World Premier International Research Center Initiative (WPI)
FY 2019 WPI Project Progress Report

Host Institution	Kyoto University	Host Institution Head	YAMAGIWA Juichi
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 2020) 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 the State of WPI Center Project Progress (write within **2 pages**)

We have been making endeavors to firmly establish the Institute for the Advanced Study of Human Biology (ASHBi) as one of the WPI Centers since its launch in October 2018. Over FY2019, we held an executive board meeting every two weeks and a PI meeting every month to accelerate the establishment of the Institute. We have organized an ASHBi colloquium every month from June 2019, in addition to periodic ASHBi seminars (20 seminars in FY2019) and an ASHBi Retreat (February 2020) to strengthen interactions and create collaborations among the ASHBi PIs.

A major renovation of the main building for ASHBi (Building B of the Faculty of Medicine Campus) has been completed, creating a total space of 1700 m^2 for the Single-Cell Genome Information Analysis Core (SignAC), interaction (lounge)/seminar rooms, administrative office (ground floor), and experimental areas/offices for overseas/new PIs (1st and 2nd floors). These sections of the building have progressively begun operation: SignAC from June 2019 and the other areas from October 2019. Moreover, we secured an additional space of 210 m^2 on the ground floor to accommodate the offices for the ASHBi director and the Administrative Director as well as for the Mathematical Science Group and the Bioethics and Philosophy Group, and of 100 m^2 on the basement floor for a conference hall, and these areas are scheduled to open by August 2020. Collectively, the space of the ASHBi main building will expand to 2010 m^2. We have also been expanding the space for maintaining cynomolgus monkeys at the Primate Genome Engineering Core (PRiME) of the Shiga University of Medical Science (a domestic satellite of ASHBi) (additional 125 m^2, 64 cages) in order to secure appropriate spaces for generating genome-engineered monkeys and retrieving oocytes/embryos for ASHBi research. Correspondingly, we have created a space for analyzing the phenotypes of genome-engineered monkeys at the Non-human Primate Phenotype Analysis Facility (NPAF) in the Med-Pharm Building of Kyoto University (360 m^2, 20 cages).

Over FY2019, the SignAC has run 167 next-generation sequences (NGSs) and provided other essential supports for ASHBi research, and the PRiME, with ethical approval, has been generating *NPHP1* (with **Yanagita**) and *DISC1* (with **Isa**) knockout monkeys and provided embryological materials essential for the ASHBi research (see **Realizing an International Research Environment: Setting up the ASHBi Main Building**).

The key papers by ASHBi PIs in 2019 include "Monkeys mutant for PKD1 recapitulate human autosomal dominant polycystic kidney disease: ***Nature Communications***" (**Ema** and **Tsukiyama**), "Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis: ***Nature***" (**Ogawa**) "Dissecting the circuit for blindsight to reveal the critical role of pulvinar and superior colliculus: ***Nature Communications***" (**Isa**), "The Ethics of Cerebral Organoid Research: Being Conscious of Consciousness: ***Stem Cell Reports***" (**Fujita**), "Self-organized formation of developing appendages from murine pluripotent stem cells: ***Nature Communications***" (**Eiraku**), and "Hydraulic control of mammalian embryo size and cell fate: ***Nature***" (**Hiiragi group**) (see **Advancing Research**

of the Highest Global Level).

The Mathematical Science Group (PI: **Hiraoka**) and the Bioethics and Philosophy Group (PI: **Fujita**) have actively performed interdisciplinary researches with scientists in the Life Science Groups. The key collaborations of **Hiraoka** include: 1) noise reduction for single-cell RNA-sequence data (with **Saitou** and **Yamamoto**), 2) topological data analysis (TDA) for cell-fate specification (with **Saitou**, **Yamamoto**, and **Ueno**), 3) inference of gene regulatory networks (GRNs) by causal discovery (with **Saitou** and others), and 4) inference and prediction of dynamic epigenetic regulations (with **Saitou**), among others. **Hiraoka** has periodically organized "Math-Biology Seminars", including TDA seminars, GRN seminars, Hi-C seminars, and AI seminars, as well as the 1st ASHBi Mathematical Biology Workshop (August 2019).

The key collaborations of **Fujita** include: 1) ethics of synthetic embryology (with **Alev** and others), 2) ethics of cerebral organoid research (with **Isa** and others), 3) ethics of epigenome editing in germ cells (with **Yamamoto** and others), and 4) ethics of research involving aborted human fetuses (with **Saitou** and others). **Fujita** has organized a number of "Bioethics/Philosophy Seminars", creating ample opportunities for biologists and medical scientists to contemplate the impacts of their research on bioethics/philosophy/society (see **Generating Fused Disciplines**).

The three overseas PIs (**Ueno**, **Hiiragi**, and **Bourque**) frequently visited ASHBi (5–7 times/year), set up their research environment, including the appointment of co-PIs (**Yoshitomi co-PI** with **Ueno**, **Inoue co-PI** with **Bourque**), and initiated their work at ASHBi. **Cantas Alev** was appointed as a new PI and started his studies at ASHBi. English has been smoothly implemented as the official language at all the meetings, seminars, workshops, retreats and administrative announcements within ASHBi. To raise the level of the international recognition of ASHBi, we organized/have been organizing a number of international meetings, including **the ASHBi Symposium 2020 on "Human Development, Genetics, and Evolution"** (Kyoto, March 2020: under rescheduling due to the COVID19 outbreak), **the EMBO workshop on "Molecular Mechanisms of Developmental and Regenerative Biology"** (Kyoto, November 2020), **the 21st Takeda Science Foundation Symposium on Bioscience called "Towards Understanding Human Development and Evolution"** (Osaka, January 2021), and **the ASHBi Symposium 2021 on "Development and Plasticity of Neural Systems"** (Kyoto, March 2021). 47 overseas researchers have visited ASHBi for seminars/discussions in ASHBi during FY2019.

