakawa	PI, Tenured Professor	RIKEN, Japan
	Fumitaka Inoue	Co-PI (Bourque G), Associate Professor	UCSF, USA
FY2021	**TBD (foreigner)**	PI, Tenured Professor/Associate Professor	

Internationalization of ASHBi researchers

The WPI follow-up report in 2020 recommended us to put more attention on the internationalization of our researchers. We have therefore intensified our recruitment of foreign researchers. However, Japanese policies in response to the COVID-19 pandemic have made it impossible for us to employ foreign researchers residing abroad. In response, we focused our search to foreign researchers

already at domestic universities and research institutes. Thus, we hired five excellent candidates as of Apr 2021 (described below), increasing the ratio of foreign researchers at ASHBi from 17% in Apr 2020 to 24% in Apr 2021 (Appendix 3-1a).

New foreign researchers who joined ASHBi in Apr FY2021

Year	Name (Nationality)	PI group/position	Research field
Apr 2021	Killian Meehan (US)	Hiraoka-G postdoc	Mathematics
	Zicong Zhang (Chinese)	Bourque/Inoue-G postdoc	Genomics
	Sofiane Hamidi (French)	Alev-G postdoc	Developmental Biology
	Shruti Bhagat (Indian)	Murakawa-G postdoc	Bioinformatics
	Tania Afroj (Bangladeshi)	R Yamamoto-G, postdoc	Hematology, Stem cell Biology

To further increase the number of foreign researchers at ASHBi, we established the "Foreign Researcher Employment Support Program". This program, which opened in Feb 2020, provides financial support (up to 5 million JPY/year for 3 years) to ASHBI PIs who hire foreign researchers. Using this program, ASHBI plans to recruit 3-5 foreign researchers in FY2021, which will raise the ratio of our foreign researchers to near or surpass the WPI standard of 30%.

Internationalization of ASHBi students

In addition, we are actively recruiting foreign graduate students. As of Apr 2021, there were 11 foreign graduate students studying in ASHBi PI labs. To increase the number of foreign graduate students, we utilized the "McGill-Kyoto International Collaborative Program in Genomic Medicine (Joint PhD)". This program was established with the KU Graduate School of Medicine and McGill University and welcomes students from McGill University to study at KU.(ASHBi PI **Bourque** is one of the main organizers at McGill University) Students accepted into this program will share their time between the two universities and will be awarded the PhD degree jointly by both universities. Through this program, ASHBi has already received two foreign students (May 2019 – Jul 2020; Nov 2020 – Oct 2021) and will receive another foreign student in FY2021.

To further accelerate the recruitment of foreign students, we introduced the "Financial Support Program for International Graduate Students" in FY2020, and open calls for this program will begin in FY2021. This program provides financial support (up to 150,000 JPY/month) to foreign graduate students by hiring them as research assistants (RA). Awardees of this program will be required to attend ASHBi's major events (e.g. ASHBi Colloquiums, International Symposium, and Retreat) in order to enhance their interactions with other ASHBi researchers and students.

Online seminars by overseas researchers

Due to the COVID-19 outbreak, it was nearly impossible to invite overseas researchers in FY2020. Nevertheless, to create opportunities for ASHBi researchers/students to interact with overseas researchers, we have held 25 Zoom online seminars in FY2020, with 11 highlighting speakers from overseas. This effort allowed us to maintain international interactions with overseas institutes despite difficulties under the COVID-19 pandemic.

We have strived to provide opportunities for researchers in and out of ASHBi to connect with global research. 1st **ASHBi SignAC Workshop** was held in 19 Feb 2021 which more than 200 scientists attended. We will hold the workshop annually to discuss recent technological innovations and the application of single-cell approaches to fundamental biological questions.

Online meetings with overseas speakers

Also, we have turned **ASHBi Seminars** into a regularly held series where each PI will host at least one seminar inviting speaker from their research field to share the recent research findings in the relevant field. Further, as mentioned earlier, the humanities/social science group organized **ASHBi Bioethics-Biology Fusion Seminars** proactively inviting internationally renowned researchers.

ASHBi international symposiums/International training school

To expand the international visibility and collaborative network of ASHBi, we originally planned to hold two international symposiums in FY2020. The first was the **"EMBO Workshop on Molecular Mechanisms of Developmental and Regenerative Biology"**, which was scheduled for 9-11 Nov 2020 (Organizers: Ian Chambers, The University of Edinburgh; Elly M. Tanaka, Research Institute of Molecular Pathology; Patrick P.L. Tam, Children's Medical Research Institute; Saitou and Hiiragi, ASHBi). The other was the **"International Symposium on Development and Plasticity of Neural Systems"**, scheduled for 8-11 Mar 2021 (Organizers: Ryoichiro Kageyama, KU; Isa and Eiraku, ASHBi). Unfortunately, both were postponed to Mar/Apr 2022 due to COVID-19.

We also postponed an international school, **"JANUBET Primate Neurobiology School"**, which would have invited overseas young researchers and students to study at ASHBi and the Primate Research Institute in Inuyama. The school is co-sponsored by ASHBI and the Research Council of Norway (Organizers: Menno Witter and Cliff Kentros, Norwegian University of Science and Technology; Masahiko Takada, KU; Ken-ichiro Tsutsui, Tohoku University; Isa, ASHBi). The school was rescheduled to Sep 2021.

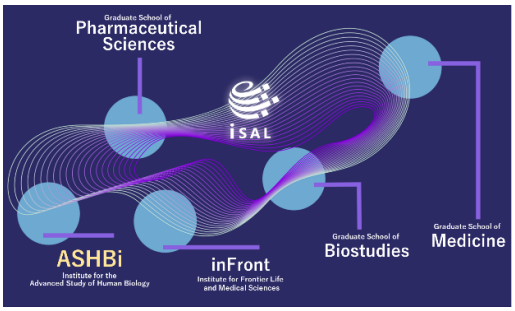
Currently, all symposiums and workshop mentioned above will be held either by onsite or online without further postponement.

4. Making Organizational Reforms

* Describe the system reforms made to the center's research operation and administrative organization, along with their background and results.
* If innovated system reforms generated by the center have had a ripple effect on other departments of the host institutions or on other research institutions, clearly describe in what ways.
* Describe the center's operation and the host institution's commitment to the system reforms.

An alliance for equipment provision to researchers inside/outside of KU

In FY 2020, ASHBi's core facility (SignAC) joined the **"Innovative Support Alliance for Life Science (iSAL)"**. iSAL was established in 2018 to provide easy access to state-of-the-art equipment in KU to researchers inside/outside of KU. This alliance consists of core facilities from the Graduate School of Medicine, the Graduate School of Pharmaceutical Sciences, the Graduate School of Biostudies, the Institute for Frontier Life and Medical Sciences, and ASHBi. iSAL has established an online system, called KUMaCo, which simplifies the booking and billing of equipment use. By joining iSAL, our advanced equipment in SignAC is more visible to researchers and supports a broader range of researches inside and outside of KU. It is also expected to stimulate joint research projects and industry-academia collaborations at ASHBi.



Innovative Support Alliance for Life Science (iSAL)

Seminars to accelerate research activity in KU and other universities/WPI centers

The Research Acceleration Unit in the ASHBi Administrative Office plays a key role in institutional support for foreign/early-stage researchers and organizes the **Research Acceleration Program**. The Unit originally consisted of Tadashi Ogawa (Administrative Director) and Makoto Shida (URA). In FY2020, we hired two more members. **Tomoki Shimizu** (Junior Associate Professor), appointed in Feb 2021, was recruited from KU's PR staff and has over 10 years of experience as a science

writer. **Hiromi Inoue** (Research Coordinator), appointed in Nov 2020, was a lab manager for 5 years at UCSF, with specialty in the life sciences. This recruitment has enabled ASHBi to develop sophisticated programs and specialized support for foreign/early-stage researchers.

ASHBi Research Acceleration Seminars/Workshops

The Research Acceleration Programs provide opportunities for early-stage researchers to gain professional knowledge/skills to perform research effectively. The programs are open to KU and other universities (including other WPI centers). As one example, in FY2020, we held a seminar jointly organized with WPI-iCeMS on writing effective KAKENHI grant proposals. After the seminar, KU URAs worked directly with early-stage researchers, resulting in several successful KAKENHI and AMED grant applications. As another example, we organized a seminar to introduce BioRender, a biomedical science-specific illustration tool widely used around the world. Currently, we are organizing a seminar that encourages researchers to promote their research findings internationally. We will invite an expert from the AAAS to share the concept and process of writing effective international press releases.

5. Efforts to Secure the Center's Future Development over the Mid- to Long-term

* Address the following items, which are essential to mid- to long-term center development:
- Future prospects with regard to the research plan, research organization and PI composition; prospects for fostering and securing of next-generation researchers
- Prospects for securing resources such as permanent positions and revenues; plan and/or implementation for defining the center's role and/or positioning the center within the host institution's institutional structure
- Measures to sustain the center as a world premier international research center after program funding ends
- Host institution's organizational reforms carried out for the center's autonomous administration simultaneously with the creation of the center.

To secure the future development of the Institute, ASHBi, KUIAS (Kyoto University Institute for Advanced Study), and KU headquarter administrative offices have been working closely together. In addition, the experiences of the other WPI center in KU (iCeMS) has allowed us to obtain effective solutions for smooth operations on the institutional management.

Tenured positions provided by the host institution

To secure the Institution's long-term development, KU has provided two tenured faculty positions to ASHBi. Utilizing these positions, we employed one new PI in Oct 2020, Yasuhiro Murakawa, as a tenured professor (Appendix 2). We also made a global open call from Oct 2020 to recruit another tenured professor/associate professor in the life and/or mathematical sciences. Efforts are being made for this second person to be a female foreign PI. The University's personnel support has greatly helped in our search for excellent researchers.

Securing external research funding and financial support from the host institution

ASHBi researchers obtained approximately 1 billion JPY in total as external research funding in FY2020 (see Appendix 3-1), which consists of funding by Grants-in-Aid for Scientific Research (274 million JPY), Commissioned Research Projects (543 million JPY) and Joint Research Projects (103 million JPY). Securing such a large amount of external funding will allow us to sustainably develop the Institute as a world-level research center.

KU continuously allows ASHBi to take half of the indirect funds associated with competitive grants acquired by ASHBi researchers. With this financial support, ASHBi was able to acquire approximately 123 million JPY as indirect funds in FY2020. Furthermore, KU has granted us a flexible multiple-year budget for indirect funds. This permission allows us to allocate our budget over two fiscal years. Accordingly, we carried over 40 million JPY from FY2020 to FY2021 to purchase a state-of-the-art

long-read DNA sequencer.

Fostering graduate students

The KU Graduate School of Medicine offers research training courses on 12 different themes. From FY2020, ASHBi has jointly organized the "Developmental Biology/Cell Biology/Systems Biology" course. This course provides discussion beyond specialized fields and is organized as a monthly seminar that includes two talks in English; one by a young researcher (30 min) and the other by an invited speaker (1 hour). In FY2020, Alev, Hiraoka, and R Yamamoto individually organized seminars and invited 6 total speakers (4 overseas and 2 Japanese researchers). In FY2021, Amemori, Murakawa and a new ASHBi PI will organize the seminar in this course. This partnership with the Graduate School of Medicine enables ASHBi to reach and recruit more graduate students.

Securing new income options for SignAC equipment and services

ASHBi has newly introduced a billing system for scientific services offered by SignAC to secure and expand the functionality of our core facility.

The billing system is currently being launched, but only for the use of two devices in addition to some analysis services. Once we optimize the operations from this trial, we will expand the targets to other equipment in ASHBi. With this earned income, SignAC should be able to pursue its mission of providing researchers open access to equipment and expertise for state-of-the-art single-cell genomics even after the program funding ends.

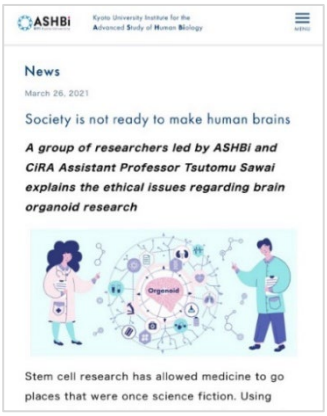
SignAC provides services, such as RNA-seq library prep and NGS support, to users.

6. Others

* Describe what was accomplished in the center's outreach activities last year and how the activities have contributed to enhancing the center's "globally visibility." In Appendix 6, describe concretely the contents of these outreach activities. In Appendix 7, describe media reports or coverage, if any, of the activities.
* In addition to the above 1-5 viewpoints, if there is anything else that deserves mention regarding the center project's progress, note it.

Enhancing global PR activities to increase our international presence

In order to enhance the international visibility of ASHBi, we recruited the PR officer Shimizu to the Research Acceleration Unit in FY2020. As a first outcome, we have developed an English press release format to promote our research findings more effectively. In accordance with international standards, the format consists of an easy-to-understand title, an appealing visual image, and jargon-free text. This will make it easier for the international media to refer to and report on our press releases, leading to an increase of our international visibility. Using this new format, we made 12 English press releases in FY 2020 on the ASHBi website. One of the press releases was distributed to EurekAlert!, which is the largest international scientific news release platform operated by AAAS.



Partial image of a press release on ASHBi's website

Strategic use of SNS for international visibility

As part of our strategy to effectively use SNS for our outreach activities, we opened a Twitter account on Dec 2020 and a Facebook page on Feb 2021. We have actively posted ASHBi's research results and academic events, such as seminars and symposia, on these sites. By the end of FY2020, we had 47 posts on Twitter and 25 posts on Facebook. To increase our followers, we have disseminated information strategically and in a timely manner. For instance, we posted information about seasonal photos like cherry blossoms and awards given to our young researchers at the ASHBi Retreat in

addition to announcing research publications. We are also following the accounts of targeted researchers and research groups globally in related fields in order to increase our followers. Currently, we have 266 followers on Twitter and 82 on Facebook, but these numbers keep growing. Furthermore, 71% of Twitter followers are foreign researchers and research groups.

* The numbers are as of 31 Mar 2021.

ASHBi

Spring has come. The cherry blossoms near our building are now in full bloom. It is much earlier than usual.

11:10 AM · Mar 23, 2021 · Twitter Web App

ASHBi
@Ashbi_KyotoU

Kumiko Yoshioka-Kobayashi, Akiko Oguchi and Masahiro Nagano got "Excellence in Research Award" at ASHBi Retreat 2021. The three recipients were granted research funding of JPY300,000 to promote their research. Congratulations!! ashbi.kyoto-u.ac.jp/news/20210220_... #ASHBi #award

3 Young Researchers received Excellence in Research Award at ASHBi Retrea...
ASHBi Director Mitinori Saitou awarded the "Excellence in Research Award" to Kumiko Yoshioka-Kobayashi (Alev Group), Akiko Oguchi (Murakawa Group) ...
ashbi.kyoto-u.ac.jp

9:02 AM · Mar 4, 2021 · Twitter Web App

Examples of SNS articles from ASHBi

7. Center's Response to Results of Last Year's Follow-up

* Transcribe the item from the "Actions required and recommendations" section in the site visit report and the Follow-up report, then note how the center has responded to them.
* If you have already provided this information, indicate where in the report.

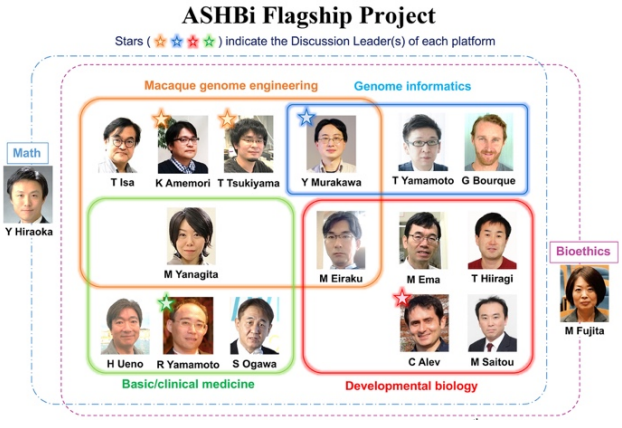
(1) We don't want ASHBi to be an organization where excellent scientists merely use common equipment and facilities. We strongly hope that scientists from different fields will always share their problems toward opening up new academic fields and obtain synergistic effects. Young PIs will become more aware of the value of ASHBi's organization and contribute to its enhancement by being actively involved in its operation.

Response 1. Please see **2. Generating Fused Disciplines**. We have been promoting fusion research and creating collaborative environments, including the inauguration of the **ASHBi Fusion Research Grant** projects for young scientists and periodical **ASHBi Retreats**, among many other interactive opportunities within ASHBi. Indeed, young researchers and PIs have been playing leading roles in these activities, and their synergistic explorations are expected to open new academic fields. Please see also **Response 2** regarding our efforts to set up the **ASHBi Flagship Projects**, in which young PIs are also playing leading roles.

(2) ASHBi should set up flagship projects in each of its 5 lines of key research goals with an aim to promote human biology, clarify principles defining species differences, generate NHP models for human diseases, reconstitute human cell lineages or tissues, and contribute to formalizing an international ethics standard. It should explain how each of its key published papers has addressed ASHBi's 5 goals.

Response 2. We would like to thank the WPI Program Committee and Working Group for their constructive comments on our activity. Please see **1. Advancing Research of the Highest Global Level**, in which we explain how each of our key papers has addressed the 5 goals of ASHBi.

We have discussed setting up the **ASHBi Flagship Projects**. We classified the ASHBi PIs into four groups (Developmental Biology, Basic/Clinical Medicine, Genome Informatics, and Macaque Genome Engineering) and a young PI(s) in each group served as a discussion leader to determine the Flagship Project candidates for each group. As a result, the following projects have been proposed as Flagship Project candidates:



Developmental Biology Group:
Mechanism and *ex vivo*/*in vitro* reconstitution of primate development

Recent studies, including those from ASHBi PIs, have shown that the mechanisms underlying early

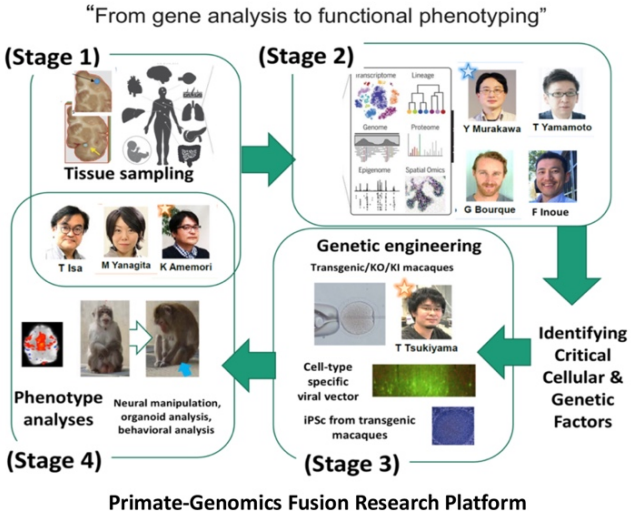
developmental processes, including cell-fate specifications in blastocysts, early post-implantation development, and germ-cell specification, are very different between mice and primates/humans. Moreover, the mechanisms for post-implantation development in primates/humans are largely unknown due to technological and ethical difficulties in accessing/manipulating relevant samples. These notions point to the importance of studying the mechanism of embryonic development in primates, which will provide critical insights into the mechanism of human development and stem cell-based regenerative medicine. Taking advantage of our better access to cynomolgus monkey embryos through PRiME and human/non-human primate PSCs, we propose "**Mechanism and *ex vivo*/*in vitro* reconstitution of primate development**" as one of the ASHBi Flagship Project candidates.

Specifically, this project will be carried out by the **Alev**, **Eiraku**, **Ema**, **Hiiragi**, **Hiraoka**, and **Saitou groups**, will focus on understanding the mechanism of pre-/post-implantation primate development and reconstituting it *ex vivo* and *in vitro*, and will consist of three inter-related efforts:
1) Understanding of the mechanism of post-implantation primate development at a single-cell resolution via, e.g., scRNA-seq combined with novel analysis methods such as xRECODE and GMM-OT developed by the **Hiraoka** group (**the Alev, Hiraoka, and Saitou groups**).
2) Development of *ex vivo* culture systems for analyzing pre-/post-implantation development of mouse and cynomolgus monkey embryos via, e.g., advanced light-sheet imaging coupled with scRNA-seq analysis (**the Ema, Hiiragi, Hiraoka, and Saitou groups**).
3) *In vitro* reconstitution and analysis of pre-/post-implantation development of human and non-human primates via, e.g., bottom-up approaches utilizing PSC-based synthetic embryo model systems analyzed via high-end 3D/4D imaging and scRNA-seq analysis (**the Alev, Eiraku, and Hiraoka groups**).

We believe that this project will significantly enhance our understanding of the mechanism of primate development, and that it is highly relevant to the ASHBi's **Themes 1**, **2** and **4**.

Genome Informatics and Macaque Genome Engineering Groups:
Establishing an interdisciplinary platform for the integrated analysis of disease-associated gene functions in primates

ASHBi PIs assigned to the Genome Informatics and Macaque Genome Engineering groups joined together to discuss the establishment of an interdisciplinary platform, the "**Primate-Genomics Fusion Research Platform**," for the integrated analysis of disease-associated gene functions in primates (the **Amemori**, **Bourque/Inoue**, **Isa**, **Murakawa**, **Tsukiyama**, **Yamamoto**, and **Yanagita** groups). The phenotypes of knockout monkeys for *NPHP1* (**Yanagita group**) and *DISC1* (**Isa group**) will be analyzed through this collaborative platform.



Primate-Genomics Fusion Research Platform

Moreover, the **Amemori** and **Murakawa groups** will perform **"A systematic study of anxiety disorders by an integrative approach that combines functional genomics and neuroscience."** Psychiatric disorders such as schizophrenia and anxiety disorders impose a major medical and social burden worldwide. Recent GWAS studies of psychiatric disorders have identified hundreds of disease susceptibility loci. However, the neurobiological mechanisms of human psychiatric illness still remain largely unsolved. In this project, using non-human primates, which

are genetically and anatomically much more similar to humans than rodents, they will systematically study the mechanisms of anxiety disorders. Disease-associated genetic variants are often mapped to non-coding enhancer regions, which activate the expression of target genes in a cell-type-specific manner. They will identify disease genes and pathways as well as disease-relevant cell types where these genes are expressed. For this purpose, the **Amemori group** will obtain tissues from the non-human primate brain circuitries that are potentially involved in anxiety disorders [the amygdala, anterior cingulate cortex (ACC), bed nucleus of stria terminalis (BNST), anterior insular cortex (including the caudal orbitofrontal cortex) (AIC), and subgenual anterior cingulate cortex (sACC), and the downstream structure including the basal ganglia and nucleus that regulates the dopaminergic activities]. The **Murakawa group** will then apply their original single-cell genomics technology to identify genes and enhancers in diverse neuronal cells that are sometimes even primate-specific. Finally, the **Amemori group** will develop viral vectors to manipulate the specific cell types and neural pathways, validating the functionality *in vivo*. Through a series of these integrative and collaborative studies, these groups aim to elucidate the molecular mechanisms underlying anxiety disorders, paving the way for innovative medicines of the future. These projects are highly relevant to the ASHBi's **Themes 1**, **2** and **3**.