To further reinforce the research at ASHBi, we have appointed six new members as PIs/co-PIs at ASHBi: **Cantas Alev** (PI: Human Development: July 2019), **Ryo Yamamoto** (PI: Hematopoietic Stem Cells: April 2020), **Hiroyuki Yoshitomi** (co-PI with **Ueno**: Human Immunology: November 2019), **Fumitaka Inoue** (co-PI with **Bourque**: Enhancer Evolution: July 2020), **Ken-ichi Amemori** (PI: Primate Evolutionary Neurobiology: September 2020), and **Yasuhiro Murakawa** (Professor at KUIAS, PI: Human Genome: September 2020). In addition, we have appointed **Tomoyuki Tsukiyama** as a PI responsible for PRiME and **Taro Tsujimura** as a lecturer in charge of SignAC (see **Realizing an International Research Environment**). We have secured one tenure professorship position for ASHBi and are currently carefully investigating potential candidates for this position (see **Realizing an International Research Environment**).

Kyoto University (KU) has made a number of reformations on the budget use. First, KU has implemented a multi-year budgeting system for indirect funds so that up to 40 million JPY can be carried over to the next FY. Accordingly, ASHBi has carried over 40 million JPY to FY2020 to establish a custom-made/high-performance microscope system. Second, KU has established a flexible system for personnel funding so that tenure PIs can use a part of their grants as a source for their salary (the total salary for the PIs was unchanged) and the substituted amounts (from multiple PIs) can be used for securing the junior-faculty positions. In the future, this system can be extended to provide incentives for tenure PIs with distinctive accomplishments. Further, the KU Institute for Advanced Study (KUIAS) and KU provided two tenure professorship positions to ASHBi as a first step for the sustainable development of ASHBi. Finally, ASHBi has begun a number of collaborations/co-operations with the Institute for Cell-Material Science (iCeMS), another WPI Center at KU, to promote mutual development (see **Making Organizational Reforms**, **Efforts to Secure the Center's Future Development over the Mid- to Long-term**, and **others**).

* 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 fusing disciplines).
  (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 2019.
* 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.

We here describe key research achievements of the ASHBi PIs during 2019 (1.1.2019-12.31.2019).

The **group of Ema** and **Tsukiyama** published a manuscript entitled "Monkeys mutant for PKD1 recapitulate human autosomal dominant polycystic kidney disease" (*Nature Communications*, **10**, 5517, 2019).

Autosomal dominant polycystic kidney diseases (ADPKD) caused by *PKD1* mutations are one of the most common hereditary disorders (6,000,000 patients worldwide). However, no definitive therapies are currently available, although many treatments have been proposed for ADPKD based on studies using animal disease models and tissue culture models. To date, the key pathological processes underlying cyst development and exacerbation in pre-symptomatic stages remain unknown, because rodent models do not recapitulate critical disease phenotypes, including disease onset in heterozygotes. It is reasonable to assume that physiological and genetic differences would explain why medications for ADPKD yield different responses between mice and humans. To overcome these limitations, we aimed to create a novel ADPKD model animal in a species closely related to humans, the cynomolgus monkey. As in humans and mice, near-complete *PKD1* depletions induced severe cyst formation mainly in the collecting ducts. Importantly, unlike in mice, *PKD1* heterozygous monkeys exhibited cyst formation perinatally in distal tubules, possibly reflecting the initial pathology in humans. Thus, our results suggest that the distal tubules may be a novel drug target in pediatric patients for whom there is currently no clinical intervention. Many monkeys in these models survived after cyst formation, and their cysts progressed with age, indicating the usefulness of the models for preclinical studies. In addition, we succeeded in generating selective heterozygous mutations using allele-specific targeting and in generating embryos with a floxed allele by gene knock-in technology. We propose that our models elucidate the onset and progression of ADPKD, which will serve as a critical basis for establishing new therapeutic strategies.

The **Ogawa group** published a manuscript entitled "Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis" (*Nature*, **577**, 260-265, 2020 (published online: 18 December 2019)).

It has recently been demonstrated that extensive tissue remodeling takes place even in apparently normal tissues in an age-dependent manner and is mediated by expansion of numerous clones carrying common cancer-related mutations. Chronic inflammation is a major cause of morbidity and mortality in the human population and explains a substantial cancer risk therein. Given the association between inflammation and cancer risk, clonal expansion of somatically mutated clones may also play a role in inflammation-associated tissue remodeling. Chronic inflammation is accompanied by recurring cycles of tissue destruction and repair, and these cycles could help explain the cancer risk posed by inflammation. However, it is poorly understood how such cycles affect the clonal composition of tissues, particularly in terms of cancer development. We showed that in patients with ulcerative colitis (UC), a common form of inflammatory bowel disease (IBD), the inflamed intestine undergoes widespread remodeling by pervasive clones positively selected by acquiring mutations commonly involving *NFKBIZ*, *TRAF3IP2*, *ZC3H12A*, *PIGR*, and *HNRNPF*, many of which are implicated in downregulation of IL-17 and other pro-inflammatory signaling pathways. The substantially different mutation profiles between UC-epithelia and cancer indicate that the two conditions have different mechanisms of positive selection. Specifically, the *NFKBIZ* mutations highly prevalent in UC epithelia were rarely found in either sporadic or colitis-associated cancer, suggesting that negative selection of NFKBIZ-mutated cells occurs during colorectal carcinogenesis, which was further supported by the significantly attenuated colitis-induced tumor formation in

Nfkbiz-deficient mice and compromised cell-competition of *NFKBIZ*-disrupted colorectal cancer cells. Our results highlight the common and discrete mechanisms of clonal selection in inflammatory tissues, which unexpectedly reveal cancer vulnerabilities that could potentially be utilized for therapeutics of colorectal cancer.

The **Isa group** published a manuscript entitled "Dissecting the circuit for blindsight to reveal the critical role of pulvinar and superior colliculus" (*Nature Communications*, **10**, 135, 2019).

Patients with damage to the primary visual cortex (V1) lose visual awareness of objects presented in the blind visual field; however, it is known that some of them can make goal-directed hand and eye movements when forced to do so. Dissociation between the visual awareness and the capacity for visuo-motor behavior observed in such patients is called "blindsight" and has attracted the interest of many scientists and philosophers for many years, although the neural mechanisms have been unclear. Using macaque monkeys with unilateral lesions of V1 and by combining the pharmacological inactivation and selective pathway-selective manipulation technique with double viral vectors, we have shown that the pathway from the midbrain superior colliculus, a phylogenetically ancient visual system, to the pulvinar plays a critical role in controlling the visually guided saccadic eye movements. Thus, we revealed a role of a subcortical visual pathway, which bypasses the V1, in blindsight.