Basic/Clinical Medicine Group:
Mechanism and regulation of aging-associated disorders

The human life cycle consists of development, growth/maturation, and aging. Among these, aging involves progressive and continuous alterations in genome function, leading to malfunctions of organs and immune/hematopoietic systems, and eventually, to critical age-associated disorders, including cancers. A major pre-condition for age-associated alterations has been thought to be chronic, low-grade inflammation, which progressively causes local injuries and is called "inflammaging." Thus, elucidation of the mechanisms associated with aging is of fundamental importance in human biology and in exploring remedies for aging-associated disorders. Based on these notions, the Basic/Clinical Medicine group will focus on the mechanism and regulation of aging-associated disorders.

The **S. Ogawa group** will focus on understanding the mechanism of hematopoietic aging, including clonal hematopoiesis, and the pathogenesis of aging-associated hematological diseases based on their expertise in large-scale genome sequence analyses. The **R. Yamamoto group** will perform complimentary basic research using mouse/macaque/human models/samples. The **S. Ogawa group** will extend their knowledge and expertise to the analysis of age-related clonal expansion in solid organs, including mammary glands, gastrointestinal tracts, brain, and urinary tracts.

The **Ueno group** will focus on defining the biology of tissue-resident immune cells in association with human aging and diseases, since the questions of how aging affects the biology of tissue-resident immune cells and how such alteration is associated with human diseases represent a largely unexplored research area of fundamental importance. Accordingly, the group will: 1) define the alterations in the phenotype, gene profiles, and functions of tissue-resident immune cells, including the human brain, liver, uterus, and secondary lymphoid tissues, by aging; 2) establish how the alterations of the tissue-resident immune cells are associated with age-related diseases, including but not limited to autoimmune diseases, Alzheimer's disease, and cancer.

Focusing on tertiary lymphoid tissues (TLTs) in aged kidneys, the **Yanagita group** will: 1) identify key cell populations responsible for TLT formation; 2) examine the role of such cells and TLTs in human kidney disease progression; 3) explore biomarkers in the blood to monitor TLT formation and validate their relevance in predicting the prognosis of kidney disease.

Moreover, to promote these investigations, the Basic/Clinical Medicine group have agreed on the

importance of establishing an integrated system with appropriate ethical underpinning to isolate and analyze human tissues/organs from healthy donors. We have therefore formed an all-ASHBi team lead by the **Fujita group**, and started a discussion to establish such an autopsy system for promoting the analysis of human tissues/organs. This is highly relevant to forming an appropriate ethical framework for using human fetal tissues in research, and we are therefore planning to establish a flagship project lead by the **Fujita group** to create an integrated framework for using human tissues, including fetal tissues, for human biology research at ASHBi and Kyoto University. These projects are highly relevant to the ASHBi's **Themes 1** and **5**.

(3) Also, more thought needs to be put into how ASHBi is going to answer or more completely address key questions: What key biological traits make us human? How can knowing these traits lead to better cures for diseases? In such ways, a basic understanding of Human Biology should be able to be applied to clinical research in the future, such as disease-oriented research.

Response 3. We would also like to thank the WPI Program Committee and Working Group for this important and thoughtful comment. ASHBi continues to strive for promoting basic science in human biology, and we believe that the three lines of Flagship Project candidates, all derived and conceived based on ongoing research projects in ASHBi, will serve as a robust foundation to address our key questions and goals.

(4) The center's goal of contributing to formalizing an international ethics standard seems to be only connected to stem cell research. This seems to be too narrow since there are so many more important questions in the area of ethics.

Response 4. Please note that the reasons why we have been focusing on examining emerging ethical issues associated with stem-cell research are:

1) Many ASHBi PIs are leading researchers in the stem-cell field and at the outset, it is highly reasonable for the **Fujita group** to perform intensive collaborations with such PIs;
2) Among current life-science fields, the stem-cell field is one of the most rapidly advancing, and its advance has engendered many novel ethical issues with critical societal impacts, including questions regarding pre-implantation genetic engineering, gametes generated in vitro, brain organoids, and human-animal chimeras.

Thus, we continue to think that it is important for us to strive to address emerging ethical issues associated with the stem-cell field. Indeed, the **Fujita group** and ASHBi have been extending our work into broader areas, such as the ethics of using human fetal tissues in research and the ethics of establishing a "warm" autopsy system at ASHBi and Kyoto University (see **Response 2**), both of which have critical implications for promoting human biology.

(5) Given the great amount of work that is involved in the genetic engineering of non-human primates, it is important for the center to have a systematic process for selecting the genes to be investigated.

Response 5. For generating disease models using cynomolgus monkeys, we selected the central nervous system (CNS) and the kidney as two primary targets based on the following considerations:

First, during human evolution, remarkable changes have been accomplished in the organization and size of the CNS, with expansion of the cerebral cortex being the most prominent. The cerebral cortex regulates context-dependent behaviors in a flexible manner, whereas the subcortical systems regulate innate and reflex-like behaviors. Primates depend more on the cortical functions, while

rodents depend more on the subcortical systems. Such differences in the CNS limit the value of rodent models of neurodegenerative or psychiatric disorders.

Second, the kidney is a critical organ that maintains homeostasis of the body fluid. Approximately 13% of adults in Japan are estimated to have chronic kidney disease (CKD), which can progress into end-stage renal failure requiring dialysis or kidney transplantation. More than 300,000 patients are receiving hemodialysis in Japan, necessitating efforts to explore effective remedies for CKD. However, mouse models for CKD have clear limitations due to the different physiology/genome functions between humans and mice.

Upon selecting a target for creating a CNS disease model, we made the following considerations: recent genome-wide association studies (GWAS) have shown that mutation of one candidate gene can cause multiple neuropsychiatric disorders, indicating that apparently distinct neuropsychiatric disorders can be a different manifestation of a common genetic mutation that interacts with various environmental factors. It would therefore be effective to target a "hub" molecule that may cause a common phenotype across multiple neuropsychiatric disorders. Accordingly, in collaboration with **Akira Sawa** at Johns Hopkins University, a member of two international consortia of genetic studies in psychiatry [(Psychiatric Genomics Consortium (PGC), and Stanley Global Neuropsychiatric Genetics Initiative (Stanley Global)], we chose *DISC1* as our first target. *DISC1* is known to play a critical role in the formation of neural circuits in the frontal cortex during development, and its mutant mice show relevant phenotypes through interactions with environmental factors. We will continue to explore new targets with the GWAS studies as critical references and with close communications with colleagues in the relevant fields to avoid overlap in the "world resources."

Regarding a model for kidney disease, we note that nephronophthisis (NPHP) is a common genetic disorder causing end-stage renal failure in children, and *NPHP1* is a major causative gene, whose precise function *in vivo* remains unclear, in part because *NPHP1*-deficient mice do not recapitulate human disease phenotypes. NPHP causes a variety of extra-renal manifestations as well, such as retinitis pigmentosa, cerebellar ataxia, bone abnormality, and liver fibrosis. Even with advances in clinical diagnostics, there is no curative treatment for NPHP. Hence, it is critical to develop a primate model for NPHP in the relevant context for the development of effective treatments.

(6) Internationalization of ASHBi is below the WPI standard. Foreign PIs are fewer than 20%. This situation must definitely be improved.

Response 6. Please see **3. Realizing an International Research Environment**, **Internationalization of ASHBi PIs (Recruiting a Foreign PI)**, **Internationalization of ASHBi Researchers**, and **Internationalization of ASHBi Students** for our efforts toward the internationalization of ASHBi, which is expected to meet the WPI standard during FY2021.

Note that many foreign postdocs and students are having serious difficulties in obtaining visas to work or study in Japan under the COVID19 pandemic, despite their having been formally appointed to the ASHBi PIs' laboratories or having passed an admittance examination for the Graduate Schools of KU during FY2020. We strongly hope an immediate resolution of this situation.

(7) ASHBi is severely behind in promoting diversity within its research force. It must develop a plan going forward to increase diversity at all levels.

Response 7. Please see **Response 6**.

Appendix 1 FY 2020 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2020. (Note: The list should be for the calendar year, not the fiscal year.)

(1) Divide the papers into two categories, A and B.

A. WPI papers
List papers whose author(s) can be identified as affiliated with the WPI program (e.g., that state "WPI" and the name of the WPI center (WPI-center name)). (Not including papers in which the names of persons affiliated with the WPI program are contained only in acknowledgements.)

B. WPI-related papers
List papers related to the WPI program but whose authors are not noted in the institutional affiliations as WPI affiliated. (Including papers whose acknowledgements contain the names of researchers affiliated with the WPI program.)

Note: On 14 December 2011, the Basic Research Promotion Division in MEXT's Research Promotion Bureau circulated an instruction requiring paper authors to include the name or abbreviation of their WPI center among their institutional affiliations. From 2012, the authors' affiliations must be clearly noted.

(2) Method of listing paper
- List only refereed papers. Divide them into categories (e.g., original articles, reviews, proceedings).
- For each, write the author name(s); year of publication; journal name, volume, page(s), and article title. Any listing order may be used as long as format is consistent. (The names of the center researchers do not need to be underlined.)
- If a paper has many authors (say, more than 10), all of their names do not need to be listed.
- Assign a serial number to each paper to be used to identify it throughout the report.
- If the papers are written in languages other than English, underline their serial numbers.
- Order of Listing

A. WPI papers
1. Original articles
2. Review articles
3. Proceedings
4. Other English articles

B. WPI-related papers
1. Original articles
2. Review articles
3. Proceedings
4. Other English articles

(3) Submission of electronic data
- In addition to the above, provide a .csv file output from the Web of Science (e.g.) or other database giving the paper's raw data including Document ID. (Note: the Document ID is assigned by paper database.)
- These files do not need to be divided into paper categories.

(4) Use in assessments
- The lists of papers will be used in assessing the state of WPI project's progress.
- They will be used as reference in analyzing the trends and whole states of research in the said WPI center, not to evaluate individual researcher performance.
- The special characteristics of each research domain will be considered when conducting assessments.

(5) Additional documents
- After all documents, including these paper listings, showing the state of research progress have been submitted, additional documents may be requested.

NOTE: The articles published after Jan 2021 in blue for reference.

A. WPI Papers

1) Original Papers

1. Pretemer, Y., Kawai, S., Nagata, S., Nishio, M., Watanabe, M., Tamaki, S., **Alev, C.**, Yamanaka, Y., Xue, J. Y., Wang, Z., Fukiage, K., Tsukanaka, M., Futami, T., Ikegawa, S., & Toguchida, J. (2021). Differentiation of Hypertrophic Chondrocytes from Human iPSCs for the In Vitro Modeling of Chondrodysplasias. ***Stem Cell Reports***, *16*(3), 610-625. doi:10.1016/j.stemcr.2021.01.014
2. Ide, K., Koshiba, H., Hawke, P., & **Fujita, M.** (2021). Guidelines Are Urgently Needed for the Use of Preprints as a Source of Information. ***Journal of Epidemiology***, *31*(1), 97-99. doi:10.2188/jea.JE20200506
3. **Sawai, T.**, Hayashi, Y., Niikawa, T., Shepherd, J., Thomas, E., Lee, T. L., Erler, A., Watanabe, M., & Sakaguchi, H. (2021). Mapping the Ethical Issues of Brain Organoid Research and Application. ***AJOB Neurosci***, 1-14. doi:10.1080/21507740.2021.1896603
4. Roffay, C., Chan, C. J., Guirao, B., **Hiiragi, T.**, & Graner, F. (2021). Inferring cell junction tension

and pressure from cell geometry. ***Development,*** *148*(18). doi:10.1242/dev.192773

5. Chen, C. Y., Matrov, D., Veale, R., Onoe, H., Yoshida, M., Miura, K., & **Isa, T.** (2021). Properties of visually guided saccadic behavior and bottom-up attention in marmoset, macaque, and human. ***J Neurophysiol,*** *125*(2), 437-457. doi:10.1152/jn.00312.2020
6. Koshimizu, Y., Isa, K., Kobayashi, K., & **Isa, T.** Double viral vector technology for selective manipulation of neural pathways with higher level of efficiency and safety. ***Gene Therapy***. doi:10.1038/s41434-020-00212-y
7. Takakuwa, N., Isa, K., Onoe, H., Takahashi, J., & **Isa, T.** (2021). Contribution of the Pulvinar and Lateral Geniculate Nucleus to the Control of Visually Guided Saccades in Blindsight Monkeys. ***Journal of Neuroscience,*** *41*(8), 1755-1768. doi:10.1523/jneurosci.2293-20.2020
8. Zubair, M., Murris, S. R., Isa, K., Onoe, H., Koshimizu, Y., Kobayashi, K., Vanduffel, W., & **Isa, T.** (2021). Divergent Whole Brain Projections from the Ventral Midbrain in Macaques. ***Cereb Cortex***. doi:10.1093/cercor/bhaa399
9. Hirabayashi, S., Shirakawa, K., Horisawa, Y., Matsumoto, T., Matsui, H., Yamazaki, H., Sarca, A. D., Kazuma, Y., Nomura, R., Konishi, Y., Takeuchi, S., Stanford, E., Kawaji, H., **Murakawa, Y.**, & Takaori-Kondo, A. (2021). APOBEC3B is preferentially expressed at the G2/M phase of cell cycle. ***Biochemical and Biophysical Research Communications,*** *546*, 178-184. doi:10.1016/j.bbrc.2021.02.008
10. Matsui, H., Shirakawa, K., Konishi, Y., Hirabayashi, S., Sarca, A.D., Fukuda, H., Nomura, R., Stanford, E., Horisawa, Y., Kazuma, Y., Matsumoto, T., Yamazaki, H., **Murakawa, Y.**, Battivelli, E., Verdin, E., Koyanagi, Y., & Takaori-Kondo, A. (2021). CAGE-Seq Reveals that HIV-1 Latent Infection Does Not Trigger Unique Cellular Responses in a Jurkat T Cell Model. ***Journal of Virology,*** *95*(8).
11. Klimkowska, M., Nannya, Y., Gran, C., Månsson, R., Douagi, I., **Ogawa, S.**, Nahi, H., & Tobiasson, M. (2021). Absence of a common founder mutation in patients with cooccurring myelodysplastic syndrome and plasma cell disorder. ***Blood,*** *137*(9), 1260-1263. doi:10.1182/blood.2020007555
12. Li, X. Y., Kim, W., Arif, M., Gao, C. X., Hober, A., Kotol, D., Strandberg, L., Forsstrom, B., Sivertsson, A., Oksvold, P., Turkez, H., Grotli, M., Sato, Y., Kume, H., **Ogawa, S.**, Boren, J., Nielsen, J., Uhlen, M., Zhang, C., & Mardinoglu, A. (2021). Discovery of Functional Alternatively Spliced PKM Transcripts in Human Cancers. ***Cancers,*** *13*(2). doi:10.3390/cancers13020348
13. Mu, A., Hira, A., Niwa, A., Osawa, M., Yoshida, K., Mori, M., Okamoto, Y., Inoue, K., Kondo, K., Kanemaki, M. T., Matsuda, T., Ito, E., Kojima, S., Nakahata, T., **Ogawa, S.**, Tanaka, K., Matsuo, K., Saito, M. K., & Takata, M. (2021). Analysis of disease model iPSCs derived from patients with a novel Fanconi anemia-like IBMFS ADH5/ALDH2 deficiency. ***Blood,*** *137*(15), 2021-2032. doi:10.1182/blood.2020009111
14. Nishimura, A., Hirabayashi, S., Hasegawa, D., Yoshida, K., Shiraishi, Y., Ashiarai, M., Hosoya, Y., Fujiwara, T., Harigae, H., Miyano, S., **Ogawa, S.**, & Manabe, A. (2021). Acquisition of monosomy 7 and a RUNX1 mutation in Pearson syndrome. ***Pediatr Blood Cancer,*** *68*(2), e28799. doi:10.1002/pbc.28799
15. Polprasert, C., Takeuchi, Y., Makishima, H., Wudhikarn, K., Kakiuchi, N., Tangnuntachai, N., Assanasen, T., Sitthi, W., Muhamad, H., Lawasut, P., Kongkiatkamon, S., Bunworasate, U., Izutsu, K., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., **Ogawa, S.**, Yoshida, K., & Rojnuckarin, P. (2021). Frequent mutations in HLA and related genes in extranodal NK/T cell lymphomas. ***Leuk Lymphoma,*** *62*(1), 95-103. doi:10.1080/10428194.2020.1821011
16. Shimada, K., Yoshida, K., Suzuki, Y., Iriyama, C., Inoue, Y., Sanada, M., Kataoka, K., Yuge, M., Takagi, Y., Kusumoto, S., Masaki, Y., Ito, T., Inagaki, Y., Okamoto, A., Kuwatsuka, Y., Nakatochi, M., Shimada, S., Miyoshi, H., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., Shiozawa, Y., Nannya, Y., Okabe, A., Kohno, K., Atsuta, Y., Ohshima, K., Nakamura, S., **Ogawa, S.**, Tomita, A., & Kiyoi, H. (2021). Frequent genetic alterations in immune checkpoint-related genes in intravascular large B-cell lymphoma. ***Blood,*** *137*(11), 1491-1502. doi:10.1182/blood.2020007245
17. Yasudo, H., Ando, T., Maehara, A., Izawa, K., Tanabe, A., Kaitani, A., Nomura, S., Seki, M., Yoshida, K., Oda, H., Okamoto, Y., Wang, H., Kamei, A., Kojima, M., Kimura, M., Uchida, K.,

Nakano, N., Kaneko, J., Ebihara, N., Hasegawa, K., Shimizu, T., Takita, J., Ogawa, H., Okumura, K., **Ogawa, S.**, Tamura, N., & Kitaura, J. (2021). A possible association between a novel NLRP1 mutation and an autoinflammatory disease involving liver cirrhosis. ***Hepatology***. doi:10.1002/hep.31818

18. Kojima, Y., Yamashiro, C., Murase, Y., Yabuta, Y., Okamoto, I., Iwatani, C., Tsuchiya, H., Nakaya, M., **Tsukiyama, T.**, Nakamura, T., **Yamamoto, T.**, & **Saitou, M.** (2021). GATA transcription factors, SOX17 and TFAP2C, drive the human germ-cell specification program. ***Life Sci Alliance,*** *4*(5). doi:10.26508/lsa.202000974
19. Io, S., Kabata, M., Iemura, Y., Semi, K., Morone, N., Minagawa, A., Wang, B., Okamoto, I., Nakamura, T., Kojima, Y., Iwatani, C., Tsuchiya, H., Kaswandy, B., Kondoh, E., Kaneko, S., Woltjen, K., **Saitou, M.**, **Yamamoto, T.**, Mandai, M., & Takashima, Y. (2021). Capturing human trophoblast development with naive pluripotent stem cells in vitro. ***Cell Stem Cell***. doi:10.1016/j.stem.2021.03.013
20. Ichijo, R., Kabata, M., Kidoya, H., Muramatsu, F., Ishibashi, R., Abe, K., Tsutsui, K., Kubo, H., Iizuka, Y., Kitano, S., Miyachi, H., Kubota, Y., Fujiwara, H., Sada, A., **Yamamoto, T.**, & Toyoshima, F. (2021). Vasculature-driven stem cell population coordinates tissue scaling in dynamic organs. ***Sci Adv,*** *7*(7). doi:10.1126/sciadv.abd2575
21. Katagiri, N., Hitomi, H., Mae, S. I., Kotaka, M., Lei, L., **Yamamoto, T.**, Nishiyama, A., & Osafune, K. (2021). Retinoic acid regulates erythropoietin production cooperatively with hypoxia-inducible factors in human iPSC-derived erythropoietin-producing cells. ***Scientific Reports,*** *11*(1). doi:10.1038/s41598-021-83431-6
22. Morimoto, H., **Yamamoto, T.**, Miyazaki, T., Ogonuki, N., Ogura, A., Tanaka, T., Kanatsu-Shinohara, M., Yabe-Nishimura, C., Zhang, H. L., Pommier, Y., Trumpp, A., & Shinohara, T. (2021). An interplay of NOX1-derived ROS and oxygen determines the spermatogonial stem cell self-renewal efficiency under hypoxia. ***Genes & Development,*** *35*(3-4). doi:10.1101/gad.339903.120
23. Sankoda, N., Tanabe, W., Tanaka, A., Shibata, H., Woltjen, K., Chiba, T., Haga, H., Sakai, Y., Mandai, M., **Yamamoto, T.,** Yamada, Y., Uemoto, S., & Kawaguchi, Y. (2021). Epithelial expression of Gata4 and Sox2 regulates specification of the squamous-columnar junction via MAPK/ERK signaling in mice. ***Nat Commun,*** *12*(1), 560. doi:10.1038/s41467-021-20906-0
24. Sano, E., Deguchi, S., Sakamoto, A., Mimura, N., Hirabayashi, A., Muramoto, Y., Noda, T., **Yamamoto, T.**, & Takayama, K. (2021). Modeling SARS-CoV-2 infection and its individual differences with ACE2-expressing human iPS cells. ***iScience***, 102428. doi:10.1016/j.isci.2021.102428
25. Yuzuriha, A, Nakamura, S, Sugimoto, N, Kihara, S, Nakagawa, M, **Yamamoto, T**, Sekiguchi, K, & Eto, K. (2021). Extracellular laminin regulates hematopoietic potential of pluripotent stem cells through integrin β1-ILK-β-catenin-JUN axis. ***Stem Cell Research,*** *53*, 102287.
26. Makino, S., Shirata, N., Trejo, J. A. O., Yamamoto-Nonaka, K., Yamada, H., Miyake, T., Mori, K., Nakagawa, T., Tashiro, Y., Yamashita, H., **Yanagita, M.**, Takahashi, R., & Asanuma, K. (2021). Impairment of Proteasome Function in Podocytes Leads to CKD. ***Journal of the American Society of Nephrology,*** *32*(3), 597-613. doi:10.1681/asn.2019101025
27. Miyanaga, T., Mizuguchi, K., Hara, S., Zoshima, T., Inoue, D., Nishioka, R., Mizushima, I., Ito, K., Fuji, H., Yamada, K., Sato, Y., **Yanagita, M.**, & Kawano, M. (2021). Tertiary lymphoid tissue in early-stage IgG4-related tubulointerstitial nephritis incidentally detected with a tumor lesion of the ureteropelvic junction: a case report. ***Bmc Nephrology,*** *22*(1). doi:10.1186/s12882-021-02240-1
28. Yamada, H., Shirata, N., Makino, S., Miyake, T., Trejo, J. A. O., Yamamoto-Nonaka, K., Kikyo, M., Empitu, M. A., Kadariswantiningsih, I. N., Kimura, M., Ichimura, K., Yokoi, H., Mukoyama, M., Hotta, A., Nishimori, K., **Yanagita, M.**, & Asanuma, K. (2021). MAGI-2 orchestrates the localization of backbone proteins in the slit diaphragm of podocytes. ***Kidney Int,*** *99*(2), 382-395. doi:10.1016/j.kint.2020.09.027
29. Matsuda, M., Yamanaka, Y., Uemura, M., Osawa, M., Saito, M. K., Nagahashi, A., Nishio, M., Guo, L., Ikegawa, S., Sakurai, S., Kihara, S., Maurissen, T. L., Nakamura, M., Matsumoto, T., Yoshitomi, H., Ikeya, M., Kawakami, N., **Yamamoto, T.**, Woltjen, K., Ebisuya, M., Toguchida, J., & **Alev, C.**