The **Fujita group** published a manuscript entitled "The Ethics of Cerebral Organoid Research: Being Conscious of Consciousness" (*Stem Cell Reports,* **13**, 440-447, 2019).

We collaborated with Jun Takahashi's laboratory at CiRA to review the latest developments in cerebral organoid research, which has made remarkable progress in recent years, and examined the ethical issues that may arise regarding the relationship between cerebral organoids and consciousness. The novelty of this article is not in its answering the question "Do cerebral organoids become ethically problematic when they have consciousness?" but in its answering the question "What type of consciousness in cerebral organoids would make them ethically problematic?" We also pointed out the possibility of consciousness in the host animal being affected when the transplanted human cerebral organoids have neural connections that make them aware of the external environment. It is unrealistic to ban all basic research at this time. However, we propose that in the future, philosophers, bioethicists, and scientists jointly examine the ethical issues regarding the conduction of studies on nerve organoids aimed at connecting them to other nerve tissue as well as studies on transplanting them to animals. **Note that this was the first article on bioethics to be published in *Stem Cell Reports*.**

The **Eiraku group** published a manuscript entitled "Self-organized formation of developing appendages from murine pluripotent stem cells" (*Nature Communications*, **10**, 3802, 2019).

Limb development starts with formation of the limb bud, which consists of tissues from two different germ layers: the lateral plate mesoderm (LPM)-derived mesenchyme and ectoderm-derived surface epithelium. Although various protocols for induction of three-dimensional tissues (organoids) from pluripotent stem cells (PSCs) have been reported, there has been no example of the self-organized induction of trunk appendages composed of mesenchymal cells covered with epidermis, such as limb buds. We developed a novel means for inducing limb bud-like tissue from PSCs, in which aggregated PSCs spontaneously differentiate into a mesenchymal/epithelial complex tissue comprising LPM-derived Hand2-positive limb progenitors covered with epidermis. ESC-derived limb bud-like tissues selectively differentiated into forelimb or hindlimb, depending on the presence or absence of retinoic acid (RA). Transcriptome analysis revealed that ESC-derived limb bud-like tissues express a gene set closer to that of limb buds than other developing mesenchymal/epithelial complex tissues such as the branchial arch, heart, and tail bud. We also found that manipulating the dorsal-ventral axis enabled us to artificially induce a structure similar to the apical ectodermal ridge (AER) at the tip of the limb bud–like tissue. Finally, in transplantation experiments, the induced tissues were engrafted in an embryonic limb bud and were differentiated into chondrocytes for digits and mesenchyme in developing limbs. This novel organoid technology could provide a novel research tool for mammalian limb development and regeneration, and opens the door to creating other mesenchymal/epithelial complex tissues from PSCs.

The **Hiiragi group** published a manuscript entitled “Hydraulic control of mammalian embryo size and cell fate” (*Nature*, **571**, 112-116, 2019).

We have discovered a new role of the fluid-filled lumen in which the interplay between luminal pressure and cell and tissue mechanics controls the tissue size and cell fate. Size control is fundamental in development and homeostasis. While the role of cell proliferation in this process has been studied, the mechanisms of tissue size sensing and control have remained elusive, due to the lack of direct measurement of tissue mechanics in vivo. In this study we used mouse blastocysts as a model to unravel a key role of the fluid-filled lumen in embryonic size control and cell fate specification. Using embryological, genetic, molecular and biophysical tools, we found that luminal pressure acts as a global mechanical signal to drive cell stretching and stiffening, which reinforces junctional maturation through vinculin mechano-sensing. This establishes a positive feedback loop to accommodate lumen growth. When the cortical tension reaches a critical threshold, cell-cell adhesion cannot be sustained upon mitotic entry, which triggers junctional rupture and fluid leakage, thereby setting a maximal size for blastocyst expansion. A theory of hydraulically-gated oscillations that integrates feedback loops across supra- to sub-cellular scales recapitulates the dynamics of blastocyst size oscillations and control. This theory further predicts that disrupted cell-cell adhesion or increased tissue stiffness lead to a smaller cavity size, which we verified by biophysical, embryological, pharmacological and genetic perturbations. We found that luminal pressure and cavity size directly affect the allocation of cells within the embryo, thereby influencing cell fate specification. This work therefore highlights the importance of fluid force in shaping tissue which can influence biological functions, such as tight junction assembly and cell fate. Given that many organ systems are built with fluid (e.g., the lungs and kidneys) or for fluid transport (e.g., the vasculature and endocrine organs), how forces feed back on their form and function is of great relevance, and the impact of this study goes beyond developmental patterning.

The **Yamamoto group** published a manuscript entitled “De novo DNA methylation at imprinted loci during reprogramming into naïve and primed pluripotency” (*Stem Cell Reports,* **12**, 1113-1128, 2019).

CpG islands (CGIs), including those in imprinting control regions (ICRs), are protected from de novo methylation in somatic cells. Previous studies demonstrated that CGIs at the *Dlk1-Dio3* imprinted gene cluster are aberrantly methylated in mouse iPSCs, and that this aberrant methylation is linked with impaired developmental potential. Moreover, a large-scale analysis of allele-specific RNA-seq data revealed that primed human iPSCs display a higher incidence of biallelic expression of imprinted genes. However, the genome-wide stability of CGI methylation during the reprogramming process and maintenance of naïve and primed pluripotency remains poorly understood. We conducted a comprehensive analysis of CGI methylation during the reprogramming of fibroblasts into naïve and primed pluripotency. Taking advantage of a large number of single nucleotide polymorphisms (SNPs) in the Japanese wild-derived mouse strain MSM/Ms, we also performed high-resolution methylation analysis for unmethylated alleles at ICRs in pluripotent stem cells (PSCs). We show that most CGIs remain unmethylated in both naïve and primed mouse PSCs. However, a subset of CGIs, particularly at ICRs, were often de novo methylated in PSCs, with greater pronouncement at paternal imprinted loci. Moreover, such de novo ICR methylation was linked with the silencing of reprogramming factors, which is required for complete reprogramming. The ICR-preferred CGI hypermethylation was similarly observed in human PSCs. Mechanistically, the suppression of DNMT3A prevented mouse and human PSCs from de novo ICR methylation. Notably, biallelic expression or silencing of imprinted genes in reprogrammed PSCs was sustained in PSC-derived differentiated cells. Since the proper establishment and maintenance of genomic imprints are important for normal development in mammals, our results may have important implications in various applications of PSCs, including regenerative medicine, faithful recapitulation of diseases in vitro, drug screening and the study of early developmental biology. On the other hand, ICR-preferred CGI hypermethylation was also observed in pediatric cancers, whereas adult cancers exhibited genome-wide global CGI hypermethylation, which underscores the shared epigenetic aberrations during reprogramming and pediatric cancer development. These results may also have important implications in the pathogenesis of pediatric cancers.

The **Saitou group** published a manuscript entitled "Induction of the Germ-Cell Fate from Pluripotent Stem Cells in Cynomolgus Monkeys" (*Biology of Reproduction*, **102**, 620-638, 2020 (published online: 13 November 2019)).

In vitro reconstitution of germ-cell development from pluripotent stem cells (PSCs) has created key opportunities to explore the fundamental mechanisms underlying germ-cell development, particularly in mice and humans. Importantly, such investigations have clarified critical species differences in the mechanisms regulating mouse and human germ-cell development, highlighting the necessity of establishing an in vitro germ-cell development system in other mammals, such as non-human primates. We showed that multiple lines of embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) in cynomolgus monkeys (*Macaca fascicularis*; cy) can be maintained stably in an undifferentiated state under a defined condition with an inhibitor for WNT signaling, and such PSCs are induced efficiently into primordial germ cell-like cells (PGCLCs) bearing a transcriptome similar to early cyPGCs. Interestingly, the induction kinetics of cyPGCLCs from cyPSCs is faster than that of human (h) PGCLCs from hPSCs, and while the transcriptome dynamics during cyPGCLC induction is relatively similar to that during hPGCLC induction, it is substantially divergent from that during mouse (m) PGCLC induction. Our findings delineate common as well as species-specific traits for PGC specification, creating a foundation for parallel investigations into the mechanism for germ-cell development in mice, monkeys and humans.

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."

The Mathematical Science Group (PI: **Hiraoka**) and the Bioethics and Philosophy Group (PI: **Fujita**), in collaboration with Life Science Groups, have initiated the following activities:

1. The Mathematical Science Group (PI: **Hiraoka**)

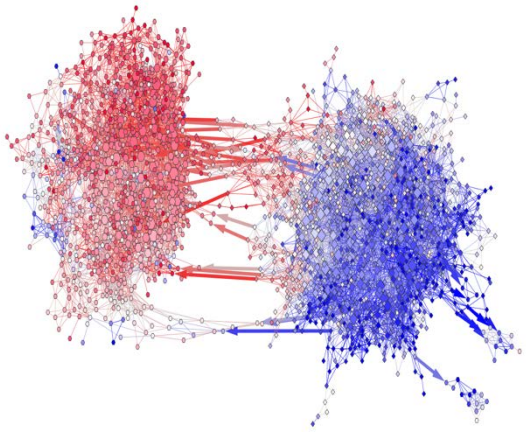
Collaborative Fusion Researches:

1) Noise reduction for single-cell RNA-sequence (scRNA-seq) data (with **Saitou** and **Yamamoto**)

Conventional methods for scRNA-seq data analysis (e.g., tSNE, MDS, PCA) suffer substantially from the noises of such data, since even a small noise in each data point culminates in massive noises in high-dimensional data spaces, making the distinction among closely related datasets difficult/impossible, a phenomenon known as the "curse of dimensionality". We developed a noise reduction method for resolving the curse of dimensionality associated with scRNA-seq data. The application of our method to such data for monkey and mouse development successfully identified a key cell type and *bona fide* developmental trajectories hidden/embedded among the data noises, demonstrating the power of our method (manuscript in preparation, patent pending).

2) Topological data analysis (TDA) for cell-fate specification (with **Saitou**, **Yamamoto**, and **Ueno**)

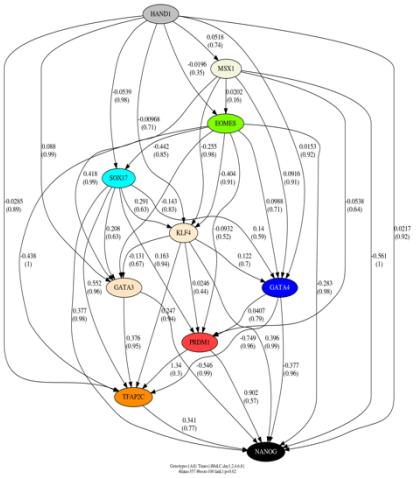
Mapper is one of the TDA methods for extracting topological structures in high-dimensional data spaces. We developed a new Mapper-based algorithm applicable not only to static data clustering, but also to the time evolutions of biological data, such as those for cell differentiation processes. A strong advantage of our method over conventional pseudo-time analysis methods is that it can create general graphs including loops, rather than just bifurcating trees. Accordingly, our method identified potential pathways for human germ-cell differentiation (Figure 1: Potential pathways during human germ-cell differentiation) as well as for mouse T-cell development, which serve as foundations



for new biological analyses. The relevant software will be made available within ASHBi.

3) Inference of gene regulatory networks (GRNs) by causal discovery (with **Saitou**, **Shimizu** (Shiga Univ.), and **Mischaikow** (Rutgers Univ.))