(2020). Recapitulating the human segmentation clock with pluripotent stem cells. ***Nature,*** *580*(7801), 124-+. doi:10.1038/s41586-020-2144-9

30. Hamidi, S., Nakaya, Y., Nagai, H., **Alev, C.**, Kasukawa, T., Chhabra, S., Lee, R., Niwa, H., Warmflash, A., Shibata, T., & Sheng, G. J. (2020). Mesenchymal-epithelial transition regulates initiation of pluripotency exit before gastrulation. ***Development,*** *147*(3). doi:10.1242/dev.184960
31. Kishimoto, K., Furukawa, K. T., Luz-Madrigal, A., Yamaoka, A., Matsuoka, C., Habu, M., **Alev, C.**, Zorn, A. M., & Morimoto, M. (2020). Bidirectional Wnt signaling between endoderm and mesoderm confers tracheal identity in mouse and human cells. ***Nature Communications,*** *11*(1). doi:10.1038/s41467-020-17969-w
32. Matsuda, M., Hayashi, H., Garcia-Ojalvo, J., Yoshioka-Kobayashi, K., Kageyama, R., Yamanaka, Y., Ikeya, M., Toguchida, J., **Alev, C.**, & Ebisuya, M. (2020). Species-specific segmentation clock periods are due to differential biochemical reaction speeds. ***Science,*** *369*(6510), 1450-+. doi:10.1126/science.aba7668
33. Groza, C., Kwan, T., Soranzo, N., Pastinen, T., & **Bourque, G**. (2020). Personalized and graph genomes reveal missing signal in epigenomic data. ***Genome Biology,*** *21*(1). doi:10.1186/s13059-020-02038-8
34. Matsumoto, S., Porter, C. J., Ogasawara, N., Iwatani, C., Tsuchiya, H., Seita, Y., Chang, Y. W., Okamoto, I., **Saitou, M.**, **Ema, M.**, Perkins, T. J., Stanford, W. L., & Tanaka, S. (2020). Establishment of macaque trophoblast stem cell lines derived from cynomolgus monkey blastocysts. ***Scientific Reports,*** *10*(1). doi:10.1038/s41598-020-63602-7
35. Seita, Y., Morimura, T., Watanabe, N., Iwatani, C., Tsuchiya, H., Nakamura, S., Suzuki, T., Yanagisawa, D., **Tsukiyama, T.**, Nakaya, M., Okamura, E., Muto, M., **Ema, M.**, Nishimura, M., & Tooyama, I. (2020). Generation of Transgenic Cynomolgus Monkeys Overexpressing the Gene for Amyloid-beta Precursor Protein. ***Journal of Alzheimers Disease,*** *75*(1), 45-60. doi:10.3233/jad-191081
36. Sawai, T., Minakawa, T., Pugh, J., Akatsuka, K., Yamashita, J. K., & **Fujita, M.** (2020). The moral status of human embryo-like structures: potentiality matters? The moral status of human synthetic embryos. ***Embo Reports,*** *21*(8). doi:10.15252/embr.202050984
37. Crane, A. T., Shen, F. X., Brown, J. L., Cormack, W., Ruiz-Estevez, M., Voth, J. P., Sawai, T., Hatta, T., **Fujita, M.**, & Low, W. C. (2020). The American Public Is Ready to Accept Human-Animal Chimera Research. ***Stem Cell Reports,*** *15*(4), 804-810. doi:10.1016/j.stemcr.2020.08.018
38. Akatsuka, K., Sasaki-Honda, M., & **Sawai, T**. (2020). Ethical Framework for Next-Generation Genome and Epigenome Editing. ***Am J Bioeth,*** *20*(8), 32-36. doi:10.1080/15265161.2020.1782524
39. Ichinomiya, T., Obayashi, I., & **Hiraoka, Y.** (2020). Protein-Folding Analysis Using Features Obtained by Persistent Homology. ***Biophysical Journal,*** *118*(12), 2926-2937. doi:10.1016/j.bpj.2020.04.032
40. **Hiraoka, Y.**, & Mikami, T. (2020). Percolation on Homology Generators in Codimension One. In ***Topological Data Analysis*** (pp. 307-342): Springer.
41. **Hiraoka, Y.**, Ochiai, H., & Shirai, T. (2020). *Zeta functions of periodic cubical lattices and cyclotomic-like polynomials.* Paper presented at the Various Aspects of Multiple Zeta Functions—in honor of Professor Kohji Matsumoto's 60th birthday.
42. Koyama, C., Tahara, S., Kohara, S., Onodera, Y., Småbråten, D.R., Selbach, S.M., Akola, J., Ishikawa, T., Masuno, A., Mizuno, A., Okada, J.T., Watanabe, Y., Nakata, Y., Ohara, K., Tamaru, H., Oda, H., Obayashi, I., **Hiraoka, Y.**, & Sakata, O. (2020). Very sharp diffraction peak in nonglass-forming liquid with the formation of distorted tetraclusters. ***Npg Asia Materials,*** *12*(1), 1-11. doi:https://doi.org/10.1038/s41427-020-0220-0
43. Onodera, Y., Kohara, S., Salmon, P. S., Hirata, A., Nishiyama, N., Kitani, S., Zeidler, A., Shiga, M., Masuno, A., Inoue, H., Tahara, S., Polidori, A., Fischer, H. E., Mori, T., Kojima, S., Kawaji, H., Kolesnikov, A. I., Stone, M. B., Tucker, M. G., McDonnell, M. T., Hannon, A. C., **Hiraoka, Y.**, Obayashi, I., Nakamura, T., Akola, J., Fujii, Y., Ohara, K., Taniguchi, T., & Sakata, O. (2020). Structure and properties of densified silica glass: characterizing the order within disorder. ***Npg Asia***

Materials, 12(1). doi:10.1038/s41427-020-00262-z

44. Suzuki, A, Miyazawa, M, Okamoto, A, Shimizu, H, Obayashi, I, **Hiraoka, Y**, Tsuji, T, Kang, PK, & Ito, T. (2020). Inferring fracture forming processes by characterizing fracture network patterns with persistent homology. *Computers & Geosciences, 143*, 104550. doi:https://doi.org/10.1016/j.cageo.2020.104550

45. Isa, K., Sooksawate, T., Kobayashi, K., Redgrave, P., & **Isa, T.** (2020). Dissecting the Tectal Output Channels for Orienting and Defense Responses. *Eneuro, 7*(5). doi:10.1523/eneuro.0271-20.2020

46. Tokuoka, K., Kasai, M., Kobayashi, K., & **Isa, T.** (2020). Anatomical and electrophysiological analysis of cholinergic inputs from the parabigeminal nucleus to the superficial superior colliculus. *Journal of Neurophysiology, 124*(6), 1968-1985. doi:10.1152/jn.00148.2020

47. Suzuki, M., Onoe, K., Sawada, M., Takahashi, N., Higo, N., Murata, Y., Tsukada, H., **Isa, T.**, Onoe, H., & Nishimura, Y. (2020). The Ventral Striatum is a Key Node for Functional Recovery of Finger Dexterity After Spinal Cord Injury in Monkeys. *Cerebral Cortex, 30*(5), 3259-3270. doi:10.1093/cercor/bhz307

48. Vancraeyenest, P., Arsenault, J. T., Li, X. L., Zhu, Q., Kobayashi, K., Isa, K., **Isa, T.**, & Vanduffel, W. (2020). Selective Mesoaccumbal Pathway Inactivation Affects Motivation but Not Reinforcement-Based Learning in Macaques. *Neuron, 108*(3), 568-+. doi:10.1016/j.neuron.2020.07.013

49. Kakiuchi, N., Yoshida, K., Uchino, M., Kihara, T., Akaki, K., Inoue, Y., Kawada, K., Nagayama, S., Yokoyama, A., Yamamoto, S., Matsuura, M., Horimatsu, T., Hirano, T., Goto, N., Takeuchi, Y., Ochi, Y., Shiozawa, Y., Kogure, Y., Watatani, Y., Fujii, Y., Kim, S. K., Kon, A., Kataoka, K., Yoshizato, T., Nakagawa, M. M., Yoda, A., Nanya, Y., Makishima, H., Shiraishi, Y., Chiba, K., Tanaka, H., Sanada, M., Sugihara, E., Sato, T., Maruyama, T., Miyoshi, H., Taketo, M. M., Oishi, J., Inagaki, R., Ueda, Y., Okamoto, S., Okajima, H., Sakai, Y., Sakurai, T., Haga, H., Hirota, S., Ikeuchi, H., Nakase, H., Marusawa, H., Chiba, T., Takeuchi, O., Miyano, S., Seno, H., & **Ogawa, S.** (2020). Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis. *Nature, 577*(7789), 260-+. doi:10.1038/s41586-019-1856-1

50. Ochi, Y., Kon, A., Sakata, T., Nakagawa, M. M., Nakazawa, N., Kakuta, M., Kataoka, K., Koseki, H., Nakayama, M., Morishita, D., Tsuruyama, T., Saiki, R., Yoda, A., Okuda, R., Yoshizato, T., Yoshida, K., Shiozawa, Y., Nannya, Y., Kotani, S., Kogure, Y., Kakiuchi, N., Nishimura, T., Makishima, H., Malcovati, L., Yokoyama, A., Takeuchi, K., Sugihara, E., Sato, T. A., Sanada, M., Takaori-Kondo, A., Cazzola, M., Kengaku, M., Miyano, S., Shirahige, K., Suzuki, H. I., & **Ogawa, S.** (2020). Combined Cohesin-RUNX1 Deficiency Synergistically Perturbs Chromatin Looping and Causes Myelodysplastic Syndromes. *Cancer Discovery, 10*(6), 836-853. doi:10.1158/2159-8290.cd-19-0982

51. Dingler, F. A., Wang, M., Mu, A. F., Millington, C. L., Oberbeck, N., Watcham, S., Pontel, L. B., Kamimae-Lanning, A. N., Langevin, F., Nadler, C., Cordell, R. L., Monks, P. S., Yu, R., Wilson, N. K., Hira, A., Yoshida, K., Mori, M., Okamoto, Y., Okuno, Y., Muramatsu, H., Shiraishi, Y., Kobayashi, M., Moriguchi, T., Osumi, T., Kato, M., Miyano, S., Ito, E., Kojima, S., Yabe, H., Yabe, M., Matsuo, K., **Ogawa, S.**, Gottgens, B., Hodskinson, M. R. G., Takata, M., & Patel, K. J. (2020). Two Aldehyde Clearance Systems Are Essential to Prevent Lethal Formaldehyde Accumulation in Mice and Humans. *Molecular Cell, 80*(6), 996-+. doi:10.1016/j.molcel.2020.10.012

52. Fukumoto, K., Sakata-Yanagimoto, M., Fujisawa, M., Sakamoto, T., Miyoshi, H., Suehara, Y., Nguyen, T. B., Suma, S., Yanagimoto, S., Shiraishi, Y., Chiba, K., Bouska, A., Kataoka, K., **Ogawa, S.**, Iqbal, J., Ohshima, K., & Chiba, S. (2020). VAV1 mutations contribute to development of T-cell neoplasms in mice. *Blood, 136*(26), 3018-3032. doi:10.1182/blood.2020006513

53. Inagaki-Kawata, Y., Yoshida, K., Kawaguchi-Sakita, N., Kawashima, M., Nishimura, T., Senda, N., Shiozawa, Y., Takeuchi, Y., Inoue, Y., Sato-Otsubo, A., Fujii, Y., Nannya, Y., Suzuki, E., Takada, M., Tanaka, H., Shiraishi, Y., Chiba, K., Kataoka, Y., Torii, M., Yoshibayashi, H., Yamagami, K., Okamura, R., Moriguchi, Y., Kato, H., Tsuyuki, S., Yamauchi, A., Suwa, H., Inamoto, T., Miyano, S., **Ogawa, S.**, & Toi, M. (2020). Genetic and clinical landscape of breast cancers with germline BRCA1/2 variants. *Communications Biology, 3*(1). doi:10.1038/s42003-020-01301-9

54. Kanamori, T., Sanada, M., Ri, M., Ueno, H., Nishijima, D., Yasuda, T., Tachita, T., Narita, T., Kusumoto, S., Inagaki, A., Ishihara, R., Murakami, Y., Kobayashi, N., Shiozawa, Y., Yoshida, K.,

Nakagawa, M. M., Nannya, Y., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., Horibe, K., Handa, H., **Ogawa, S.**, & Iida, S. (2020). Genomic analysis of multiple myeloma using targeted capture sequencing in the Japanese cohort. *British Journal of Haematology, 191*(5), 755-763. doi:10.1111/bjh.16720

55. Katagiri, S., Makishima, H., Azuma, K., Nannya, Y., Saitoh, Y., Yoshizawa, S., Akahane, D., Fujimoto, H., Ito, Y., Velaga, R., Umezu, T., Ohyashiki, J. H., **Ogawa, S.**, & Ohyashiki, K. (2020). Predisposed genomic instability in pre-treatment bone marrow evolves to therapy -related myeloid neoplasms in malignant lymphoma. *Haematologica, 105*(7), E337-E339. doi:10.3324/haematol.2019.229856

56. Kimura, S., Seki, M., Kawai, T., Goto, H., Yoshida, K., Isobe, T., Sekiguchi, M., Watanabe, K., Kubota, Y., Nannya, Y., Ueno, H., Shiozawa, Y., Suzuki, H., Shiraishi, Y., Ohki, K., Kato, M., Koh, K., Kobayashi, R., Deguchi, T., Hashii, Y., Imamura, T., Sato, A., Kiyokawa, N., Manabe, A., Sanada, M., Mansour, M. R., Ohara, A., Horibe, K., Kobayashi, M., Oka, A., Hayashi, Y., Miyano, S., Hata, K., **Ogawa, S.**, & Takita, J. (2020). DNA methylation-based classification reveals difference between pediatric T-cell acute lymphoblastic leukemia and normal thymocytes. *Leukemia, 34*(4), 1163-1168. doi:10.1038/s41375-019-0626-2

57. Koyamaishi, S., Kamio, T., Kobayashi, A., Sato, T., Kudo, K., Sasaki, S., Kanezaki, R., Hasegawa, D., Muramatsu, H., Takahashi, Y., Sasahara, Y., Hiramatsu, H., Kakuda, H., Tanaka, M., Ishimura, M., Nishi, M., Ishiguro, A., Yabe, H., Sarashina, T., Yamamoto, M., Yuza, Y., Hyakuna, N., Yoshida, K., Kanno, H., Ohga, S., Ohara, A., Kojima, S., Miyano, S., **Ogawa, S.**, Toki, T., Terui, K., & Ito, E. Reduced-intensity conditioning is effective for hematopoietic stem cell transplantation in young pediatric patients with Diamond-Blackfan anemia. *Bone Marrow Transplantation*. doi:10.1038/s41409-020-01056-1

58. Kubota, Y., Seki, M., Kawai, T., Isobe, T., Yoshida, M., Sekiguchi, M., Kimura, S., Watanabe, K., Sato-Otsubo, A., Yoshida, K., Suzuki, H., Kataoka, K., Fujii, Y., Shiraishi, Y., Chiba, K., Tanaka, H., Hiwatari, M., Oka, A., Hayashi, Y., Miyano, S., **Ogawa, S.**, Hata, K., Tanaka, Y., & Takita, J. (2020). Comprehensive genetic analysis of pediatric germ cell tumors identifies potential drug targets. *Communications Biology, 3*(1). doi:10.1038/s42003-020-01267-8

59. Li, X. Y., Turanli, B., Juszczak, K., Kim, W., Arif, M., Sato, Y., **Ogawa, S.**, Turkez, H., Nielsen, J., Boren, J., Uhlen, M., Zhang, C., & Mardinoglu, A. (2020). Classification of clear cell renal cell carcinoma based on PKM alternative splicing. *Heliyon, 6*(2). doi:10.1016/j.heliyon.2020.e03440

60. Matsuo, H., Yoshida, K., Nakatani, K., Harata, Y., Higashitani, M., Ito, Y., Kamikubo, Y., Shiozawa, Y., Shiraishi, Y., Chiba, K., Tanaka, H., Okada, A., Nannya, Y., Takeda, J., Ueno, H., Kiyokawa, N., Tomizawa, D., Taga, T., Tawa, A., Miyano, S., Meggendorfer, M., Haferlach, C., **Ogawa, S.**, & Adachi, S. (2020). Fusion partner-specific mutation profiles and KRAS mutations as adverse prognostic factors in MLL-rearranged AML. *Blood Advances, 4*(19), 4623-4631. doi:10.1182/bloodadvances.2020002457

61. Mylonas, E., Yoshida, K., Frick, M., Hoyer, K., Christen, F., Kaeda, J., Obenaus, M., Noerenberg, D., Hennch, C., Chan, W., Ochi, Y., Shiraishi, Y., Shiozawa, Y., Zenz, T., Oakes, C. C., Sawitzki, B., Schwarz, M., Bullinger, L., le Coutre, P., Rose-Zerilli, M. J. J., **Ogawa, S.**, & Damm, F. (2020). Single-cell analysis based dissection of clonality in myelofibrosis. *Nature Communications, 11*(1). doi:10.1038/s41467-019-13892-x

62. Ogura, H., Ohga, S., Aoki, T., Utsugisawa, T., Takahashi, H., Iwai, A., Watanabe, K., Okuno, Y., Yoshida, K., **Ogawa, S.**, Miyano, S., Kojima, S., Yamamoto, T., Yamamoto-Shimojima, K., & Kanno, H. (2020). Novel COL4A1 mutations identified in infants with congenital hemolytic anemia in association with brain malformations. *Human Genome Variation, 7*(1). doi:10.1038/s41439-020-00130-w

63. Okano, T., Imai, K., Naruto, T., Okada, S., Yamashita, M., Yeh, T. W., Ono, S., Tanaka, K., Okamoto, K., Tanita, K., Matsumoto, K., Toyofuku, E., Kumaki-Matsumoto, E., Okamura, M., Ueno, H., **Ogawa, S.**, Ohara, O., Takagi, M., Kanegane, H., & Morio, T. (2020). Whole-Exome Sequencing-Based Approach for Germline Mutations in Patients with Inborn Errors of Immunity. *Journal of Clinical Immunology, 40*(5), 729-740. doi:10.1007/s10875-020-00798-3

64. Polprasert, C, Takeda, J, Niparuck, P, Rattanathammethee, T, Pirunsarn, A, Suksusut, A,

Kobbuaklee, S, Wudhikarn, K, Lawasut, P, Kongkiatkamon, S, Chuncharunee, S, Songserm, K, Phowthongkum, P, Bunworasate, U, Nannya, Y, Yoshida, K, Makishima, H, **Ogawa, S**, & Rojnuckarin, P. (2020). Novel DDX41 variants in Thai patients with myeloid neoplasms. *International Journal of Hematology, 111*(2), 241-246. doi:10.1007/s12185-019-02770-3

65. Sekiguchi, M., Seki, M., Kawai, T., Yoshida, K., Yoshida, M., Isobe, T., Hoshino, N., Shirai, R., Tanaka, M., Souzaki, R., Watanabe, K., Arakawa, Y., Nannya, Y., Suzuki, H., Fujii, Y., Kataoka, K., Shiraishi, Y., Chiba, K., Tanaka, H., Shimamura, T., Sato, Y., Sato-Otsubo, A., Kimura, S., Kubota, Y., Hiwatari, M., Koh, K., Hayashi, Y., Kanamori, Y., Kasahara, M., Kohashi, K., Kato, M., Yoshioka, T., Matsumoto, K., Oka, A., Taguchi, T., Sanada, M., Tanaka, Y., Miyano, S., Hata, K., **Ogawa, S.**, & Takita, J. (2020). Integrated multiomics analysis of hepatoblastoma unravels its heterogeneity and provides novel druggable targets. *Npj Precision Oncology, 4*(1). doi:10.1038/s41698-020-0125-y

66. Shrestha, R., Sakata-Yanagimoto, M., Maie, K., Oshima, M., Ishihara, M., Suehara, Y., Fukumoto, K., Nakajima-Takagi, Y., Matsui, H., Kato, T., Muto, H., Sakamoto, T., Kusakabe, M., Nannya, Y., Makishima, H., Ueno, H., Saiki, R., **Ogawa, S.**, Chiba, K., Shiraishi, Y., Miyano, S., Mouly, E., Bernard, O. A., Inaba, T., Koseki, H., Iwama, A., & Chiba, S. (2020). Molecular pathogenesis of progression to myeloid leukemia from TET-insufficient status. *Blood Advances, 4*(5), 845-854. doi:10.1182/bloodadvances.2019001324

67. Todisco, G., Creignou, M., Gall, A., Guglielmelli, P., Rumi, E., Roncador, M., Rizzo, E., Nannya, Y., Pietra, D., Elena, C., Bono, E., Molteni, E., Rosti, V., Catrical, S., Sarchi, M., Dimitriou, M., Ungerstedt, J., Vannucchi, A. M., Hellstrom-Lindberg, E., **Ogawa, S.**, Cazzola, M., & Malcovati, L. Co-mutation pattern, clonal hierarchy, and clone size concur to determine disease phenotype of SRSF2(P95)-mutated neoplasms. *Leukemia*. doi:10.1038/s41375-020-01106-z

68. Ueno, H., Yoshida, K., Shiozawa, Y., Nannya, Y., Iijima-Yamashita, Y., Kiyokawa, N., Shiraishi, Y., Chiba, K., Tanaka, H., Isobe, T., Seki, M., Kimura, S., Makishima, H., Nakagawa, M. M., Kakiuchi, N., Kataoka, K., Yoshizato, T., Nishijima, D., Deguchi, T., Ohki, K., Sato, A., Takahashi, H., Hashii, Y., Tokimasa, S., Hara, J., Kosaka, Y., Kato, K., Inukai, T., Takita, J., Imamura, T., Miyano, S., Manabe, A., Horibe, K., **Ogawa, S.**, & Sanada, M. (2020). Landscape of driver mutations and their clinical impacts in pediatric B-cell precursor acute lymphoblastic leukemia. *Blood Advances, 4*(20), 5165-5173. doi:10.1182/bloodadvances.2019001307

69. Yasuda, T., Sanada, M., Nishijima, D., Kanamori, T., Iijima, Y., Hattori, H., Saito, A., Miyoshi, H., Ishikawa, Y., Asou, N., Usuki, K., Hirabayashi, S., Kato, M., Ri, M., Handa, H., Ishida, T., Shibayama, H., Abe, M., Iriyama, C., Karube, K., Nishikori, M., Ohshima, K., Kataoka, K., Yoshida, K., Shiraishi, Y., Goto, H., Adachi, S., Kobayashi, R., Kiyoi, H., Miyazaki, Y., **Ogawa, S.**, Kurahashi, H., Yokoyama, H., Manabe, A., Iida, S., Tomita, A., & Horibe, K. (2020). Clinical utility of target capture-based panel sequencing in hematological malignancies: A multicenter feasibility study. *Cancer Science, 111*(9), 3367-3378. doi:10.1111/cas.14552

70. Murase, Y., Yabuta, Y., Ohta, H., Yamashiro, C., Nakamura, T., **Yamamoto, T.**, & **Saitou, M.** (2020). Long-term expansion with germline potential of human primordial germ cell-like cells in vitro. *Embo Journal, 39*(21). doi:10.15252/embj.2020104929

71. Nagaoka, S. I., Nakaki, F., Miyauchi, H., Nosaka, Y., Ohta, H., Yabuta, Y., Kurimoto, K., Hayashi, K., Nakamura, T., **Yamamoto, T.**, & **Saitou, M.** (2020). ZGLP1 is a determinant for the oogenic fate in mice. *Science, 367*(6482), 1089-+. doi:10.1126/science.aaw4115

72. Ohta, H, Yabuta, Y, Kurimoto, K, Nakamura, T, Murase, Y, **Yamamoto, T**, & **Saitou, M**. (2020). Cyclosporin A and FGF signaling support the proliferation/survival of mouse primordial germ cell-like cells in vitro. *Biology of Reproduction*. doi: 10.1093/biolre/ioaa195

73. Sakai, Y., Nakamura, T., Okamoto, I., Gyobu-Motani, S., Ohta, H., Yabuta, Y., **Tsukiyama, T.**, Iwatani, C., Tsuchiya, H., **Ema, M.**, Morizane, A., Takahashi, J., **Yamamoto, T.**, & **Saitou, M**. (2020). Induction of the germ cell fate from pluripotent stem cells in cynomolgus monkeys. *Biology of Reproduction, 102*(3), 620-638. doi:10.1093/biolre/ioz205

74. Yamashiro, C., Sasaki, K., Yokobayashi, S., Kojima, Y., & **Saitou, M**. (2020). Generation of human oogonia from induced pluripotent stem cells in culture. *Nature Protocols, 15*(4), 1560-1583. doi:10.1038/s41596-020-0297-5

75. Senoo, M., Hozoji, H., Ishikawa-Yamauchi, Y., Takijiri, T., Ohta, S., Ukai, T., Kabata, M., **Yamamoto, T**., Yamada, Y., Ikawa, M., & Ozawa, M. (2020). RNA-binding protein Ptbp1 regulates alternative splicing and transcriptome in spermatogonia and maintains spermatogenesis in concert with Nanos3. *Journal of Reproduction and Development, 66*(5), 459-467.

76. Yagi, M., Kabata, M., Tanaka, A., Ukai, T., Ohta, S., Nakabayashi, K., Shimizu, M., Hata, K., Meissner, A., **Yamamoto, T**., & Yamada, Y. (2020). Identification of distinct loci for de novo DNA methylation by DNMT3A and DNMT3B during mammalian development. *Nature Communications, 11*(1). doi:10.1038/s41467-020-16989-w

77. Sato, Y., Boor, P., Fukuma, S., Klinkhammer, B. M., Haga, H., Ogawa, O., Floege, J., & **Yanagita, M**. (2020). Developmental stages of tertiary lymphoid tissue reflect local injury and inflammation in mouse and human kidneys. *Kidney International, 98*(2), 448-463. doi:10.1016/j.kint.2020.02.023

78. Yamamoto, S., Yamamoto, M., Nakamura, J., Mii, A., Takahashi, M., Kaneko, K., Uchino, E., Sato, Y., Fukuma, S., Imamura, H., Matsuda, M., & **Yanagita, M**. (2020). Spatiotemporal ATP Dynamics during AKI Predict Renal Prognosis. *Journal of the American Society of Nephrology, 31*(12), 2855-2869. doi:10.1681/asn.2020050580

79. Fujimura, R., Yamamoto, T., Takabatake, Y., Takahashi, A., Namba-Hamano, T., Minami, S., Sakai, S., Matsuda, J., Hesaka, A., Yonishi, H., Nakamura, J., Matsui, I., Matsusaka, T., Niimura, F., **Yanagita, M**., & Isaka, Y. (2020). Autophagy protects kidney from phosphate-induced mitochondrial injury. *Biochemical and Biophysical Research Communications, 524*(3), 636-642. doi:10.1016/j.bbrc.2020.01.137

80. Hata, Y., Kuwabara, T., Mori, K., Kan, Y., Sato, Y., Umemoto, S., Fujimoto, D., Kanki, T., Nishiguchi, Y., Yokoi, H., Kakizoe, Y., Izumi, Y., **Yanagita, M**., & Mukoyama, M. (2020). Ablation of Myeloid Cell MRP8 Ameliorates Nephrotoxic Serum-induced Glomerulonephritis by Affecting Macrophage Characterization through Intraglomerular Crosstalk. *Sci Rep, 10*(1), 3056. doi:10.1038/s41598-020-59970-9

81. Matsuda, J., Takahashi, A., Takabatake, Y., Sakai, S., Minami, S., Yamamoto, T., Fujimura, R., Namba-Hamano, T., Yonishi, H., Nakamura, J., Kimura, T., Kaimori, J. Y., Matsui, I., Takahashi, M., Nakao, M., Izumi, Y., Bamba, T., Matsusaka, T., Niimura, F., **Yanagita, M**., Yoshimori, T., & Isaka, Y. (2020). Metabolic effects of RUBCN/Rubicon deficiency in kidney proximal tubular epithelial cells. *Autophagy, 16*(10), 1889-1904. doi:10.1080/15548627.2020.1712107

82. Miyajima, Y., Ealey, K. N., Motomura, Y., Mochizuki, M., Takeno, N., **Yanagita, M**., Economides, A. N., Nakayama, M., Koseki, H., & Moro, K. (2020). Effects of BMP7 produced by group 2 innate lymphoid cells on adipogenesis. *International Immunology, 32*(6), 407-419. doi:10.1093/intimm/dxaa013

83. Ozawa, S., Matsubayashi, M., Nanaura, H., **Yanagita, M**., Mori, K., Asanuma, K., Kajiwara, N., Hayashi, K., Ohashi, H., Kasahara, M., Yokoi, H., Kataoka, H., Mori, E., & Nakagawa, T. (2020). Proteolytic cleavage of Podocin by Matriptase exacerbates podocyte injury. *Journal of Biological Chemistry, 295*(47), 16002-16012. doi:10.1074/jbc.RA120.013721

84. Tomita, I., Kume, S., Sugahara, S., Osawa, N., Yamahara, K., Yasuda-Yamahara, M., Takeda, N., Chin-Kanasaki, M., Kaneko, T., Mayoux, E., Mark, M., **Yanagita, M**., Ogita, H., Araki, S., & Maegawa, H. (2020). SGLT2 Inhibition Mediates Protection from Diabetic Kidney Disease by Promoting Ketone Body-Induced mTORC1 Inhibition. *Cell Metabolism, 32*(3), 404-+. doi:10.1016/j.cmet.2020.06.020

85. Uchino, E., Suzuki, K., Sato, N., Kojima, R., Tamada, Y., Hiragi, S., Yokoi, H., Yugami, N., Minamiguchi, S., Haga, H., **Yanagita, M**., & Okuno, Y. (2020). Classification of glomerular pathological findings using deep learning and nephrologist-AI collective intelligence approach. *International Journal of Medical Informatics, 141*. doi:10.1016/j.ijmedinf.2020.104231

86. Yamamoto, T., Takabatake, Y., Minami, S., Sakai, S., Fujimura, R., Takahashi, A., Namba-Hamano, T., Matsuda, J., Kimura, T., Matsui, I., Kaimori, J. Y., Takeda, H., Takahashi, M., Izumi, Y., Bamba, T., Matsusaka, T., Niimura, F., **Yanagita, M**., & Isaka, Y. Eicosapentaenoic acid attenuates renal lipotoxicity by restoring autophagic flux. *Autophagy*. doi:10.1080/15548627.2020.1782034

2) Review Articles

87. Kakiuchi, N., & **Ogawa, S.** (2021). Clonal expansion in non-cancer tissues. ***Nature Reviews Cancer,*** *21*(4), 239-256. doi:10.1038/s41568-021-00335-3

88. Nagaoka, SI, **Saitou, M**, & Kurimoto, K. (2021). Reconstituting oogenesis in vitro: recent progress and future prospects. ***Current Opinion in Endocrine and Metabolic Research***.

89. **Saitou, M.** (2021). Mammalian germ cell development: from mechanism to in vitro reconstitution. ***Stem Cell Reports***. doi:10.1016/j.stemcr.2021.01.008

90. Yoshitomi, H., & **Ueno, H.** (2021). Shared and distinct roles of T peripheral helper and T follicular helper cells in human diseases. ***Cellular & Molecular Immunology,*** *18*(3), 523-527. doi:10.1038/s41423-020-00529-z

91. Watanabe, C., Imaizumi, T., Kawai, H., Suda, K., Honma, Y., Ichihashi, M., **Ema, M.**, & Mizutani, K. (2020). Aging of the Vascular System and Neural Diseases. ***Frontiers in Aging Neuroscience,*** *12*. doi:10.3389/fnagi.2020.557384

92. Chan, C. J., & **Hiiragi, T.** (2020). Integration of luminal pressure and signalling in tissue self-organization. ***Development,*** *147*(5). doi:10.1242/dev.181297

93. **Ogawa, S.** (2020). Genetic basis of myelodysplastic syndromes. ***Proceedings of the Japan Academy Series B-Physical and Biological Sciences,*** *96*(3), 107-121. doi:10.2183/pjab.96.009

94. Sato, Y., Takahashi, M., & **Yanagita, M.** (2020). Pathophysiology of AKI to CKD progression. ***Semin Nephrol,*** *40*(2), 206-215. doi:10.1016/j.semnephrol.2020.01.011

3) Proceedings N/A

4) Other English articles

95. Koo, B. K., Bartfeld, S., & **Alev, C.** (2021). Organoids: ready for the revolution? ***J Mol Med (Berl),*** *99*(4), 441-442. doi:10.1007/s00109-021-02063-5

96. McIntyre, B., Asahara, T., & **Alev, C.** (2020). Overview of Basic Mechanisms of Notch Signaling in Development and Disease. In J. Reichrath & S. Reichrath (Eds.), ***Notch Signaling in Embryology and Cancer: Molecular Biology of Notch Signaling, 2nd Edition*** (Vol. 1227, pp. 9-27).

B. WPI-related Papers

1) Original Papers

97. Schwerdt, HN, Gibson, DJ, **Amemori, K**, Stanwicks, LL, Yoshida, T, Cima, MJ, & Graybiel, AM. (2021). *Chronic multi-modal monitoring of neural activity in rodents and primates.* Paper presented at the Integrated Sensors for Biological and Neural Sensing.

98. Caron, M., St-Onge, P., Sontag, T., Wang, Y. C., Richer, C., Ragoussis, I., Sinnett, D., & **Bourque, G.** (2021). Single-cell analysis of childhood leukemia reveals a link between developmental states and ribosomal protein expression as a source of intra-individual heterogeneity (vol 10, 8079, 2020). ***Scientific Reports,*** *11*(1). doi:10.1038/s41598-021-85034-7

99. Cheng, A. P., Cheng, M. P., Gu, W., Sesing Lenz, J., Hsu, E., Schurr, E., **Bourque, G.**, Bourgey, M., Ritz, J., Marty, F. M., Chiu, C. Y., Vinh, D. C., & De Vlaminck, I. (2021). Cell-free DNA tissues of origin by methylation profiling reveals significant cell, tissue, and organ-specific injury related to COVID-19 severity. ***Med (N Y),*** *2*(4), 411-422.e415. doi:10.1016/j.medj.2021.01.001

100. Dankner, M., Caron, M., Al-Saadi, T., Yu, W., Ouellet, V., Ezzeddine, R., Maritan, S. M., Annis, M. G., Le, P. U., Nadaf, J., Neubarth, N. S., Savage, P., Zuo, D., Couturier, C. P., Monlong, J., Djambazian, H., Altoukhi, H., **Bourque, G.**, Ragoussis, J., Diaz, R. J., Park, M., Guiot, M. C., Lam, S., Petrecca, K., & Siegel, P. M. (2021). Invasive growth associated with Cold-Inducible RNA-Binding Protein expression drives recurrence of surgically resected brain metastases. ***Neuro Oncol***. doi:10.1093/neuonc/noab002

101. Otsu, K., Ida, H. Y., Ikezaki, S., **Ema, M.**, Hitomi, J., Ohshima, H., & Harada, H. (2021). Oxygen regulates epithelial stem cell proliferation via RhoA-actomyosin-YAP/TAZ signal in mouse incisor. ***Development,*** *148*(4). doi:10.1242/dev.194787

102. Okada, T., Kuribayashi, H., Kaiser, L. G., Urushibata, Y., Salibi, N., Seethamraju, R. T., Ahn, S., Thuy, D. H. D., Fujimoto, K., & **Isa, T**. (2021). Repeatability of proton magnetic resonance spectroscopy of the brain at 7 T: effect of scan time on semi-localized by adiabatic selective refocusing and short-echo time stimulated echo acquisition mode scans and their comparison. ***Quantitative Imaging in Medicine and Surgery,*** *11*(1), 9-20. doi:10.21037/qims-20-517

103. Takahashi, T., Kawaji, H., **Murakawa, Y**., Hayashizaki, Y., Murakami, T., Yabushita, Y., Homma, Y., Kumamoto, T., Matsuyama, R., & Endo, I. (2021). Significance of HMGA2 expression as independent poor prognostic marker in perihilar and distal cholangiocarcinoma resected with curative intent. ***Eur J Surg Oncol,*** *47*(2), 394-400. doi:10.1016/j.ejso.2020.08.005

104. **Higashi, H**., Kato, Y., Fujita, T., Iwasaki, S., Nakamura, M., Nishimura, Y., Takenaka, M., & Shikanai, T. (2021). The pentatricopeptide repeat protein PGR3 is required for the translation of petL and ndhG by binding their 5'UTRs. ***Plant Cell Physiol***. doi:10.1093/pcp/pcaa180

105. Ishida, Y., Kakiuchi, N., Yoshida, K., Inoue, Y., Irie, H., Kataoka, T. R., Hirata, M., Funakoshi, T., Matsushita, S., Hata, H., Uchi, H., Yamamoto, Y., Fujisawa, Y., Fujimura, T., Saiki, R., Takeuchi, K., Shiraishi, Y., Chiba, K., Tanaka, H., Otsuka, A., Miyano, S., Kabashima, K., & **Ogawa, S.** (2021). Unbiased Detection of Driver Mutations in Extramammary Paget Disease. ***Clinical Cancer Research,*** *27*(6), 1756-1765. doi:10.1158/1078-0432.ccr-20-3205

106. Boons, E., Nogueira, T. C., Dierckx, T., Menezes, S. M., Jacquemyn, M., Tamir, S., Landesman, Y., Farre, L., Bittencourt, A., Kataoka, K., **Ogawa, S.**, Snoeck, R., Andrei, G., Van Weyenbergh, J., & Daelemans, D. (2021). XPO1 inhibitors represent a novel therapeutic option in Adult T-cell Leukemia, triggering p53-mediated caspase-dependent apoptosis. ***Blood Cancer Journal,*** *11*(2). doi:10.1038/s41408-021-00409-3

107. Fujishima, N., Kohmaru, J., Koyota, S., Kuba, K., Saga, T., Omokawa, A., Moritoki, Y., Ueki, S., Ishida, F., Nakao, S., Matsuda, A., Ohta, A., Tohyama, K., Yamasaki, H., Usuki, K., Nakashima, Y., Sato, S., Miyazaki, Y., Nannya, Y., **Ogawa, S.**, Sawada, K., Mitani, K., & Hirokawa, M. (2021). Clonal hematopoiesis in adult pure red cell aplasia. ***Sci Rep,*** *11*(1), 2253. doi:10.1038/s41598-021-81890-5

108. Hosokawa, K., Mizumaki, H., Yoroidaka, T., Maruyama, H., Imi, T., Tsuji, N., Urushihara, R., Tanabe, M., Zaimoku, Y., Nguyen, M. A. T., Tran, D. C., Ishiyama, K., Yamazaki, H., Katagiri, T., Takamatsu, H., Hosomichi, K., Tajima, A., Azuma, F., **Ogawa, S.**, & Nakao, S. (2021). HLA class I allele-lacking leukocytes predict rare clonal evolution to MDS/AML in patients with acquired aplastic anemia. ***Blood***. doi:10.1182/blood.2020010586

109. Kaburagi, T., Yamato, G., Shiba, N., Yoshida, K., Hara, Y., Tabuchi, K., Shiraishi, Y., Ohki, K., Sotomatsu, M., Arakawa, H., Matsuo, H., Shimada, A., Taki, T., Kiyokawa, N., Tomizawa, D., Horibe, K., Miyano, S., Taga, T., Adachi, S., **Ogawa, S.**, & Hayashi, Y. (2021). Clinical significance of RAS pathway alterations in pediatric acute myeloid leukemia. ***Haematologica***. doi:10.3324/haematol.2020.269431

110. Kimura, S., Sekiguchi, M., Watanabe, K., Hiwatarai, M., Seki, M., Yoshida, K., Isobe, T., Shiozawa, Y., Suzuki, H., Hoshino, N., Hayashi, Y., Oka, A., Miyano, S., **Ogawa, S.**, & Takita, J. (2021). Association of high-risk neuroblastoma classification based on expression profiles with differentiation and metabolism. ***Plos One,*** *16*(1). doi:10.1371/journal.pone.0245526

111. Lundgren, S., Keränen, M. A. I., Kankainen, M., Huuhtanen, J., Walldin, G., Kerr, C. M., Clemente, M., Ebeling, F., Rajala, H., Brück, O., Lähdesmäki, H., Hannula, S., Hannunen, T., Ellonen, P., Young, N. S., **Ogawa, S.**, Maciejewski, J. P., Hellström-Lindberg, E., & Mustjoki, S. (2021). Somatic mutations in lymphocytes in patients with immune-mediated aplastic anemia. ***Leukemia***. doi:10.1038/s41375-021-01231-3

112. Nakamura, F., Arai, H., Nannya, Y., Ichikawa, M., Furuichi, S., Nagasawa, F., Takahashi, W., Handa, T., Nakamura, Y., Tanaka, H., Sasaki, K., Miyano, S., **Ogawa, S.**, & Mitani, K. Development of Philadelphia chromosome-negative acute myeloid leukemia with IDH2 and NPM1 mutations in a

patient with chronic myeloid leukemia who showed a major molecular response to tyrosine kinase inhibitor therapy. *International Journal of Hematology*. doi:10.1007/s12185-020-03074-7

113. Okabe, M., Morishita, T., Yasuda, T., Sakaguchi, H., Sanada, M., Kataoka, K., **Ogawa, S.**, Shiraishi, Y., Ichiki, T., Kawaguchi, Y., Ohbiki, M., Matsumoto, R., Osaki, M., Goto, T., Ozawa, Y., & Miyamura, K. (2021). Targeted deep next generation sequencing identifies potential somatic and germline variants for predisposition to familial Burkitt lymphoma. *Eur J Haematol*. doi:10.1111/ejh.13629

114. Sakurai, M., Nannya, Y., Yamazaki, R., Yamaguchi, K., Koda, Y., Abe, R., Yokoyama, K., **Ogawa, S.**, & Mori, T. Germline RUNX1 translocation in familial platelet disorder with propensity to myeloid malignancies. *Annals of Hematology*. doi:10.1007/s00277-021-04430-1

115. Tamamitsu, AM, Nakagama, Y, Domoto, Y, Yoshida, K, **Ogawa, S**, Hirono, K, Shindo, T, Ogawa, Y, Nakano, K, & Asakai, H. (2021). Poor Myocardial Compaction in a Patient with Recessive MYL2 Myopathy. *International heart journal, 62*(2), 445-447.

116. Ashida, S., Ochi, H., Hamatani, M., Fujii, C., Kimura, K., Okada, Y., Hashi, Y., Kawamura, K., **Ueno, H**., Takahashi, R., Mizuno, T., & Kondo, T. (2021). Immune Skew of Circulating Follicular Helper T Cells Associates With Myasthenia Gravis Severity. *Neurol Neuroimmunol Neuroinflamm, 8*(2). doi:10.1212/NXI.0000000000000945

117. Tomizawa, T, Nishitani, K, Ito, H, Okae, Y, Morita, Y, Doi, K, Saito, M, Ishie, S, Yoshida, S, Murata, K, **Yoshitomi, H**, Kuroda, Y, & Matsuda, S. (2021). The limitations of mono-and combination antibiotic therapies on immature biofilms in a murine model of implant-associated osteomyelitis. *Journal of Orthopaedic Research®, 39*(2), 449-457.

118. Yamashita, A., **Yoshitomi, H**., Kihara, S., Toguchida, J., & Tsumaki, N. (2021). Culture substrate-associated YAP inactivation underlies chondrogenic differentiation of human induced pluripotent stem cells. *Stem Cells Transl Med, 10*(1), 115-127. doi:10.1002/sctm.20-0058

119. **Amemori, K. I.**, Amemori, S., Gibson, D. J., & Graybiel, A. M. (2020). Striatal Beta Oscillation and Neuronal Activity in the Primate Caudate Nucleus Differentially Represent Valence and Arousal Under Approach-Avoidance Conflict. *Frontiers in Neuroscience, 14*. doi:10.3389/fnins.2020.00089

120. Amemori, S., **Amemori, K. I**., Yoshida, T., Papageorgiou, G. K., Xu, R., Shimazu, H., Desimone, R., & Graybiel, A. M. (2020). Microstimulation of primate neocortex targeting striosomes induces negative decision-making. *Eur J Neurosci, 51*(3), 731-741. doi:10.1111/ejn.14555

121. Ironside, M., **Amemori, K**., McGrath, C. L., Pedersen, M. L., Kang, M. S., Amemori, S., Frank, M. J., Graybiel, A. M., & Pizzagalli, D. A. (2020). Approach-Avoidance Conflict in Major Depressive Disorder: Congruent Neural Findings in Humans and Nonhuman Primates. *Biological Psychiatry, 87*(5), 399-408. doi:10.1016/j.biopsych.2019.08.022

122. Schwerdt, H. N., **Amemori, K**., Gibson, D. J., Stanwicks, L. L., Yoshida, T., Bichot, N. P., Amemori, S., Desimone, R., Langer, R., Cima, M. J., & Graybiel, A. M. (2020). Dopamine and beta-band oscillations differentially link to striatal value and motor control. *Sci Adv, 6*(39). doi:10.1126/sciadv.abb9226

123. Bogdan, L., Barreiro, L., & **Bourque, G**. (2020). Transposable elements have contributed human regulatory regions that are activated upon bacterial infection. *Philosophical Transactions of the Royal Society B-Biological Sciences, 375*(1795). doi:10.1098/rstb.2019.0332

124. Caron, M., St-Onge, P., Sontag, T., Wang, Y. C., Richer, C., Ragoussis, I., Sinnett, D., & **Bourque, G**. (2020). Single-cell analysis of childhood leukemia reveals a link between developmental states and ribosomal protein expression as a source of intra-individual heterogeneity. *Scientific Reports, 10*(1). doi:10.1038/s41598-020-64929-x

125. Hocking, T. D., & **Bourque, G**. (2020). Machine learning algorithms for simultaneous supervised detection of peaks in multiple samples and cell types. *Pac Symp Biocomput, 25*, 367-378.