This project aims to develop a mathematical/statistical method to infer GRNs involved in cellular pathways from (single-cell/bulk) RNA-seq data. In collaborations with **Shimizu** (Associate Investigator of ASHBi) and **Mischaikow**, we applied a mathematical theory called "Dynamic Signatures Generated by Regulatory Networks (DSGRN)" to a causal discovery model called the "Linear non-Gaussian Acyclic Model (LiNGAM)", creating a method powerful and computationally efficient for precisely inferring GRNs with large size. This allows us to identify types of regulations (activation/inhibition) and also to detect recurrent regulations modeled by cycles in GRNs. We applied this method to the human germ-cell specification pathway and identified a potential GRN (Figure 2: Potential GRN for human germ-cell specification).



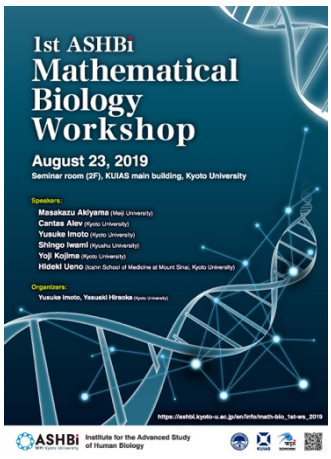
4) Inference and prediction of dynamic epigenetic regulations (with **Saitou**)

This project aims to develop a method for estimating the extent of contribution of active and passive mechanisms for genome-wide DNA demethylation in PGCs based on a mathematical model for DNA methylation reprogramming. Our method predicts species-specific differences in the contribution of active and passive mechanisms in different genomic regions, providing novel insights into the evolution of the mechanism for epigenetic reprogramming in germ cells.

Organization:

1) Math-biology seminars

Hiraoka organized a series of math-biology seminars that meet about once a week: the TDA seminar, GRN seminar, Hi-C seminar, and AI seminar. The TDA and GRN seminars were continued from the previous year and have regularly yielded new observations as a basis for publication. Hi-C and AI seminars were initiated this year: the Hi-C seminar, which was initiated by young researchers in ASHBi (graduate students and assistant professors), aims to characterize relationships between epigenetic characteristics and DNA 3D structures by applying TDA to adjacency matrices encoded in Hi-C data. The AI seminar aims to identify cutting-edge biological themes relevant to the activities of ASHBi, which are potentially solved by AI. We aim to identify novel biology-AI research themes that leverage the strengths of ASHBi.



2) 1st ASHBi Mathematical Biology Workshop (Poster 1)

To enhance math-biology fusion researches in ASHBi as well as to build a relevant network, **Hiraoka** organized the 1st ASHBi mathematical biology workshop in 23 August 2019. The main subject of the workshop was mathematical modellings. **Hiraoka** selected pairs of speakers, one from the field of biology and the other from mathematics, for several biological themes, such as human immunology, human mesoderm development, and GRNs. Active discussions were made among participants (around 40), and the second workshop focusing on AI will be held in September 2020.

2. The Bioethics and Philosophy Group (PI: **Fujita**)

Collaborative Fusion Researches:

1) Ethics of synthetic embryology (with **Alev** and others)

We investigated ethical issues involved in research generating embryo-like structures *in vitro* (synthetic embryology). In particular, we engaged in intensive discussions of the implications of such research on the "14-day rule" (an international rule for the period of embryo culture outside the body: 14 days after fertilization or until the formation of a primitive streak) (under preparation).

2) Ethics of cerebral organoid research (with **Isa** and others)

We investigated ethical issues associated with cerebral organoid research. Scientists involved assessed the current situation and future predictions of cerebral organoid research, while philosophers and ethicists identified philosophical issues surrounding consciousness and other ethical issues. Moreover, jurists identified legal issues involving studies and clinical applications in which cerebral organoids are used. Periodical discussions are in progress (the ASHBi/CiRA Bioethics Symposium and other relevant seminars were cancelled due to COVID19).

3) Ethics of epigenome editing in germ cells (with **Yamamoto** and others)

Epigenome editing may be clinically applied in the future, and we investigated the ethical issues associated with epigenome editing in germ cells. We evaluated the technical differences between genome editing (e.g., CRISPR-Cas9) and epigenome editing (e.g., dCas9), and identified the ethical issues common to both and those specific to epigenome editing. Periodical discussions are in progress (a seminar entitled "The Ethics of Editing the Human Epigenome" by Alexandre Erler, a researcher and assistant professor of the Chinese University of Hong Kong, was cancelled due to COVID19).

4) Ethics of research involving aborted human fetuses (with **Saitou** and others).

We aim to clarify the academic rationale for research involving aborted human fetuses, to create a guideline for performing such research, and to clarify items to be written in the informed consent presented to donors. We held a seminar entitled "Ethical Issues on the Use of Dead Fetuses for Research and the Regulation" by Dr. Yoshimori Mori (Associate Professor, Hannan University) (July 2019). For the full-scale implementation of this research, we hired a postdoc focusing on this theme and acquired external funding (SECOM Science and Technology Foundation, Special Area Research Grant, 2020–2022).

Organizations:

1) Bioethics/Philosophy seminars

We organized a seminar entitled "The Theory of Life in Nishida Philosophy" that was presented by Tetsuro Nagaoka (a part-time lecturer at Kyoto University), who specializes in the philosophy of Kitaro Nishida (January 2020). Based on Nishida's philosophy, we discussed key questions such as What is human? What is life? and What is a pure experience? We discussed the philosophical implications of human procreation using germ cells generated in vitro.

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)

Recruiting PIs/co-PIs to Strengthen Research Activities

In FY2019, we have actively continued our international recruitment activities to hire excellent researchers to strengthen the organization.

During the year, we have carefully recruited and selected five new PIs, two co-PIs, and a core manager. These people have strong knowledge in human/primate biology and will contribute to the interdisciplinary research of our institute. As seen in Table 1, two PIs have already started their research activities at ASHBi, and the other three PIs will join the institution in FY2020.