126. Zhuang, Q. K. W., Galvez, J. H., Xiao, Q., AlOgayil, N., Hyacinthe, J., Taketo, T., **Bourque, G**., & Naumova, A. K. (2020). Sex Chromosomes and Sex Phenotype Contribute to Biased DNA

Methylation in Mouse Liver. *Cells, 9*(6). doi:10.3390/cells9061436

127. Gordon, M. G., **Inoue, F.**, Martin, B., Schubach, M., Agarwal, V., Whalen, S., Feng, S. Y., Zhao, J. J., Ashuach, T., Ziffra, R., Kreimer, A., Georgakopoulos-Soares, I., Yosef, N., Ye, C. J., Pollard, K. S., Shendure, J., Kircher, M., & Ahituv, N. lentiMPRA and MPRAflow for high-throughput functional characterization of gene regulatory elements (vol 15, 2387, 2020). *Nature Protocols*. doi:10.1038/s41596-020-00422-z

128. Klein, J. C., Agarwal, V., **Inoue, F**., Keith, A., Martin, B., Kircher, M., Ahituv, N., & Shendure, J. (2020). A systematic evaluation of the design and context dependencies of massively parallel reporter assays. *Nature Methods, 17*(11), 1083-+. doi:10.1038/s41592-020-0965-y

129. Kisu, I., Emoto, K., Masugi, Y., Yamada, Y., Matsubara, K., Obara, H., Matoba, Y., Banno, K., Kato, Y., Saiki, Y., Itagaki, I., Kawamoto, I., Iwatani, C., Murase, M., Nakagawa, T., Tsuchiya, H., Ishigaki, H., Urano, H., **Ema, M**., Ogasawara, K., Aoki, D., Nakagawa, K., & Shiina, T. (2020). Clinical features of irreversible rejection after allogeneic uterus transplantation in cynomolgus macaques. *Scientific Reports, 10*(1). doi:10.1038/s41598-020-70914-1

130. Kisu, I., Kato, Y., Masugi, Y., Ishigaki, H., Yamada, Y., Matsubara, K., Obara, H., Emoto, K., Matoba, Y., Adachi, M., Banno, K., Saiki, Y., Sasamura, T., Itagaki, I., Kawamoto, I., Iwatani, C., Nakagawa, T., Murase, M., Tsuchiya, H., Urano, H., **Ema, M**., Ogasawara, K., Aoki, D., Nakagawa, K., & Shiina, T. (2020). First Successful Delivery after Uterus Transplantation in MHC-Defined Cynomolgus Macaques. *Journal of Clinical Medicine, 9*(11). doi:10.3390/jcm9113694

131. Takahashi, M., Misaki, M., Shibata, S., Iga, T., Shindo, T., Tai-Nagara, I., Hirata, A., Ogawa, M., Miyamoto, T., Nakagawa, T., **Ema, M**., Ichiyama, Y., Shima, D. T., Hozumi, K., Nishimura, S., & Kubota, Y. (2020). Macrophages fine-tune pupil shape during development. *Developmental Biology, 464*(2), 137-144. doi:10.1016/j.ydbio.2020.06.004

132. Wu, Y. F., Seong, Y. J., Li, K., Choi, D., Park, E., Daghlian, G. H., Jung, E., Bui, K., Zhao, L. P., Madhavan, S., Daghlian, S., Daghlian, P., Chin, D., Cho, I. T., Wong, A. K., Heur, M., Zhang-Nunes, S., Tan, J. C., **Ema, M**., Wong, T. T., Huang, A. S., & Hong, Y. K. (2020). Organogenesis and distribution of the ocular lymphatic vessels in the anterior eye. *Jci Insight, 5*(13). doi:10.1172/jci.insight.135121

133. Cui, W. P., Aida, T., Ito, H., Kobayashi, K., Wada, Y., Kato, S., Nakano, T., Zhu, M. N., Isa, K., **Isa, T**., Tanaka, K., & Aizawa, H. (2020). Dopaminergic Signaling in the Nucleus Accumbens Modulates Stress-Coping Strategies during Inescapable Stress. *Journal of Neuroscience, 40*(38), 7241-7254. doi:10.1523/jneurosci.0444-20.2020

134. Kawamura, A., Katayama, Y., Nishiyama, M., Shoji, H., Tokuoka, K., Ueta, Y., Miyata, M., **Isa, T**., Miyakawa, T., Hayashi-Takagi, A., & Nakayama, K. I. (2020). Oligodendrocyte dysfunction due to Chd8 mutation gives rise to behavioral deficits in mice. *Human Molecular Genetics, 29*(8), 1274-1291. doi:10.1093/hmg/ddaa036

135. Susaki, E. A., Shimizu, C., Kuno, A., Tainaka, K., Li, X., Nishi, K., Morishima, K., Ono, H., Ode, K. L., Saeki, Y., Miyamichi, K., Isa, K., Yokoyama, C., Kitaura, H., Ikemura, M., Ushiku, T., Shimizu, Y., Saito, T., Saido, T. C., Fukayama, M., Onoe, H., Touhara, K., **Isa, T**., Kakita, A., Shibayama, M., & Ueda, H. R. (2020). Versatile whole-organ/body staining and imaging based on electrolyte-gel properties of biological tissues. *Nature Communications, 11*(1). doi:10.1038/s41467-020-15906-5

136. Ooki, A., Onodera, S., Saito, A., Oguchi, A., **Murakawa, Y**., Sakamoto, T., Sueishi, K., Nishii, Y., & Azuma, T. (2020). CAGE-seq analysis of osteoblast derived from cleidocranial dysplasia human induced pluripotent stem cells. *Bone, 141*. doi:10.1016/j.bone.2020.115582

137. Tsujimoto, H., **Kasahara, T**., Sueta, S. I., Araoka, T., Sakamoto, S., Okada, C., Mae, S. I., Nakajima, T., Okamoto, N., Taura, D., Nasu, M., Shimizu, T., Ryosaka, M., Li, Z., Sone, M., Ikeya, M., Watanabe, A., & Osafune, K. (2020). A Modular Differentiation System Maps Multiple Human Kidney Lineages from Pluripotent Stem Cells. *Cell Rep, 31*(1), 107476. doi:10.1016/j.celrep.2020.03.040

138. Bernard, E., Nannya, Y., Hasserjian, R. P., Devlin, S. M., Tuechler, H., Medina-Martinez, J. S., Yoshizato, T., Shiozawa, Y., Saiki, R., Malcovati, L., Levine, M. F., Arango, J. E., Zhou, Y. Y., Sole,

F., Cargo, C. A., Haase, D., Creignou, M., Germing, U., Zhang, Y. M., Gundem, G., Sarian, A., van de Loosdrecht, A. A., Jadersten, M., Tobiasson, M., Kosmider, O., Follo, M. Y., Thol, F., Pinheiro, R. F., Santini, V., Kotsianidis, I., Boultwood, J., Santos, F. P. S., Schanz, J., Kasahara, S., Ishikawa, T., Tsurumi, H., Takaori-Kondo, A., Kiguchi, T., Polprasert, C., Bennett, J. M., Klimek, V. M., Savona, M. R., Belickova, M., Ganster, C., Palomo, L., Sanz, G., Ades, L., Della Porta, M. G., Smith, A. G., Werner, Y., Patel, M., Viale, A., Vanness, K., Neuberg, D. S., Stevenson, K. E., Menghrajani, K., Bolton, K. L., Fenaux, P., Pellagatti, A., Platzbecker, U., Heuser, M., Valent, P., Chiba, S., Miyazaki, Y., Finelli, C., Voso, M. T., Shih, L. Y., Fontenay, M., Jansen, J. H., Cervera, J., Atsuta, Y., Gattermann, N., Ebert, B. L., Bejar, R., Greenberg, P. L., Cazzola, M., Hellstrom-Lindberg, E., **Ogawa, S**., & Papaemmanuil, E. (2020). Implications ofTP53allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nature Medicine, 26*(10), 1549-+. doi:10.1038/s41591-020-1008-z

139. Donovan, F. X., Solanki, A., Mori, M., Chavan, N., George, M., Kumar, C. S., Okuno, Y., Muramastsu, H., Yoshida, K., Shimamoto, A., Takaori-Kondo, A., Yabe, H., **Ogawa, S**., Kojima, S., Yabe, M., Ramanagoudr-Bhojappa, R., Smogorzewska, A., Mohan, S., Rajendran, A., Auerbach, A. D., Takata, M., Chandrasekharappa, S. C., & Vundinti, B. R. (2020). A founder variant in the South Asian population leads to a high prevalence of FANCL Fanconi anemia cases in India. *Human Mutation, 41*(1), 122-128. doi:10.1002/humu.23914

140. Fujioka, M., Itonaga, H., Kato, T., Nannya, Y., Hashimoto, M., Kasai, S., Toriyama, E., Kamijo, R., Taguchi, M., Taniguchi, H., Sato, S., Atogami, S., Imaizumi, Y., Hata, T., Moriuchi, Y., **Ogawa, S**., & Miyazaki, Y. (2020). Persistent clonal cytogenetic abnormality with del(20q) from an initial diagnosis of acute promyelocytic leukemia. *International Journal of Hematology, 111*(2), 311-316. doi:10.1007/s12185-019-02731-w

141. Gu, M. X., Zwiebel, M., Ong, S. H., Boughton, N., Nomdedeu, J., Basheer, F., Nannya, Y., Quiros, P. M., **Ogawa, S**., Cazzola, M., Rad, R., Butler, A. P., Vijayabaskar, M. S., & Vassiliou, G. S. (2020). RNAmut: robust identification of somatic mutations in acute myeloid leukemia using RNA-sequencing. *Haematologica, 105*(6), E290-E293. doi:10.3324/haematol.2019.230821

142. Hashimoto, M, Itonaga, H, Nannya, Y, Taniguchi, H, Fukuda, Y, Furumoto, T, Fujioka, M, Kasai, S, Taguchi, M, Sato, S, Sawayama, Y, Atogami, S, Iwasaki, K, Hata, T, Soda, H, Moriuchi, Y, Nakata, K, **Ogawa, S**, & Miyazaki, Y. (2020). Secondary Pulmonary Alveolar Proteinosis Following Treatment with Azacitidine for Myelodysplastic Syndrome. *Internal Medicine, 59*(8), 1081-1086. doi:10.2169/internalmedicine.3770-19

143. Imataki, O., Ishida, T., Kubo, H., Uemura, M., Nanya, Y., Kawakami, K., **Ogawa, S**., & Kadowaki, N. (2020). A Case of Tyrosine Kinase Inhibitor-Resistant Chronic Myeloid Leukemia, Chronic Phase with ASXL1 Mutation. *Case Reports in Oncology, 13*(1), 449-455. doi:10.1159/000506452

144. Jo, T., Nishikori, M., Kogure, Y., Arima, H., Sasaki, K., Sasaki, Y., Nakagawa, T., Iwai, F., Momose, S., Shiraishi, A., Kiyonari, H., Kagaya, N., Onuki, T., Shin-ya, K., Yoshida, M., Kataoka, K., **Ogawa, S**., Iwai, K., & Takaori-Kondo, A. (2020). LUBAC accelerates B-cell lymphomagenesis by conferring resistance to genotoxic stress on B cells. *Blood, 136*(6), 684-697. doi:10.1182/blood.2019002654

145. Madan, V, Li, J, Zhou, SQ, Teoh, WW, Han, L, Meggendorfer, M, Malcovati, L, Cazzola, M, **Ogawa, S**, Haferlach, T, Yang, H, & Koeffler, HP. (2020). Distinct and convergent consequences of splice factor mutations in myelodysplastic syndromes. *American Journal of Hematology, 95*(2), 133-143. doi:10.1002/ajh.25673

146. Mori, M, Hira, A, Yoshida, K, Muramatsu, H, Okuno, Y, Shiraishi, Y, Anmae, M, Yasuda, J, Tadaka, S, Kinoshita, K, Osumi, T, Noguchi, Y, Adachi, S, Kobayashi, R, Kawabata, H, Imai, K, Morio, T, Tamura, K, Takaori-Kondo, A, Yamamoto, M, Miyano, S, Kojima, S, Ito, E, **Ogawa, S**, Matsuo, K, Yabe, H, Yabe, M, & Takata, M. (2020). Pathogenic mutations identified by a multimodality approach in 117 Japanese Fanconi anemia patients (vol ,104 pg 1962, 2019). *Haematologica, 105*(4), 1166-1167. doi:10.3324/haematol.2019.245720

147. Nakagama, Y, Takeda, N, **Ogawa, S**, Takeda, H, Furutani, Y, Nakanishi, T, Sato, T, Hirata, Y, Oka, A, & Inuzuka, R. (2020). Noonan syndrome-associated biallelic LZTR1 mutations cause cardiac

hypertrophy and vascular malformations in zebrafish. *Molecular Genetics & Genomic Medicine, 8*(3). doi:10.1002/mgg3.1107

148. Nguyen, M. A. T., Hosokawa, K., Yoroidaka, T., Maruyama, H., Espinoza, J. L., Elbadry, M. I., Mohiuddin, M., Tanabe, M., Katagiri, T., Nakagawa, N., Chonabayashi, K., Yoshida, Y., Arima, N., Kashiwase, K., Saji, H., **Ogawa, S**., & Nakao, S. (2020). Resistance of KIR Ligand-Missing Leukocytes to NK Cells In Vivo in Patients with Acquired Aplastic Anemia. *Immunohorizons, 4*(7), 430-441. doi:10.4049/immunohorizons.2000046

149. Nguyen, T. B., Sakata-Yanagimoto, M., Fujisawa, M., Nuhat, S. T., Miyoshi, H., Nannya, Y., Hashimoto, K., Fukumoto, K., Bernard, O. A., Kiyoki, Y., Ishitsuka, K., Momose, H., Sukegawa, S., Shinagawa, A., Suyama, T., Sato, Y., Nishikii, H., Obara, N., Kusakabe, M., Yanagimoto, S., **Ogawa, S**., Ohshima, K., & Chiba, S. (2020). Dasatinib Is an Effective Treatment for Angioimmunoblastic T-cell Lymphoma. *Cancer Research, 80*(9), 1875-1884. doi:10.1158/0008-5472.can-19-2787

150. Secardin, L., Limia, C. E. G., di Stefano, A., Bonamino, M. H., Saliba, J., Kataoka, K., Rehen, S. K., Raslova, H., Marty, C., **Ogawa, S**., Vainchenker, W., Monte-Mor, B. D. R., & Ploa, I. (2020). TET2 haploinsufficiency alters reprogramming into induced pluripotent stem cells. *Stem Cell Research, 44*. doi:10.1016/j.scr.2020.101755

151. Shirai, R., Osumi, T., Terashima, K., Kiyotani, C., Uchiyama, M., Tsujimoto, S., Yoshida, M., Yoshida, K., Uchiyama, T., Tomizawa, D., Shioda, Y., Sekiguchi, M., Watanabe, K., Keino, D., Ueno-Yokohata, H., Ohki, K., Takita, J., Ito, S., Deguchi, T., Kiyokawa, N., Ogiwara, H., Hishiki, T., **Ogawa, S**., Okita, H., Matsumoto, K., Yoshioka, T., & Kato, M. (2020). High prevalence of SMARCB1 constitutional abnormalities including mosaicism in malignant rhabdoid tumors. *European Journal of Human Genetics, 28*(8), 1124-1128. doi:10.1038/s41431-020-0614-z

152. Taguchi, M., Mishima, H., Shiozawa, Y., Hayashida, C., Kinoshita, A., Nannya, Y., Makishima, H., Horai, M., Matsuo, M., Sato, S., Itonaga, H., Kato, T., Taniguchi, H., Imanishi, D., Imaizumi, Y., Hata, T., Takenaka, M., Moriuchi, Y., Shiraishi, Y., Miyano, S., **Ogawa, S**., Yoshiura, K. I., & Miyazaki, Y. (2020). Genome analysis of myelodysplastic syndromes among atomic bomb survivors in Nagasaki. *Haematologica, 105*(2), 358-365. doi:10.3324/haematol.2019.219386

153. Wu, J., Cheng, H., Wang, H. L., Zang, G. X., Qi, L. L., Lv, X. P., Liu, C. Y., Zhu, S., Zhang, M. Y., Cui, J. W., **Ueno, H**., Liu, Y. J., Suo, J., & Chen, J. T. (2021). Correlation Between Immune Lymphoid Cells and Plasmacytoid Dendritic Cells in Human Colon Cancer. *Frontiers in Immunology, 12*. doi:10.3389/fimmu.2021.601611

154. Maekawa, H., Kawai, S., Nishio, M., Nagata, S., Jin, Y., **Yoshitomi, H**., Matsuda, S., & Toguchida, J. (2020). Prophylactic treatment of rapamycin ameliorates naturally developing and episode -induced heterotopic ossification in mice expressing human mutant ACVR1. *Orphanet J Rare Dis, 15*(1), 122. doi:10.1186/s13023-020-01406-8

155. Okahata, A., Ito, H., Furu, M., Ishikawa, M., Fujii, T., Hashimoto, M., Tanaka, M., Morita, Y., Azukizawa, M., Tomizawa, T., Doi, K., Nishitani, K., Murata, K., **Yoshitomi, H**., Mimori, T., & Matsuda, S. (2020). Soluble Lectin-like Oxidized Low-Density Lipoprotein Receptor 1 Predicts the Changes of Rheumatoid Factor Titers in Rheumatoid Arthritis. *J Clin Rheumatol, 26*(7), 295-300. doi:10.1097/RHU.0000000000001116

156. Bouchareychas, L., Duong, P., Covarrubias, S., Alsop, E., Phu, T. A., Chung, A., Gomes, M., Wong, D., Meechoovet, B., Capili, A., **Yamamoto, R**., Nakauchi, H., McManus, M. T., Carpenter, S., Van Keuren-Jensen, K., & Raffai, R. L. (2020). Macrophage Exosomes Resolve Atherosclerosis by Regulating Hematopoiesis and Inflammation via MicroRNA Cargo. *Cell Reports, 32*(2). doi:10.1016/j.celrep.2020.107881

157. Choi, J., Park, J. E., Tsagkogeorga, G., **Yanagita, M**., Koo, B. K., Han, N., & Lee, J. H. (2020). Inflammatory Signals Induce AT2 Cell-Derived Damage-Associated Transient Progenitors that Mediate Alveolar Regeneration. *Cell Stem Cell, 27*(3), 366-+. doi:10.1016/j.stem.2020.06.020

158. Fukushima, K., Satoh, T., Sugihara, F., Sato, Y., Okamoto, T., Mitsui, Y., Yoshio, S., Li, S. L., Nojima, S., Motooka, D., Nakamura, S., Kida, H., Standley, D. M., Morii, E., Kanto, T., **Yanagita, M**., Matsuura, Y., Nagasawa, T., Kumanogoh, A., & Akira, S. (2020). Dysregulated Expression of

the Nuclear Exosome Targeting Complex Component Rbm7 in Nonhematopoietic Cells Licenses the Development of Fibrosis. *Immunity, 52*(3), 542-+. doi:10.1016/j.immuni.2020.02.007

159. Sato, N., Kakuta, M., Hasegawa, T., Yamaguchi, R., Uchino, E., Kobayashi, W., Sawada, K., Tamura, Y., Tokuda, I., Murashita, K., Nakaji, S., Imoto, S., **Yanagita, M**., & Okuno, Y. (2020). Metagenomic analysis of bacterial species in tongue microbiome of current and never smokers. *Npj Biofilms and Microbiomes, 6*(1). doi:10.1038/s41522-020-0121-6

160. Sato, N., Kakuta, M., Hasegawa, T., Yamaguchi, R., Uchino, E., Murashita, K., Nakaji, S., Imoto, S., **Yanagita, M**., & Okuno, Y. (2020). Metagenomic profiling of gut microbiome in early chronic kidney disease. *Nephrol Dial Transplant*. doi:10.1093/ndt/gfaa122

161. Sato, N., Kakuta, M., Uchino, E., Hasegawa, T., Kojima, R., Kobayashi, W., Sawada, K., Tamura, Y., Tokuda, I., Imoto, S., Nakaji, S., Murashita, K., **Yanagita, M**., & Okuno, Y. (2020). The relationship between cigarette smoking and the tongue microbiome in an East Asian population. *Journal of Oral Microbiology, 12*(1). doi:10.1080/20002297.2020.1742527

2) Review Articles

162. Malcovati, L., Stevenson, K., Papaemmanuil, E., Neuberg, D., Bejar, R., Boultwood, J., Bowen, D. T., Campbell, P. J., Ebert, B. L., Fenaux, P., Haferlach, T., Heuser, M., Jansen, J. H., Komrokji, R. S., Maciejewski, J. P., Walter, M. J., Fontenay, M., Garcia-Manero, G., Graubert, T. A., Karsan, A., Meggendorfer, M., Pellagatti, A., Sallman, D. A., Savona, M. R., Sekeres, M. A., Steensma, D. P., Tauro, S., Thol, F., Vyas, P., Van de Loosdrecht, A. A., Haase, D., Tuchler, H., Greenberg, P. L., **Ogawa, S.**, Hellstrom-Lindberg, E., & Cazzola, M. (2020). SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. *Blood, 136*(2), 157-170. doi:10.1182/blood.2020004850

163. **Ueno, H.** (2020). The IL-12-STAT4 axis in the pathogenesis of human systemic lupus erythematosus. *Eur J Immunol, 50*(1), 10-16. doi:10.1002/eji.201948134

164. **Yoshitomi, H.** (2020). CXCL13-producing PD-1. *Immunol Med, 43*(4), 156-160. doi:10.1080/25785826.2020.1781998

165. **Yamamoto, R.**, & Nakauchi, H. (2020). In vivo clonal analysis of aging hematopoietic stem cells. *Mechanisms of Ageing and Development, 192*. doi:10.1016/j.mad.2020.111378

166. **Yamamoto, R.**, Wilkinson, A. C., & Nakauchi, H. (2020). In vivoandex vivohaematopoietic stem cell expansion. *Current Opinion in Hematology, 27*(4), 273-278. doi:10.1097/moh.0000000000000593

3) Proceedings N/A

4) Other English Articles N/A

2. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings

- List up to 10 main presentations during FY 2020 in order from most recent.
- For each, write the date(s), lecturer/presenter's name, presentation title, and conference name.

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
2021/3/4	Cantas Alev	Towards reconstituting human somitogenesis in vitro	3DMM2O Conference 2021 "3D Hybrid Organotypic Systems" (Germany)
2021/3/3	Cantas Alev	Towards reconstituting human somitogenesis in vitro	3rd SY-Stem Symposium on Stem Cell Research (Vienna, Austria)
2021/2/2	Hideki Ueno	Generation and plasticity of memory Tfh cells in humans	The Royal Society: T cell/B cell collaboration in autoimmunity
2021/1/8	Yasuaki Hiraoka	Characterizing rare events in persistent homology	Joint Mathematics Meetings 2021
2020/12/15	Mitinori Saitou	Mechanism and In Vitro Reconstitution of Mammalian Germ-Cell Development	The 19th International Symposium Pediatric Neuro-Oncology
2020/12/11	Yasuaki Hiraoka	Characterizing rare events in persistent homology	Topological Data Analysis and Beyond. Workshop at NeurIPS 2020
2020/11/16	Guillaume Bourque	Impact of transposable elements on human gene regulatory networks	Institut de Recherches Clinique de Montreal. Invited Speaker Series.
2020/11/6	Mototsugu Eiraku	Functional 3D tissue formation by in vitro manipulation and cell autonomy	The 15th International Symposium of The Institute Network for Biomedical Sciences: Cutting Edge of Biomedical and Metabolic Sciences.
2020/10/21	Takashi Hiiragi	Self-organization in mouse development	Kavli Institute for Theoretical Physics conference "Symmetries in Morphogenesis: from Mechanisms to Principles"
2020/10/4	Motoko Yanagita	AKI to / on CKD] in [AKI Detection, Diagnosis, and Prognosis	18th Asian Pacific Congress of Nephrology
2020/9/13	Guillaume Bourque	Personalized and graph genomes reveal missing signal in epigenomic data.	T2T/HPRC consortium meeting
2020/9/13	Tadashi Isa	Systems neuroscience of functional recovery after brain and spinal cord injury	Plenary Lecture in the 1st Taiwan Society for Neuroscience Meeting
2020/6/26	Mitinori Saitou	ISSCR Momentum Award Lecture	ISSCR 2020
2020/6/24	Misao Fujita	Stakeholder views – How scientists and various publics view brain organoid research and who should be making decisions on its regulation?	ISSCR 2020 VIRTUAL

2020/5/27	Mitinori Saitou	Cancelled Mechanism and In Vitro Reconstitution of Mammalian Germ Cell Development	The 85th CSHL Symposium: Genome Stability & Integrity

3. Major Awards

- List up to 10 main awards received during FY 2020 in order from the most recent.
- For each, write the date issued, the recipient's name, and the name of award.
- In case of multiple recipients, underline those affiliated with the center.

Date	Recipient's name	Name of award
2020/12/6	Guillaume Bourque	Canada Research Chair (Tier 1), Computational Genomics and Medicine
2020/11/2	Motoko Yanagita	57th Baelz Prize (2nd Prize), Boehringer Ingelheim
2020/7/7	Mitinori Saitou	EMBO Associate Member
2020/6/26	Mitinori Saitou	The ISSCR 2020 Momentum Award
2020/6/5	Yasuaki Hiraoka	Award of the Outstanding papers published in the JCS-Japan in 2019
2020/4/30	Guillaume Bourque	Research Scholars emeritus, Fonds de Recherche en Santé du Québec
2020/4/6	Mitinori Saitou	Imperial Prize and Japan Academy Prize, Japan Academy

Appendix 2　FY 2020 List of Principal Investigators

NOTE:

*Underline names of principal investigators who belong to an overseas research institution.

*In the case of researcher(s) not listed in the latest report, attach a "Biographical Sketch of a New Principal Investigator"(Appendix 2a).

*Enter the host institution name and the center name in the footer.

<Results at the end of FY2020> **Principal Investigators Total: 17**

Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Center director Mitinori SAITOU	50	Professor Kyoto University Institute for Advanced Study, Kyoto University	MD, PhD Cell Biology, Developmental Biology	90%	Oct.30, 2018	Usually stays at the center and participates in the center's activities as Center Director and Executive Board member	
Cantas ALEV	46	Associate Professor Institute for the Advanced Study of Human Biology (ASHBi) Kyoto University	MD, PhD Developmental Biology	100%	Jul.1, 2019	Usually stays at the center and participates in the center's activities	
Ken-ichi AMEMORI	47	Associate Professor Institute for the Advanced Study of Human Biology (ASHBi) Kyoto University	PhD Neuroscience	100%	Sep. 1, 2020	Usually stays at the center and participates in the center's activities	
Guillaume BOURQUE	44	Professor Human Genetics, McGill University	PhD Bioinformatics, Genomics, Epigenomics	25%	Oct.30, 2018	Stays at Kyoto University 3 times per year for 3-4 weeks (total ~11 weeks)	Has recruited Co-PI and a Foreign researcher at the Center
Mototsugu EIRAKU	46	Professor Laboratory of Developmental System, Institite for Frontier Life and Medical Sciences, Kyoto University	PhD Developmental Biology	70%	Oct.30, 2018	Usually stays at the center and participates in the center's activities	

Masatsugu EMA	53	Professor Department of Stem Cells and Human Disease Models Research Center for Animal Life Science, Shiga University of Medical Science	PhD Developmental Biology, Developmental Engineering	70%	Oct.30, 2018	Usually stays at the center and participates in the center's activities	
Misao FUJITA	51	Professor Center for iPS Cell Research and Application, Kyoto University	MS MPH PhD Bioethics	70%	Oct.30, 2018	Usually stays at the center and participates in the center's activities	
Takashi HIIRAGI	53	Group Leader Developmental Biology, European Molecular Biology Laboratory	MD, PhD Developmental Biology	20%	Oct.30, 2018	Stays at the center every 2-3 months and participates in the center's activities	Setting up the laboratory, recruiting co-PI
Vice director Yasuaki HIRAOKA	43	Professor Kyoto University Institute for Advanced Study, Kyoto University	PhD Applied Mathematics	70%	Oct.30, 2018	Usually stays at the center and participates in the center's activities as Vice Director and Executive Board member	
Vice director Tadashi ISA	60	Professor Graduate School of Medicine, Kyoto University	MD, PhD Neuroscience	80%	Oct.30, 2018	Usually stays at the center and participates in the center's activities as Vice Director and Executive Board member	
Yasuhiro MURAKAWA	38	Professor Kyoto University Institute for Advanced Study, Kyoto University	MD, PhD Human Genomics, Medical Science, Systems Biology	100%	Sep. 1, 2020	Usually stays at the center and participates in the center's activities	
Seishi OGAWA	58	Professor Pathology and Tumor Biology,Graduate School of Medicine,Kyoto Univerisity/ Guest professor Department of Molecular Hematology, Karolinska Institute	MD, PhD Molecular Oncology	90%	Oct.30, 2018	Usually stays at the center and participates in the center's activities	

Tomoyuki TSUKIYAMA	37	Associate Professor, Research Center for Animal Life Science, Shiga University of Medical Science	PhD Developmental Engineering, Reproductive and Stem Cell Biology	100%	Jan.1, 2020	Usually stays at the center and participates in the center's activities	
Hideki UENO	53	Professor Department of Microbiology, Icahn School of Medicine at Mount Sinai, NY, USA	MD, PhD Immunology	95%	Oct.30, 2018	Stays at the center every 2-3 months and participates in the center's activities	Has recrutied a Co-PI at the Center
Ryo YAMAMOTO	45	Associate Professor Institute for the Advanced Study of Human Biology (ASHBi) Kyoto University	MD, PhD Hematology	100%	Sep. 1, 2020	Usually stays at the center and participates in the center's activities	
Head of the Single-cell Genome Information Analysis Core Takuya YAMAMOTO	43	Associate Professor, Department of Life Science Frontiers, Center for iPS Cell Research & Application, Kyoto University	PhD Molecular Biology, Bioinformatics	80%	Oct.30, 2018	Usually stays at the center and participates in the center's activities as Executive Board member	
Motoko YANAGITA	51	Professor Graduate School of Medicine, Kyoto University	MD, PhD Nephrology	70%	Oct.30, 2018	Usually stays at the center and participates in the center's activities	

*Percentage of time that the principal investigator devotes to working for the center vis-à-vis his/her total working hours.

Principal investigators unable to participate in project in FY 2020

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken

Appendix 2a Biographical Sketch of a New Principal Investigator

Name (Age)
Ken-ichi Amemori (47)
Affiliation and position
Associate Professor, Institute for the Advanced Study of Human Biology, Kyoto University
Academic degree and specialty
Ph. D. (neuroscience)
Effort
100 %
* Percentage of time that the principal investigator devote to working for the center vis-à-vis his/her total working hours.

Research and education history
Ken-ichi Amemori graduated from Kyoto University and obtained his Ph.D. from Nara Institute of Science and Technology (2001). After he was appointed as an instructor of Hokkaido University School of Medicine, he moved to the U.S. He then undertook postdoctoral training at the Massachusetts Institute of Technology (2005-2009) and then was appointed as a research scientist (2009-2017). After becoming a program-specific associate professor at the Hakubi Center for Advanced Research and the Primate Research Institute of Kyoto University, he moved to ASHBi as a principal investigator in 2020.

Achievements and highlights of past research activities
Many of our decisions involve weighing benefits against costs. The Approach-Avoidance (Ap-Av) conflict is an essential psychological concept and has been used to characterize anxiety-like behavior and pessimistic decision-making. An optimistic view leads to more approach decisions; a pessimistic view leads to more avoidance decisions. Decisions under approach-avoidance conflict have primarily contributed to characterize the effect of various types of anti-anxiety drugs. However, the underlying neural mechanisms of the approach-avoidance conflict have been less explored. To derive the internal state of optimism and pessimism in the emotional evaluation, we introduced the "Ap-Av conflict task" and could successfully characterize the value judgment in decision-making. With this task, we identified the cortical source of "anxiety" in primates. We discovered an essential function of the pregenual anterior cingulate cortex (pACC). Based on the electrophysiological activity recorded in the pACC, we discovered that the pACC contained neurons that encoded value evaluation (Amemori et al., J. Neurosci., 2015). To further substantiate the correlation between these neurons and value evaluation behavior, we directly microstimulated these pACC cells. This microstimulation induced the monkey's pessimistic decision-making. We further administrated an anxiolytic drug while we microstimulated the pACC, and observed recovery from the pessimistic state, supporting the idea that the pACC activation correlated with anxiety (Amemori & Graybiel, Nature Neuroscience, 2012). Importantly, we recently found that the pACC responses for the Ap-Av conflict were homologous between humans and macaques (Ironside+, Amemori+, et al., Biological Psychiatry, 2020). These results indicate the macaque's pACC studies are critically important for the understanding of human emotional circuitry.

We identified that the cortico-striosome pathway is a causal pathway of the "anxiety" network. After identifying the site in which the microstimulation induced a change in the decision, we then injected anterograde viral tracers to identify the network. We found that the local circuits of pACC are causally involved in pessimistic decision-making, and the stimulation-effective sites have major projections to the striatum, especially to the striosome compartment. These results showed that one of the major outputs of the limbic cortices related to the generation of an anxiety-like state is the striosomes compartment (Amemori, Amemori et al., EJN, 2020). The striosome is an anatomical structure that was histochemically identified by Dr. Graybiel and colleagues in the 1970s. However, very little has been discovered about the function. We searched for a brain region in rodents that showed a similar projection pattern to the pACC and confirmed that the anterior part of the prelimbic cortex (PL) of rodents sends preferential projection to the striosomes similarly to macaques. We performed selective inhibition of the PL-striosomes pathway using halorhodopsin and could increase the frequency of approaching a conflict offer. These results suggest that the striosome compartment's activity is causally involved in generating pessimistic valuation

under conflict, which is regarded as an anxiety-like state. From these series of studies, we concluded that the projections from the pACC in macaques and the PL in rats to the striosome compartment of the striatum are essential in the generation and control of an anxiety-like state (Friedman et al. Cell, 2015; 2017). Microstimulation of the primate striatum also supports these findings (Amemori et al., Neuron, 2018).

Achievements

(1) International influence * Describe the kind of attributes listed below.

a) Recipient of international awards

b) Member of a scholarly academy in a major country

c) Guest speaker or chair of related international conference and/or director or honorary member of a major international academic society in the subject field

d) Editor of an international academic journal

Topic editor of Frontiers in Neuroscience.

e) Peer reviewer for an overseas competitive research program (etc.)

British Medical Research Council, Science (twice), Biological Psychiatry (twice), Current Biology, European Journal of Neuroscience, Frontiers in Neuroscience, PLOS Biology and so on.

(2) Receipt of major large-scale competitive funds (over the past 5 years)

2020-2025 **Grant-in-Aid for Scientific Research (B)** from Japan Society for the Promotion of Science, Japan "Identifying primate's striosomal function aiming at controlling anxiety disorder." Role: Principal Investigator

2020-2022 **Grant-in-Aid for Scientific Research on Innovative Areas** (Hyper-adaptability) from Japan Society for the Promotion of Science, Japan "Oscillatory striatal and limbic cortical activities during and recovery period of anxiety disorder." Role: Principal Investigator

2018-2022 **Grant-in-Aid for Scientific Research on Innovative Areas** (Brain information dynamics) from Japan Society for the Promotion of Science, Japan "Identifying the spike pattern that controls valuation in the dopamine circuits in primates." Role: Principal Investigator

2020-2021 **Research Grant** from the Takeda Science Foundation "Analyzing primate's striosomal function to control an anxiety disorder." Role: Principal Investigator

2018-2020 **Grant-in-Aid for Challenging Exploratory Research** from Japan Society for the Promotion of Science, Japan "Identifying the local circuit that causes changes in social rank in primates." Role: Principal Investigator

2018-2020 **Grant-in-Aid for Scientific Research on Innovative Areas** (Non-linear neuro-oscillology) from Japan Society for the Promotion of Science, Japan "Novel beta oscillation correlated with pessimistic judgment in the cortico-striatal circuitry." Role: Principal Investigator

2019-2020 **Research Grant** from the Sumitomo Foundation "Analyzing primate's striosomal function to control an anxiety disorder." Role: Principal Investigator

2018-2019 **Research Grant** from the Uehara Memorial Foundation "Functional identification of primate nucleus accumbens related to an anxiety and pessimistic judgment." Role: Principal Investigator

2018-2019 **Research Grant** from the Naito Foundation "Functional identification of primate nucleus accumbens related to an anxiety and persistent pessimistic state." Role: Principal Investigator

(3) Major publications (Titles of major publications, year of publication, journal name, number of citations)

Ironside, M+., Amemori, K+., McGrath, C. L., Pedersen, L. M., Kang, M. S., Amemori, S., Frank, M. J., Graybiel, A. M. and Pizzagalli, D. A. Approach-avoidance conflict in major depression: Congruent neural findings in human and non-human primates. Biological Psychiatry, 87 (2020):

399-408. (+: equal contribution) (cited by 7)

Amemori, S., Amemori, K., Yoshida, T., Papageorgiou, G. K., Xu, R., Shimazu, H., Desimone, R. and Graybiel, A. M. Microstimulation of primate neocortex targeting striosomes induces negative decision-making. European Journal of Neuroscience, 51 (2020): 731-741. (cited by 4)

Amemori, K.+, Amemori, S.+, Gibson, D. J. and Graybiel, A. M. Striatal microstimulation induces persistent and repetitive negative decision-making predicted by striatal beta-band oscillation. Neuron, 99 (2018): 829-841. (+: equal contribution) (cited by 27)

Dagdeviren C, Ramadi KB, Joe P, Spencer K, Schwerdt HN, Shimazu H, Delcasso S, Amemori KI, Nunez-Lopez C, Graybiel AM, Cima MJ, Langer R. Miniaturized neural system for chronic, local intracerebral drug delivery. Sci Transl Med. 2018 Jan 24;10(425): eaan2742 (cited by 43)

Friedman, A., Homma, D., Bloem, B., Gibb, L. G., Amemori, K., Hu, D., Delcasso, S., Truong, T. F., Yang, J., Hood, A. S., Mikofalvy, K. A., Beck, D. W., Nguyen, N., Nelson, E. D., Toro Arana, S. E., Vorder Bruegge, R. H., Goosens K. A. and Graybiel A. M. Chronic stress alters striosome-circuit dynamics, leading to aberrant decision-making. Cell, 171 (2017):1191-1205. (cited by 65)

Desrocher, T. M., Amemori, K. and Graybiel, A. M. Habit learning by naive macaques is marked by dynamic response sharpening of striatal neurons representing the cost and outcome of acquired action sequences. Neuron, 87 (2015): 853-868. (cited by 43)

Friedman, A., Homma, D., Gibb, L., Amemori, K., Rubin, S., Hood, A., Riad, M. and Graybiel, A. M. A corticostriatal path targeting striosomes controls decision-making under conflict. Cell, 161 (2015): 1320-1333. (cited by 195)

Amemori, K., Amemori, S. and Graybiel, A. M. Motivation and affective judgments differentially recruit neurons in the primate dorsolateral prefrontal and anterior cingulate cortex. Journal of Neuroscience, 35 (2015): 1939-1953. (cited by 37)

Amemori, K. and Graybiel, A. M. Localized microstimulation of primate pregenual cingulate cortex induces negative decision-making. Nature Neuroscience, 15 (2012): 776–785. (cited by 206)

Amemori, K., Gibb, L. G. and Graybiel, A. M. Shifting responsibly: the importance of striatal modularity to reinforcement learning in uncertain environments. Frontiers in human neuroscience 5 (2011): 47. (cited by 61)

(4) Others (Other achievements indicative of the PI's qualification as a top-world researcher, if any.)

2017 Hakubi Researcher, Kyoto University
2006 National Parkinson Foundation Lynn Diamond Fellow
2002 Best Paper Award, Institute of Systems, Control & Information Engineers, Japan
1999 Best Student Award, Nara Institute of Science & Technology

Appendix 2a Biographical Sketch of a New Principal Investigator

Name (Age)

Yasuhiro Murakawa (38)

Affiliation and position

Professor, Institute for the Advanced Study of Human Biology, KUIAS, Kyoto University

Academic degree and specialty

M.D. (Kyoto University), Ph.D. (Free University of Berlin)

Human Genomics, Medical Science, Systems Biology

Effort **100 %**

* Percentage of time that the principal investigator devote to working for the center vis-à-vis his/her total working hours.

Research and education history

He graduated from Kyoto University School of Medicine (2008). After completing his residency at Kyoto University Hospital, he moved to the Max Delbrück Center for Molecular Medicine in Berlin, Germany. He obtained his PhD from Free University of Berlin (2014). He has been leading a laboratory at RIKEN since 2016 (Unit Leader at RIKEN Innovation Center since 2016, Team Leader at RIKEN Center for Integrative Medical Sciences since 2018, Group leader at IFOM in Milan since 2018). In 2020, he became a professor at the Kyoto University Institute for Advanced Study (KUIAS). He combines classical biochemistry, molecular biology, systems biology, informatics, primatology and medicine to study the human genome that makes us human as well as to elucidate the molecular mechanisms of human diseases. Through integrated analysis of (epi)genomic data with clinical information, he explores molecular therapeutic targets and biomarkers.

Achievements and highlights of past research activities

"What is encoded in the human genome" remains largely unknown. He has developed original high-throughput sequencing technologies, to study multi-layered regulatory mechanisms of the human genome (Cell 2014, Nature Communications 2015, Cell Reports 2017). More recently, he has succeeded in identifying non-coding enhancers which are the key cis-regulatory DNA elements that control spatiotemporal gene expression (Nature genetics 2019). For this, he developed an original "NET-CAGE" technology to globally determine 5'-ends of nascent RNAs, thereby sensitively detecting unstable transcripts including enhancer-derived RNAs. NET-CAGE enabled ultra-sensitive detection of a number of new enhancers and super-enhancers at single nucleotide resolution. He also successfully quantified real-time dynamics of promoter and enhancer activation (Nature Genetics 2019). He is applying the NET-CAGE technology to describe active cis-regulatory landscape across hundreds of diverse disease-relevant tissues and cell types, and discover differentially regulated enhancers, super-enhancers, genes and long non-coding RNAs. He is further developing a series of original technologies to investigate connectivity and functionality of cis-regulatory elements at both population and single-cell level.

Achievements

(1) International influence * Describe the kind of attributes listed below.

a) Recipient of international awards; N/A

b) Member of a scholarly academy in a major country; N/A

c) Guest speaker or chair of related international conference and/or director or honorary member of a major international academic society in the subject field; Guest speaker and session chair at the 1st International Symposium of CCII - Bioinformatics and its application to cancer and other diseases (25/01/2021)

d) Editor of an international academic journal; Editorial Board Member; NAR Cancer, Stem Cell Reviews and Reports

e) Peer reviewer for an overseas competitive research program (etc.) N/A

(2) Receipt of major large-scale competitive funds (over the past 5 years)

1. 2020 Takeda Science Foundation Research Grant (PI); 50,000,000 yen
2. 2020 KAKENHI Grant-in-Aid for Scientific Research (Fostering Joint International Research B) (PI); 18,720,000 yen
3. 2020 KAKENHI Grant-in-Aid for Scientific Research (A) (co-PI); 15,600,000 yen
4. 2020 AMED Grant (co-PI); 69,000,000 yen
5. 2019 AMED-CREST (co-PI); 58,500,000 yen
6. 2018 KAKENHI Grant-in-Aid for Scientific Research (A) (PI); 44,720,000 yen
7. 2018 AMED-CREST (co-PI); 13,000 yen
8. 2016 KAKENHI Grant-in-Aid for Young Scientists (A) (PI); 27,430 yen
9. 2016 Takeda Science Foundation Research Grant (PI); 10,000,000 yen

(3) Major publications (Titles of major publications, year of publication, journal name, number of citations)

1. NET-CAGE Characterizes Dynamics and Topology of Human Transcribed Cis-regulatory Elements. 2019 Nature Genetics, Citation 26
2. Hotspots of de novo point mutations in induced pluripotent stem cells. 2017 Cell Reports, Citation 34
3. Genomic stability of iPSCs: challenges towards their clinical applications. 2016 Stem Cell Reviews and Reports, Citation 157
4. Enhanced identification of transcriptinal enhancers provides mechanistic insights into diseases. 2016 Trends in Genetics, Citation 63
5. RC3H1 represses the IKK/NF-κB negative feedback regulator A20 by binding to a 3'UTR composite structure-sequence element. 2015 Nature Communications, Citation 78
6. Regnase-1 and Roquin Regulate a Common Element in Inflammatory mRNAs by Spatiotemporally Distinct Mechanisms. 2015 Cell, Citation 216
7. A variety of Dicer substrates in human and C.elegans. 2014 Cell, Citation 89
8. Roquin binding to stem-loop mRNAs induces protein dimerization and involves a winged helix-turn-helix motif. 2014 Nature Communications, Citation 34
9. The mRNA-bound proteome and its global occupancy profile on protein-coding transcripts. 2012 Molecular Cell, Citation 965
10. Inhibitors of the proteasome suppress homologous DNA recombination in mammalian cells. 2007 Cancer research, Citation 115
11. A critical role for the ubiquitin-conjugating enzyme Ubc13 in initiating homologous recombination. 2007 Molecular Cell, Citation 254

(4) Others (Other achievements indicative of the PI's qualification as a top-world researcher, if any.)