Table 1. Names of new PIs/co-PIs joining ASHBi in FY2019 and FY2020

Year	Name	Position	Former affiliation
FY2019	**Cantas Alev**	PI	Kyoto University (CiRA), Japan
	Tomoyuki Tsukiyama	PI/Core Head, PRiME	Shiga U of Medicine, Japan
	Hiroyuki Yoshitomi	co-PI, Ueno G	Kyoto University (CiRA), Japan
	Taro Tsujimura	Core Manager, SignAC	Keio University, Japan
FY2020	**Ryo Yamamoto**	PI	Stanford U, USA
	Kenichi Amemori	PI	Kyoto University (PRI), Japan
	Yasuhiro Murakawa	PI	RIKEN, Japan
	Fumitaka Inoue	co-PI Bourque G	UCSF, USA

Appointment of Associate Investigator to Strengthen Math-Biology Fusion Research
Hiraoka (the mathematical science group) has organized a series of math-biology seminars and led several collaborations with life science groups within ASHBi (see **Generating Fused Disciplines**). To further enhance the progress of math-biology interdisciplinary research, we created a new position title of "**Associate Investigator**" as a PI-level researcher in FY2019, and invited two excellent mathematical researchers outside of Kyoto University to take this position at ASHBi (**Shohei Shimizu**, Professor Shiga University; **Shingo Iwami**, Associate Professor, Kyushu University). The participation of PI-level mathematical scientists will boost up math-biology interdisciplinary research at ASHBi.

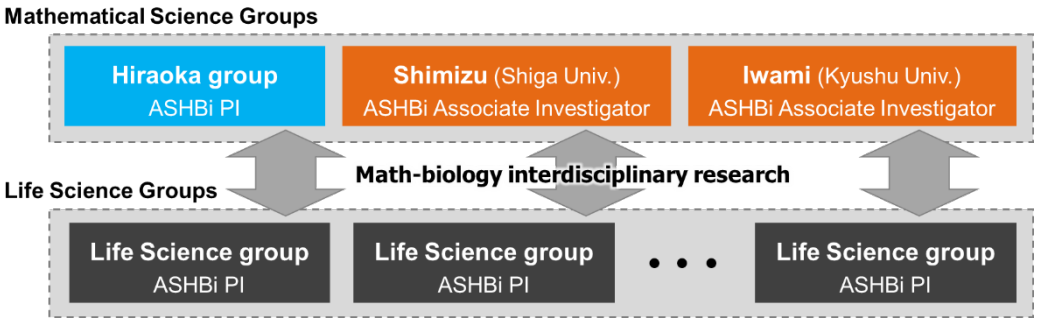


Figure 3. Mathematical science groups in ASHBi.

ASHBi International Symposium 2020 (rescheduled due to the COVID-19 outbreak)
To enhance the research activities and expand the international networking of the Institute, we had planned to hold the ASHBi International Symposium 2020 under the theme of "Human development,

Figure 4. ASHBi Symposium 2020. (postponed to FY2021)

genetics, and evolution" on 19-20 March 2020. The event was co-organized by two ASHBi PIs (**Saitou** and **Hiiragi**) and two distinguished foreign researchers (**James Briscoe**, the Francis Crick Institute; **Barbara Treutlein**, ETH Zurich). The satellite meeting "On the Discovery of Genomic Imprinting" was also planned on 21 March 2020, with **Davor Solter** and **Azim Surani**, winners of the 2018 Canada Gairdner International Award, joining as guest speakers. Twenty-one world leading researchers were invited to speak at the symposium, but unfortunately we had to postpone the symposium to FY2021 due to the COVID-19 outbreak.

Seminars to Enhance Mutual Understanding / Interactions for Collaboration

To enhance interdisciplinary activities between PI groups, we have hosted a total of 32 seminars/workshops in FY 2019. We have put great effort in holding regular events such as the **ASHBi Colloquium**, **ASHBi Seminar** and **ASHBi Retreat** to develop a foundation for interdisciplinary research based on the understanding of other research fields. The ASHBi Colloquium serves as an opportunity for PIs to introduce their research to other PI groups. At each ASHBi Colloquium, two PI groups provide overviews of their research and latest findings to their ASHBi colleagues. At the ASHBi Seminars, an outside researcher invited by a host PI presents his/her research to the Institute. The seminars provide an opportunity for our researchers to learn recent findings from the guests from various research fields. The ASHBi Retreat is the largest interactive event at the Institution. Here, researchers present their findings through oral and poster sessions and can have intensive networking with other PI group members during the night session. Along with these events, we hold specific events that promote fusion research or the fostering of young researchers. These events have served as a concrete foundation to the interdisciplinary activities between ASHBi PI groups.

Table 2. Events held at ASHBi in FY2019.

Events	Times	Description
ASHBi Colloquium	7	2 PI groups talk about recent research topics
ASHBi Seminar	20	Invited talks hosted by PI groups on specific topics
ASHBi Retreat	1	Oral/Posters of PI groups to enhance interactions within
CiRA/ASHBi Ethics lecture	2	Invited talks to enhance understanding of bioethical issues
ASHBi Mathematical Biology Workshop	1	Workshop on interdisciplinary mathematics and biology research
ASHBi Young Researcher Meeting	1	Talks by young researchers to connect with researchers from different fields

ASHBi Fusion Research Grant

ASHBi highly encourages interdisciplinary research beyond the boundaries of existing research fields. To this end, we have established a new research grant to strengthen interdisciplinary research for three categories (math-biology, bioethics-biology and biology-biology). The point of this grant system is that the proposed project must form a research team consisting of at least two researchers from different PI groups to generate a collaborative atmosphere within ASHBi. In FY2019, as a testbed, we provided grants to six projects under the condition that the support period is limited to one year. We expect that this grant system will be a good platform to create new interdisciplinary research at our institute.

Table 3. ASHBi fusion research grant: categories, support period, and funding.

Category	Support period	Funding per project
Math-biology studies	1-3 years	< 9 million JPY in total (< 3 million for each year)
Bioethics-biology studies		
Biology-biology studies*		

*In the case of the biology-biology category, ASHBi encourages projects pioneering new research themes in human biology or developing new experimental techniques for biological studies.

Setting up the ASHBi Main Building

We have made a great effort to set up ASHBi's main building by renovating Building B on the Faculty of Medicine campus (Fig. 5). In 2019, Kyoto University provided more space in this building for ASHBi research activity, increasing the total space from 1,700 m^2 to 2,010 m^2. The building is in walking distance from most ASHBi PI groups, enabling researchers to easily meet up and discuss with each other. (see also Campus Map in Appendix 3-1). We have also established a core facility for single-cell genome information analysis on the ground floor and shared laboratory and office spaces for overseas/young PIs on the 1st and 2nd floors.