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)

Ryo Yamamoto (45)

Affiliation and position (Position title, department, organization, etc.)

Associate Professor, ASHBi

SunRise Fellow

Academic degree and specialty

MD. PhD (Medicine)

Stem cell biology, hematology

Effort 100 %

* Percentage of time that the principal investigator devote to working for the center vis-à-vis his/her total working hours.

Research and education history

March. 2015 – March.2020; Research associate, Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine

March. 2014 – Feb. 2015; Postdoctoral scholar, Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine

April. 2009 – Feb. 2014; Postdoctoral scholar, Institute for Medical Science, the University of Tokyo

April. 2005 – March. 2009; Kyoto University, Graduate School of Medicine, Kyoto
Ph.D., Medicine (Jan. 25th, 2010)

April. 1995 – March. 2001; Kyoto University, Faculty of Medicine, Kyoto
M.D.

Achievements and highlights of past research activities

Following my clinical training as a hematologist, I transitioned into biomedical research with the aim of developing improved patient treatments through understanding the biology of health and disease. I started my research career focusing on tumor immunology and lymphomagenesis, and was the first to report that the PD-1/PD-1 ligand pathway was a therapeutic target in Hodgkin lymphoma and anaplastic large cell lymphoma. This research directly contributed to the development of novel immunotherapy targeting the PD-1 pathway in cancer via immune checkpoint inhibitors. My interest in hematologic malignancy naturally led me to work on normal hematopoiesis.

Hematopoietic stem cells (HSCs) are essential to maintain lifelong homeostasis of the blood system. Although adult hematopoiesis has been well studied, there remain significant gaps in the literature. I am focused on resolving some of the unanswered questions regarding the

functionality of HSCs at the single cell level. While platelets and erythrocytes are the two most abundant and essential blood components, these lineages have largely been ignored in HSC research. To allow the progeny of HSCs to be monitored throughout the full spectrum of hematopoiesis, I developed a Kusabira-Orange (KuO) transgenic mouse line and combined this with single cell transplantation assays to evaluate of developmental potential of clonal HSCs. I also incorporated this technology with paired daughter cell (PDC) assays to understand the regulation of cell fate. With these technological advances, I discovered novel myeloid-restricted stem/progenitor cell types with long-term in vivo repopulating capacity (MySC/MyRP). This observation led to a re-evaluation of self-renewal, which was previously thought to be a characteristic unique to multipotent HSCs and not possessed by lineage-restricted progenitor cells. My findings strongly suggested that multipotency and self-renewal activity are dissociated (i.e. separable cellular characteristics). I also identified a novel HSC differentiation pathway (the Myeloid Bypass Pathway), thereby revising the traditional HSC-MPP pathway model of hematopoietic differentiation. I next applied these technologies to HSC aging, and identified significant increases in MyRP frequency with age (Fig. 1). These results implicate MyRPs as a major contributor to the HSC aging phenotype and a target for therapeutic intervention. I also identified a novel functional stem cell population exclusive to the aged HSC compartment, termed latent-HSCs. Latent-HSCs display only myeloid-restricted output in primary recipients for over six months, but following secondary transplantation display full multipotent (myeloid and lymphoid) output. A better understanding of the latent-HSC phenotype could help to develop therapeutic strategies to "rebalance" hematopoiesis in aged individuals. I have also investigated functional HSC differentiation-bias in five blood lineages by interrogating these large chimerism datasets using bioinformatics tools. From these studies, I have defined a new classification system for functional HSCs, including previously unreported HSC biases that suggest HSC differentiation is regulated by more complicated molecular mechanisms than those currently understood. Finally, to gain understanding of the molecular mechanisms of HSC heterogeneity and aging, I performed single cell RNA-sequencing using 1,500 young and aged HSCs (Yamamoto et al. In Preparation). I am now elucidating the genetic and epigenetic mechanisms underlying HSC aging. My overall scientific goal is to elucidate the biology and mechanisms of stem cell self-renewal, differentiation, and aging, using HSCs as a model system. By understanding these mechanisms, I aim to identify novel targets and therapeutic strategies for hematological disease treatment and tissue rejuvenation.

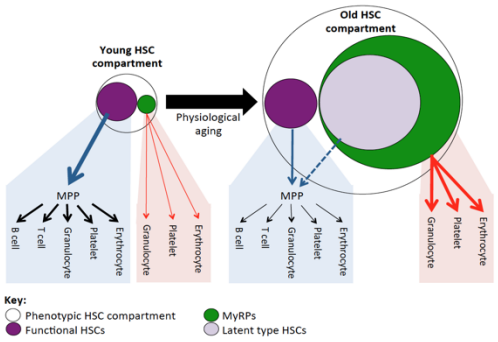


Figure 1: Schematic of model of aged HSCs. With age, the phenotypic HSC compartment expands but the function of the hematopoietic system gradually declines due to MySC/MyRP expansion. I have also identified a subset of MySC/MyRPs in old mice that can re-acquire lymphoid lineage output when transplanted into secondary recipients (termed latent-HSCs).

Achievements

(1) International influence * Describe the kind of attributes listed below.

a) Recipient of international awards; N/A

b) Member of a scholarly academy in a major country; N/A

c) Guest speaker or chair of related international conference and/or director or honorary member of a major international academic society in the subject field; N/A

d) Editor of an international academic journal; Editorial Board Member; N/A

e) Peer reviewer for an overseas competitive research program (etc.) N/A

(2) Receipt of major large-scale competitive funds (over the past 5 years)

Uehara (2021) 5,000,000 yen

SunRISE (2021-2026) 50,000,000 yen

AMED (2021-2023) 66,000,000 yen

(3) Major publications (Titles of major publications, year of publication, journal name, number of citations)

Wilkinson, A. C. *, R. Ishida*, M. Kikuchi, K. Sudo, M. Morita, R. V. Crisostomo, R. Yamamoto, K. M. Loh, Y. Nakamura, M. Watanabe, H. Nakauchi, and S. Yamazaki. "Long-term ex vivo expansion of hematopoietic stem cells affords non-conditioned transplantation."
Nature, 571 (2019): 117-121 (*Equal contribution) (number of citations; 88)

Yamamoto, R., A. C. Wilkinson, J. Ooehara, X. Lan, C. Y. Lai, Y. Nakauchi, J. K. Pritchard, and H. Nakauchi. "Large-Scale Clonal Analysis Resolves Aging of the Mouse Hematopoietic Stem Cell Compartment."
Cell Stem Cell, 22 (2018): 600-07 e4. (number of citations; 64)

R. Yamamoto*, Y. Morita*, J. Ooehara, S. Hamanaka, M. Onodera, K. L. Rudolph, H. Ema, and H. Nakauchi. Clonal Analysis Unveils Self-Renewing Lineage-Restricted Progenitors Generated Directly from Hematopoietic Stem Cells.
Cell, 154 (2013): 1112-26. (*Equal contribution) (number of citations; 545)

Yoshida, K*., M. Sanada*, Y. Shiraishi*, D. Nowak*, Y. Nagata*, R. Yamamoto, Y. Sato, A. Sato-Otsubo, A. Kon, M. Nagasaki, G. Chalkidis, Y. Suzuki, M. Shiosaka, R. Kawahata, T. Yamaguchi, M. Otsu, N. Obara, M. Sakata-Yanagimoto, K. Ishiyama, H. Mori, F. Nolte, W. K. Hofmann, S. Miyawaki, S. Sugano, C. Haferlach, H. P. Koeffler, L. Y. Shih, T. Haferlach, S. Chiba, H. Nakauchi, S. Miyano, and S. Ogawa. Frequent Pathway Mutations of Splicing Machinery in Myelodysplasia.
Nature, 478 (2011): 64-9. (*Equal contribution) (number of citations; 1779)

Yamamoto, R., M. Nishikori, T. Kitawaki, T. Sakai, M. Hishizawa, M. Tashima, T. Kondo, K. Ohmori, M. Kurata, T. Hayashi, and T. Uchiyama. "PD-1-PD-1 Ligand Interaction Contributes to Immunosuppressive Microenvironment of Hodgkin Lymphoma."
Blood 111(2008): 3220-4. (number of citations; 387)

(4) Others (Other achievements indicative of the PI's qualification as a top-world researcher, if any.)

Appendix 3-1 FY 2020 Records of Center Activities

1. Researchers and center staff, satellites, partner institutions

1-1. Number of researchers in the "core" established within the host institution

- Regarding the number of researchers at the Center, fill in the table in Appendix 3-1a.

Special mention

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.
- As background to how the Center is working on the global circulation of world's best brains, give good examples, if any, of how career paths are being established for the Center's researchers; that is, from which top-world research institutions do researchers come to the Center and to which research institutions do the Center's researchers go, and how long are their stays at those institutions.

Using the new tenured professor/associate professor position provided by Kyoto University, we started an international call to recruit one foreign PI in Oct 2020 and are currently in the selection process. This new foreign PI is scheduled to join ASHBi in FY2021.

1-2. Satellites and partner institutions

- List the satellite and partner institutions in the table below.
- Indicate newly added and deleted institutions in the "Notes" column.
- If satellite institutions have been established overseas, describe by satellite the Center's achievements in coauthored papers and researcher exchanges in Appendix 4.

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes
Shiga University of Medical Science	Mototsugu Ema Tomoyuki Tsukiyama	 Core Head, PRiME (Primate Genome Editing Core)

<Partner institutions>

Institution name	Principal Investigator(s), if any	Notes

<Clinical doctors in collaboration with ASHBi>

Institution name	Collaborating Researcher	ASHBi PIs
Kyoto University Hospital (KUHP)	Ryosuke Takahashi (Neurology) Toshiya Murai (Psychiatry) Shunsuke Akamatsu(Urology) Motoko Yanagita(Nephrology) Hajime Yoshifuji (Rheumatology) Akifumi Kondo-Takaori (Hematology and Oncology) Masaki Mandai (Gynecology and Obstetrics) Etsuro Hatano (Hepato-Biliary-Pancreatic Surgery and Transplantation) Koichi Omori (Otolaryngology, Head and Neck Surgery) Shuichi Matsuda (Orthopedic Surgery) Toyohiro Hirai (Respiratory Medicine)	Isa/Ueno Isa/Ueno Murakawa Murakawa Murakawa Ogawa/Murakawa Saitou/Ueno Ueno Ueno Ueno/Murakawa Ueno
The McLean Hospital, Harvard Medical School	Diego A. Pizzagalli (Psychiatry)	Amemori
Johns Hopkins University	Akira Sawa (Psychiatry)	Isa
Mayo Clinic	Michael Fautsch	Murakawa
Cleveland Clinic	Jaroslaw P. Maciejewski (Translational Hematology and Oncology Research)	Ogawa
Kalorinska University Hospital	Eva Hellstrom Lindberg (Hematology)	Ogawa
Munich Leukemia Laboratory (MLL)	Torsten Haferlach (Hematology)	Ogawa
University of Pavia	Mario Cazzola (Hematology)	Ogawa

UCSF	Robert Raffai (Surgery)	R Yamamoto
Shiga University of Medical Science	Yuji Ozeki (Psychiatry)	Amemori
Kobe City Eye Hospital	Masayo Takahashi (Ophthalmology)	Eiraku
National Institute of Sensory Organs, Tokyo Medical Center	Takeshi Iwata (Ophthalmology)	Murakawa
Osaka University Hospital	Koji Nishida (Ophthalmology)	Murakawa
RIKEN IMS	Chikashi Terao (Immunology)	Murakawa
Yokohama City University	Itaru Endo (Surgery)	Murakawa
Juntendo University	Yoshiyuki Suehara (Orthopedic Surgery)	Murakawa
University of Tsukuba	Shigeru Chiba (Hematology)	Ogawa
Showa University	Tsuyoshi Makamaki (Hematology)	Ogawa
Nagasaki University	Yasushi Miyazaki (Hematology)	Ogawa
Tokai University	Makoto Onizuka (Hematology and Oncology)	Ogawa
Jichi Medical University	Yoshinobu Kanda (Hematology)	Ogawa
Gifu University	Hisashi Tsurumi (Hematology)	Ogawa
Gifu Municipal Hospital	Senji Kasahara (Hematology)	Ogawa
Chugoku Central Hospital	Toru Kiguchi (Hematology)	Ogawa
University of Tokyo	Katsuhito Fujii (Cardiovascular Medicine)	R Yamamoto
Akita University	Tomonori Habuchi (Urology)	Yanagita
Toranomon Hospital	Yoshifumi Ubara (Rheumatology)	Yanagita

2. Holding international research meetings

- Indicate the number of international research conferences or symposiums held in FY2020 and give up to three examples of the most representative ones using the table below.

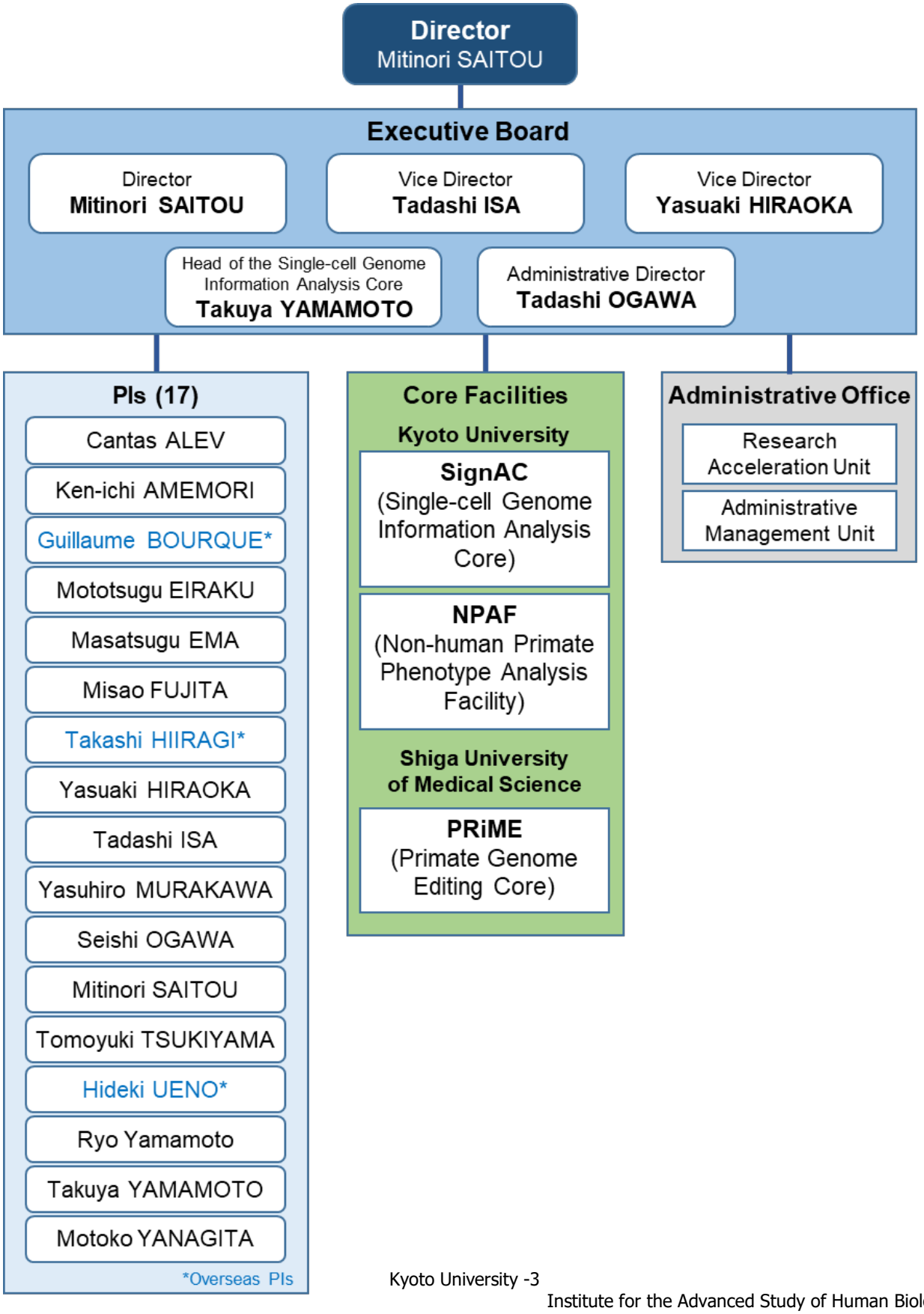
FY 2020: 0 meetings*

Major examples (meeting titles and places held)	Number of participants
POSTPONED to 10-16 Sep 2021 **JANUBET* Primate Neurobiology School** Originally scheduled on 24-30 Sep 2020 at Kyoto University Organizers: Tadashi Isa(ASHBi), XXXX (Norway) **JANUBET: Japan and Norway United in Brain, Educations and Therapeutics supported by INTPART, Norway*	Invited Speakers From domestic institutions: 12 From overseas institutions: 7
POSTPONED to 26-28 Apr 2022 **EMBO Workshop (co-organized by ASHBi)** **"Molecular mechanisms of developmental and regenerative biology"** Originally scheduled on 9-11 Nov 2020 at Kyoto University Organizers: Saitou (ASHBi), XXX	Invited Speakers From domestic institutions: 5 From overseas institutions: 19
POSTPONED to 13-17 Mar 2022 **International Symposium on Development and Plasticity of Neural Systems (co-organized by ASHBi)** Originally scheduled on 8-11 Mar 2021 at Kyoto University Organizers: Isa, Eiraku (ASHBi), Kageyama (InFRONT, KU)	Invited Speakers From domestic institutions: 22 From overseas institutions: 18

**All scheduled meetings have been postponed due to COVID-19 pandemic*

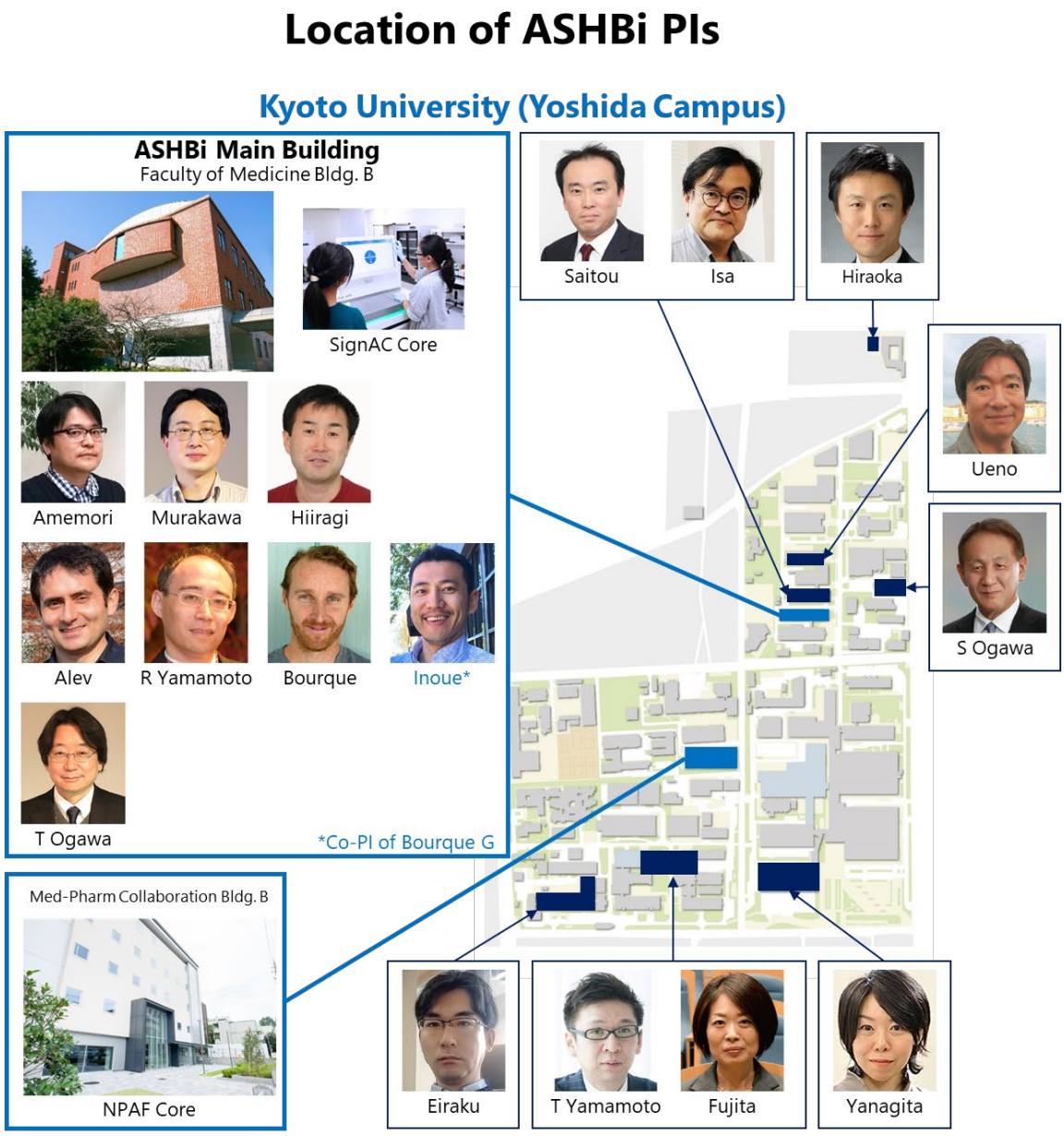
3. Diagram of management system

- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any new changes have been made in the management system from that in the latest "center project" last year, describe them. Especially describe any important changes made in such as the center director, administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research).



4. Campus Map

- Draw a simple map of the campus showing where the main office and principal investigator(s) are located.



5. Securing external research funding*

External research funding secured in FY2020

Total: **995,030,974** yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.
* External research funding includes "KAKENHI," funding for "commissioned research projects," "joint research projects," and for others (donations, etc.) as listed under "Research projects" in Appendix 3-2, Project Expenditures.