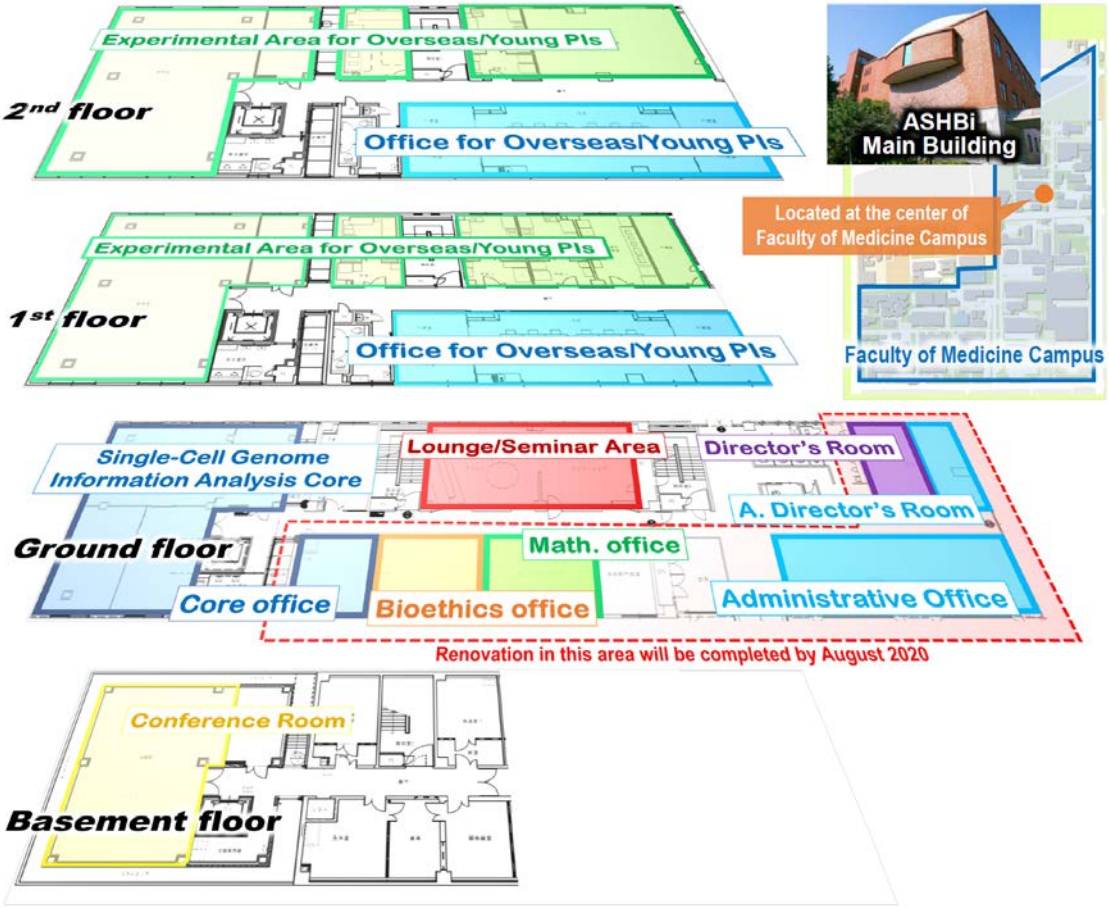


Figure 5. Floor map of ASHBi main building.

With the aim of making this building an interaction hub for ASHBi researchers, we have constructed a lounge on the ground floor for casual research discussions, and a seminar room (ground floor) and conference room (basement floor) for holding seminars and workshops. Furthermore, in order to progress interdisciplinary research in math-biology and bioethics-biology within ASHBi, we started constructing the researcher rooms for mathematics and bioethics on the ground floor in front of the lounge. We also started constructing the ASHBi Director's room, the Administrative Director's room and the Administrative Office room in the main building. The construction of these rooms is scheduled to finish by August 2020.

Setting up the Single-cell Genome Information Analysis Core Facility (SignAC)

We established the Single-Cell Genome Information Analysis Core (SignAC) on the ground floor of the ASHBi main building in FY2018. This core facility contains ultra-high–throughput sequencing systems that enable large-scale genomics analysis (e.g. Illumina Novaseq 6000 system, Nextseq 550system, HiSeq 2500 system, etc.). In FY2019, to improve facility performance and to accumulate technical know-how, we appointed **Taro Tsujimura** as the Core Manager dedicated to SignAC. He has strong expertise in analyzing the epigenome. In addition, we have also hired two staff to support

the operation of SignAC by **Tsujimura** and **Yamamoto** (Fig. 6). The team has started several projects to develop new methods for genome analyses through collaborative research within ASHBi. Besides adding to research quality, these appointments are enhancing the competitiveness and visibility of the facility. During FY2019, SignAC has run 167 next generation sequences (NGSs) and provided other essential support to ASHBi research.

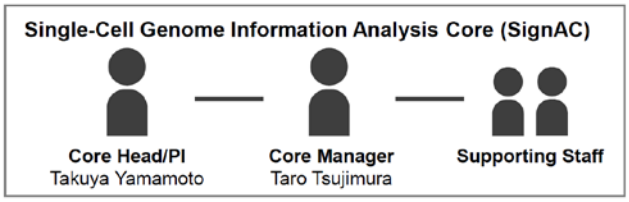


Figure 6. Organization chart of SignAC

Setting up the Primate Genome Engineering Core Facility (PRiME)

In addition to SignAC, ASHBi has established facilities for genome engineered primates to uncover the primate-specific functions of key genes and to create critical disease models using cynomolgus monkeys. The main facility is the Primate Genome Engineering Core (PRiME) at the Research Center for Animal Life Science, Shiga University of Medical Science, which maintains one of the largest primate colonies and some of the most advanced reproductive technologies both in Japan and the world (~700 cages). In FY2019, an additional 125 m^2 (64 cages) was renovated and secured for ASHBi to generate genome-engineered monkeys and to retrieve oocytes/embryos specifically for ASHBi research (Fig. 7). Further, we have appointed **Tomoyuki Tsukiyama** as the PI responsible for PRiME and two staff to support **Tsukiyama**. During FY2019, PRiME, following ethical approval, has been generating NPHP1 (with **Yanagita**) and DISC1 (with **Isa**) knockout monkeys and provided embryological materials essential for ASHBi research.