[Breakdown according to type of funding]

Type of Funding	Funding Amount (Proportionally distributed)
Grants-in-Aid for Scientific Research (KAKENHI)	273,510,297 yen
Commissioned Research Projects	542,604,209 yen
Joint Research Projects	103,496,421 yen
Others (Donation funds, etc)	75,420,047 yen
Total* (total for above mentioned)	**995,030,974 yen**

[Acquired large-scale research grants (30,000,000+ yen in secured amount)]

Organization	Fund name	PI	Funding amount (Secured amount)
AMED	AMED-CREST	Seishi Ogawa	89,798,800 yen
JSPS	KAKENHI Grant-in-Aid for Specially Promoted Research	Mitinori Saitou	89,600,000 yen
AMED	AMED-CREST	Hideki Ueno	63,327,000 yen
AMED	Project for Cancer Research and Therapeutic Evolution (P-CREATE)	Seishi Ogawa	58,477,731 yen
MHLW	The prospective trial of patient-proposed healthcare services with multiple targeted agent based on the result of gene profiling by multigene panel test. (BELIEVE)	Seishi Ogawa	50,000,000 yen
AMED	Practical Research for Innovative Cancer Control	Seishi Ogawa	46,500,000 yen
Pythias Fund	Pythias Fund	Mitinori Saitou	45,695,619 yen
JSPS	KAKENHI Grant-in-Aid for Scientific Research(S)	Seishi Ogawa	30,200,000 yen

Appendix 3-1a FY 2020 Records of Center Activities

Researchers and other center staff

Number of researchers and other center staff

* Fill in the number of researchers and other center staff in the table blow.
* Describe the final goals for achieving these numbers and dates when they will be achieved described in the last "center project."

a) Principal Investigators

(full professors, associate professors or other researchers of comparable standing)

(number of persons)

	At the beginning of project	At the end of FY 2020	Final goal (Date: March, 2022)
Researchers from within the host institution	8	12	12
Researchers invited from overseas	4	3	4
Researchers invited from other Japanese institutions	1	2	2
Total principal investigators	13	17	18

b) Total members

	At the beginning of project		At the end of FY 2020		Final goal (Date: March, 2022)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	13		40		56	
Overseas researchers	4	31	7 Ratio as of April,2021 ※1	18 **24**	18	32
Female researchers	3	23	5 Ratio as of April,2021 ※2	13 **22**	17	30
Principal investigators	13		17		18	
Overseas PIs	4	31	3	18	4	22
Female PIs	3	23	2	12	3	17
Other researchers	0		15		22	
Overseas researchers	0		2	13	5	23
Female researchers	0		2	13	8	36
Postdocs	0		8		16	
Overseas postdocs	0		2	25	9	56
Female postdocs	0		1	13	6	38
Research support staffs	2		23		25	
Administrative staffs	3		14		14	
Total number of people who form the "core" of the research center	18		77		95	

※1) 24%…**12**(Overseas researchers) / **50**(Total researchers) as of April ,2021

※2) 22%…**11**(Female researchers) / **50**(Total Researchers) as of April ,2021

Appendix 3-2　Project Expenditures

1) Overall project funding

* In the "Total costs" column, enter the total amount of funding required to implement the project, without dividing it into funding sources.
* In the "Amount covered by WPI funding" column, enter the amount covered by WPI within the total amount.
* In the "Personnel," "Project activities," "Travel," and "Equipment" blocks, the items of the "Details" column may be changed to coincide with the project's actual content.

(Million yens)

Cost items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total costs	Amount covered by WPI funding
Personnel	Center director and administrative director	29	4
	Principal investigators (no. of persons):14	129	46
	Other researchers (no. of persons):26	130	118
	Research support staff (no. of persons):16	43	43
	Administrative staff (no. of persons):30	88	42
	Subtotal	419	253
Project activities	Research startup cost	89	62
	Cost of Young Researcher Foster programs	15	12
	Cost of satellite organizations (no. of satellite organizations):1	78	78
	Cost of international symposiums (no. of symposiums):1	1	1
	Rental fees for facilities	24	24
	Cost of utilities	5	3
	Cost of operating of Core Facility	10	10
	Cost of maintenance of Core Facility	33	33
	Cost of maintenance contracts	19	14
	Cost of outreach activities	3	2
	Cost of communication, copy machine rental and maintenance fee	1	0
	Cost of consumables, small equipments	53	25
	Subtotal	331	264
Travel	Domestic travel costs	0	0
	Overseas travel costs	1	0
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):0	0	0
	Travel cost for scientists on transfer (no. of domestic scientists):1 (no. of overseas scientists):2	2	2
	Subtotal	3	2
Equipment	Cost of laboratory maintenance (repair work, etc.)	89	89
	Cost of research equipments in SignAC and open laboratory equipments maintenance	136	92
	Subtotal	225	181
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1	12	
	KAKENHI	274	
	Commissioned research projects, etc.	543	
	Joint research projects	103	
	Others (donations, etc.)	75	
	Subtotal	1,007	0
Total		1,985	700

Costs (Million yens)

WPI grant in FY 2020	700
Costs of establishing and maintaining facilities	58
Repairing facilities	56
(Number of facilities: 1 , about 2,010 m²)	
Others	2
Costs of equipment procured	123
Microscope (1)	68
Freezers (2)	3
Others	52

*1. Management Expenses Grants (including Management Enhancements Promotion Expenses (機能強化経費)), subsidies including National university reform reinforcement promotion subsidy (国立大学改革強化推進補助金) etc., indirect funding, and allocations from the university's own resources.
*2 When personnel, travel, equipment (etc.) expenses are covered by KAKENHI or under commissioned research projects or joint research projects, the amounts should be entered in the "Research projects" block.

*1 運営費交付金（機能強化経費を含む）、国立大学改革強化推進補助金等の補助金、間接経費、その他大学独自の取組による学内リソースの配分等による財源
*2 科研費、受託研究費、共同研究費等によって人件費、旅費、設備備品等費を支出している場合も、その額は「研究プロジェクト費」として計上すること

2) Costs of satellites

(Million yens)

Cost items	Details	Total costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):2		
	Other researchers (no. of persons):2		
	Research support staff (no. of persons):1		
	Administrative staff (no. of persons):0		
	Subtotal	36	26
Project activities	Subtotal	29	29
Travel	Subtotal	0	0
Equipment	Subtotal	23	23
Research projects	Subtotal	37	0
Total		125	78

Appendix 4 FY 2020 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2020 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2021 and not described in Appendix 1.

Overseas Satellite 1 **Name** (Total: 0 papers)

1)
2)
3)
4)

Overseas Satellite 2 **Name** (Total: 0 papers)

1)
2)
3)
4)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2019. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

Overseas Satellite 1:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2020					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2020					

Overseas Satellite 2:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2020					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2020					

Appendix 5　FY 2020 Visit Records of Researchers from Abroad

* If researchers have visited/ stayed at the Center, provide information on them in the below table.
* Enter the host institution name and the center name in the footer.

Total: 2

	Name	Age	Affiliation		Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
			Position title, department, organization	Country				
1	Shahragim Tajbakhsh	50's	Professor, Institute Pasteur	France	PhD, Developmental Biology	He is a world-leading scientist in the field of comparative skeletal muscle development and muscle biology (embryonic/adult).	several days during March & April 2020	scientific discussions; preperations for future collaborative research
2	Takafumi Ichikawa	34	Postdoc, EMBL	Germany	PhD, Biology	He is a postdoc at EMBL who has a spcial knowledge with the InVi-SPIM which has been installed at ASHBi.	2 days, 06.01.2021, 20.02.2021	Set up InVi-SPIM (microscope), Participation in ASHBi retreat 2020
3	Bernard de Massy	62	Research Director, Univ Montpellier	France	PhD Molecular Biology	Research Director and Head of Meiosis and recombination research team, Institut de Genetique Humaine, CNRS 2016 Coups d'Élan Awards for French Research, Bettencourt Schueller Foundation 2012 médaille d'argent du CNRS	Nov. 6-27, 2020	short-term stay for joint research. Canceled due to COVID19
4								
5								
6								
7								
8								
9								
10								

Appendix 6 FY2020 State of Outreach Activities

* Fill in the numbers of activities and times held during FY2020 by each activity.
* Describe the outreach activities in the "6. Others" of Progress Report, including those stated below that warrant special mention.

Activities	FY2020 (number of activities, times held)
Website	ASHBi website development (research news pages, member pages etc.)
SNS	Twitter (16 Dec 2020 open, 266 followers, 47 posts) YouTube (14 Feb 2021 open, 2 videos, 297 views) Facebook (26 Feb 2021 open, 82 followers, 25 posts)
Multimedia	ASHBi introduction video ASHBi introduction video by the director for secondary and high school students
PR brochure, pamphlet	**[Brochure]** WPI brochure vol 16 KUIAS Brochure 2020 **[Flyers]** 9 ASHBi Colloquium flyers 12 ASHBi Seminar flyers 5 ASHBi Bioethics-Biology Fusion Seminar flyers 1 ASHBi Fusion Research Grant Workshop flyer 1 ASHBi Mathematical Biology Workshop flyer 1 ASHBi/CiRA Bioethics Lecture flyer 1 ASHBi SignAC workshop flyer 1 Primate Developmental Biology Seminar flyer 1 ASHBi Research Tips Seminar (BioRender) flyer 1 KAKENHI Writing Seminar flyer
Lectures, seminars for general public	16 Feb 2021 7th Kyoto University-Inamori Foundation Joint Kyoto Prize Symposium (online)
Participating, exhibiting in events	7 Feb 2021 9th WPI Science Symposium (online) 26 Dec 2020 WPI Science Symposium for high school students (online) 18 May WPI Fundraising Seminar (online)
Press releases	**[12 press releases for ASHBi research papers]** 23 Mar 2021 K. S. Kim, S. Iwami, et al., "A quantitative model used to compare within-host SARS-CoV-2, MERS-CoV and SARS-CoV dynamics provides insights into the pathogenesis and treatment of SARS-CoV-2," *PLoS Biology* 24 Dec 2020 K. Shimada, S. Ogawa, et.al., "Frequent Genetic Alterations in Immune Checkpoint-Related Genes in Intravascular Large B-Cell Lymphoma," *Blood* 13 Oct 2020 S. Yamamoto, M. Yanagita, et al., "Spatiotemporal ATP dynamics during acute kidney injury predicts renal prognosis," *Journal of American Society of Nephrology* 25 Sep 2020 H. N. Schwerdt, K. Amemori, et al., "Dopamine and beta-band oscillations differentially link to striatal value and motor control," *Science Advances* 18 Sep 2020 M. Matsuda, C. Alev, et al., "Species-specific segmentation clock periods are due to differential biochemical reaction speeds," *Science* 3 Sep 2020 K. Kishimoto, C. Alev, et al., "Bidirectional Wnt signaling between endoderm and mesoderm confers tracheal identity in mouse and human cells", *Nature Communications* 20 Aug 2020 T. Sawai, M. Fujita, et al., "The moral status of human embryo-like structures: Potentiality matters?" *EMBO Reports* 11 Aug 2020 P. Vancraeyenest, T. Isa, et al., "Selective mesoaccumbal pathway inactivation affects motivation but not reinforcement-based learning in macaques," *NEURON* 31 Jul 2020 S. Iwanami, S. Iwami, et al., "Should a viral genome stay in the host cell or leave? A quantitative dynamics study of how hepatitis C virus deals with this dilemma," *PLoS Biology*

	24 Jun 2020 M. Yagi, T. Yamamoto, et al., "Identification of distinct loci for de novo DNA methylation by DNMT3A and DNMT3B during mammalian development," *Nature Communications* 28 May 2020 Y. Sato, M. Yanagita, et al., "Developmental stages of tertiary lymphoid tissue reflect local injury and inflammation in murine and human kidneys," *Kidney International* 2 Apr 2020 Y. Yamanaka, C. Alev, et al., "Recapitulating the Human Segmentation Clock with Pluripotent Stem Cells," *Nature* * Underlines indicate ASHBi researchers. **[1 press release for prize]** 2 Nov 2020 M. Yanagita wins Baelz Prize
Others (Major Visits to ASHBi)	28 Aug 2020 MEXT State Minister visits ASHBi

*If there are any rows on activities the center didn't implement, delete that (those) row(s). If you have any activities other than the items stated above, fill in the space between parentheses after "Others" on the bottom with the name of those activities and state the numbers of activities and times held in the space on the right. A row of "Others" can be added, if needed.

Outreach Activities and Their Results

List up to three of the Center's outreach activities carried out in FY 2020 that have contributed to enhancing the brand or recognition of your Center and/or the brand of the overall WPI program, and describe its concrete contents and effect in narrative style. (Where possible, indicate the results in concrete numbers.)

Examples:
- As a result of using a new OO press-release method, a OO% increase in media coverage was obtained over the previous year.
- By holding seminars for the public that include people from industry, requests for joint research were received from companies.
- We changed our public relations media. As a resulting of using OO to disseminate information, a OO% increase in inquiries from researchers was obtained over the previous year.
- As a result of vigorously carrying out OO outreach activity, ¥OO in external funding was acquired.

1. Publishing English introductory articles for ASHBi research papers on website

Twelve introductory articles have been prepared and published for research papers already published on the ASHBi website (see list below). These articles were prepared in accordance with the international standard format of press release in order to ensure that the content of our research papers could be disseminated effectively abroad, whereas the previous web pages for research papers only contained the bibliographic information on the papers.

List of 12 newly published introductory articles

Research Group	Title of Introductory Article	Title of Research Paper	Journal
Saitou G	Master regulators for human germ cell specification	GATA transcription factors, SOX17 and TFAP2C, drive the human germ-cell specification program	Life Science Alliance (LSA)
Ogawa G	Kyoto medical researchers find new liquid marker for a type of lymphoma	Frequent Genetic Alterations in Immune Checkpoint-Related Genes in IntravascularLarge B-Cell Lymphoma	Blood
Yanagita G	Kyoto scientists zoom in on kidney damage	Spatiotemporal ATP dynamics during acute kidney injury predicts renal prognosis	Journal of the American Society of Nephrology
Bourque G	Reading between the lines of the human genome	A systematic evaluation of the design and context dependencies of massively parallel reporter assays	Nature Methods
Amemori G	Probing the deep mysteries of Parkinson's disease	Dopamine and beta-band oscillations differentially link to striatal value	Science Advances

		and motor control	
Saitou G	Hunting for perfect egg recipe	Long-term expansion with germline potential of human primordial germ cell-like cells in vitro	EMBO Journal
Fujita G	ASHBi presents a new framework to guide policies on human gene editing	Ethical Framework for Next-Generation Genome and Epigenome Editing	American Journal of Bioethics
Isa G	Is the reward always worth the effort?	Selective Mesoaccumbal Pathway Inactivation Affects Motivation but Not Reinforcement-Based Learning in Macaques	Neuron
Yanagita G	New method for mapping kidney disease and drug discovery	Developmental stages of tertiary lymphoid tissue reflect local injury and inflammation in murine and human kidneys	Kidney International
Saitou G	Cracking the code of egg production	ZGLP1 is a determinant for the oogenic fate in mice	Science
Ogawa G	Cancer snubs mutant crypts in inflammatory bowel disease	Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis	Nature
Tsukiyama G	New animal model boosts kidney research	Monkeys mutant for PKD1 recapitulate human autosomal dominant polycystic kidney disease	Nature Communications

* Arranged in descending order by publication date.

2. Establishing and Managing Twitter, Facebook and YouTube accounts for Active outreach

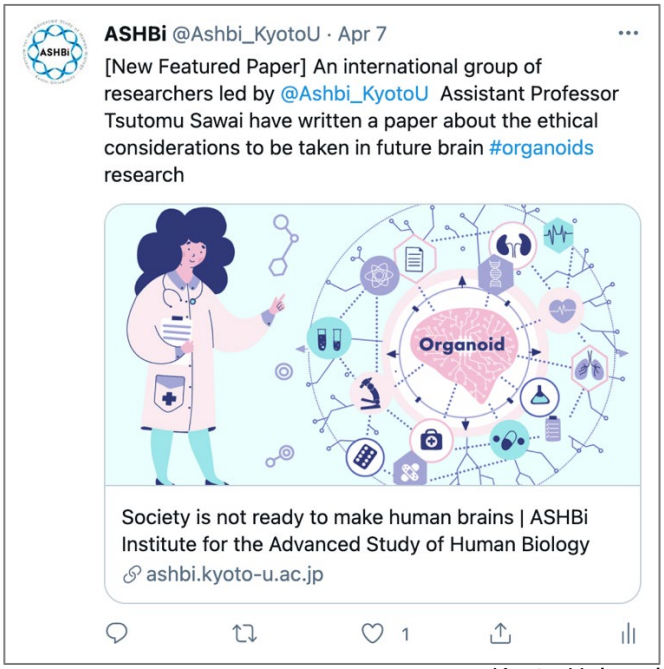
We opened Twitter account, Facebook page and YouTube channel in the second half of FY2020. The number of followers and posts is as below.

SNS activities

SNS	Opening Date	Number of Follower	Number of Posts	Number of Reactions
Twitter	16 Dec 2020	266	47	59,884 impressions
Facebook	26 February 2021	82	25	2,033 reaches
Youtube	14 February 2021	9	2	297 views

* The numbers are as at March 31, 2021.
* On Twitter, "impression" is the number of times a post has been shown to followers.
* On Facebook, "reach" is the number of times a post has been shown to followers.

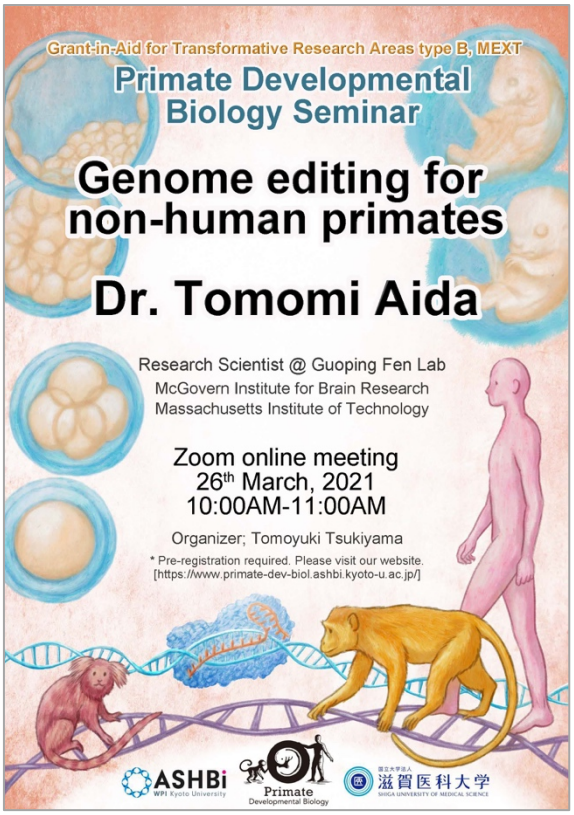
Examples of posts on Twitter

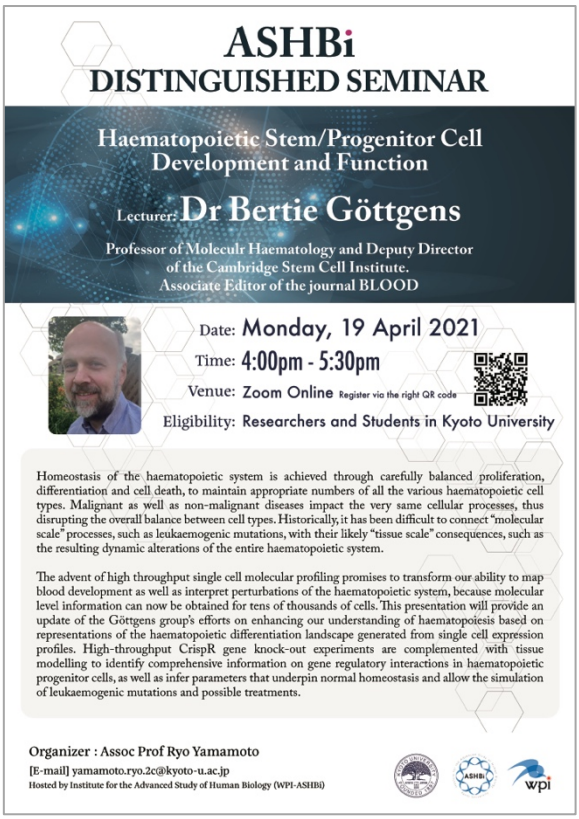


3. Creating flyers to attract the target audience

We have actively promoted the creation of flyers for seminars and workshops organized by ASHBi in collaboration with professional designers in order to attract researchers and other target audiences.

Examples of flyers





Appendix 7 FY 2020 List of Project's Media Coverage

* List and describe media coverage (e.g., articles published, programs aired) in FY2019.

* Enter the host institution name and the center name in the footer.

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
1	02 Apr 2020	newspaper 2, news website 6	[Nikkan Kogyo Shimbun Apr.2, NIKKEI Apr. 6, Science Codex Apr.2, ScienceDaily Apr.2, National Tribune Apr.2, Technology Networks Apr.2, Phys.org Apr.2, 生物帮生命科学网 Apr.2] - Introduction of the research result published in *Nature* by Alev Group
2	06 Apr 2020	news website 44	[JIJI.COM・The Mainichi Newspapers・NIKKEI・Tokyo Shimbun・The Nishinippon Shimbun・The Hokkaido Shimbun Press・The Niigata Nippo・The Tokushima Shimbun・Chiba Nippo・YAHOO Japan・The Asahi Shimbun・Akita Sakigake Shimpo・msn news・The Sanyo Shimbun・The Fukushima Minyu Sshimbun・The Shizuoka Shimbun・Jomo Shimbun・goo news・So-net news・The Kitanippon Sshimbun・Oita Godo News・KYODO・Daily Sports・Rakuten Infoseek News・The Daily Tohoku Shimbun・Kobe Shimbun NEXT・ORICON NEWS・The Ryukyu Shimpo・livedoor NEWS・NEWS CAFE・dmenu news・Ibaraki news・The Chunichi Shimbun・mixi news・nifty news・Nara newspaper・BIGLOBE news・The Yamanashi Nichinichi Shimbun・NEWS collect・JORUDAN SOCRA NEWS・modelpress・Nagasaki Shimbunsha・Ameba news・47NEWS] - Introduction of The Imperial Prize and The Japan Academy Prize for Prof. Saitou
3	20 May 2020	newspaper 2	[Nikkan Kogyo Shimbun May.29, Kyoto Shimbun Jun.3] - Introduction of the research result published in *Kidney International* by Yanagita Group
4	01 Jun 2020	news website 2	[Scienmag Jun.1, 7th Space Jun.2] - Introduction of ISSCR Momentum Award Lecture by Porf. Saitou
5	13 Oct 2020	newspaper 1	[Nikkan Kogyo Shimbun Nov.23] - Introduction of the research result published in *Journal of the American Society of Nephrology* by Yanagita Group
6	20 Jan 2021	news website 1	[Business Insider Japan Jan.20] - Interview article with Mitinori Saitou
7	21 Mar 2021	television 1, newspaper 2	[Asahi Shimbun Mar. 18, NHK Mar.21] - Comments for the research papers on Nature about iPS cell by Prof. Saitou. [Yomiuri Shimbun Mar.21] Comment for same papers by Assist. Prof. Sawai
8			
9			
10			