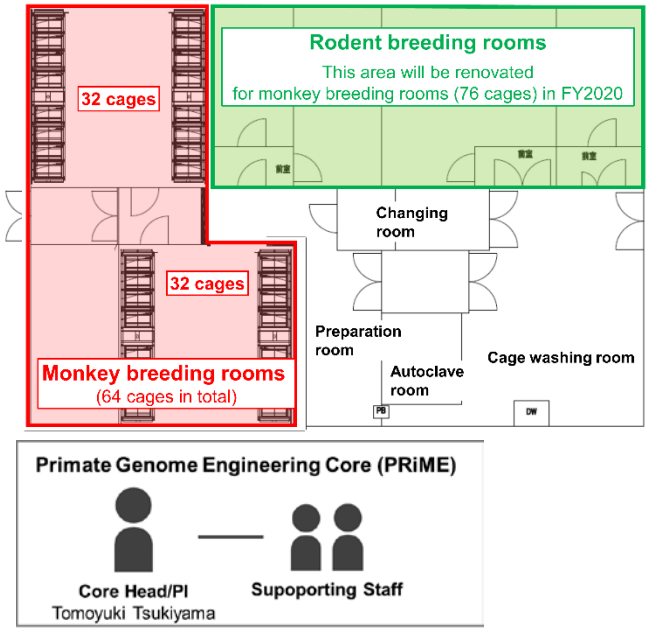


Figure 7. Floor map and organization chart of the Primate Genome Engineering Core (PRiME) in Shiga.

Furthermore, to create space for analyzing the phenotypes of genome-engineered monkeys at Kyoto University, we have established the **Non-human Primate Phenotype Analysis Facility (NPAF)** in the Med-Pharm Building in the Faculty of Medicine Campus (360 m^2). **Isa** has been appointed as the supervisor in charge of NPAF. This facility allows us to analyze the phenotype of genome-edited non-human primates, such as behavior including social interactions and other physiological functions. In FY2019, we installed mother-infant cages and pair-cages for observing social interactions (20 cages), and have established rooms and equipment for physiological experiments (Fig. 8).

Figure 8. Non-human Primate Phenotype Analysis Facility (NPAF) in Kyoto.

Organizing Research Support System within ASHBi

The Administrative Office of ASHBi consists of the Administrative Director (**Tadashi Ogawa**), Strategic Research Acceleration Unit, and Administrative Management Unit. We have secured one URA (**Makoto Shida**) and two dedicated staffs in the Strategic Research Accelerating Unit, which plays a key role in planning and implementing research support programs for overseas/young researchers as well as fostering programs for early-stage researchers at ASHBi.

<SIMPLIFYING COMPLEX RESEARCH APPROVALS AND REGULATORY PROCEDURES>

For researchers coming from abroad, setting up a new biological laboratory in Japan is a difficult and complicated task. The procedure for setting up the biological research environment requires many regulatory approvals supervised by different departments, making it difficult to grasp the overall system. To solve this issue, the ASHBi URA has prepared a guide that provides an overview of the required steps to launch biological research at Kyoto University (Fig. 9). This guide is intended to assist researchers in their understanding of which procedures and approvals are required and to identify which procedures can be processed in parallel to speed up the process. The ASHBi URA provides customized consultation to the researcher as well as necessary coordination with multiple university departments in order to obtain the necessary approval smoothly.

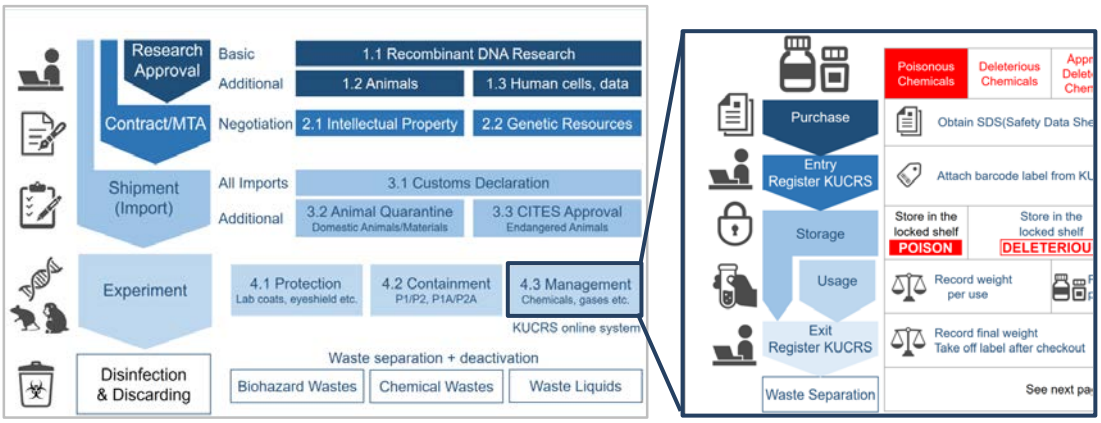


Figure 9. A schematic of the guidebook for new researchers joining ASHBi.

<COORDINATING SHARED EQUIPMENT >

The ASHBi URA also provides support for optimizing the purchase and installation of shared equipment at ASHBi. Newly appointed young PIs have to set up their experimental environment. To maximize the utilization of the allocated budget to each PI, some PIs have agreed to the joint purchase of expensive equipment to share among them. To enable this, the ASHBi URA holds close communication with each PI to identify what kind of equipment is needed. The URA collects their requests and coordinates the discussions among PIs to decide which equipment should be purchased and where it should be installed (Fig. 10). This support strongly contributes to the optimized use of limited budget for experimental setup among young PIs.

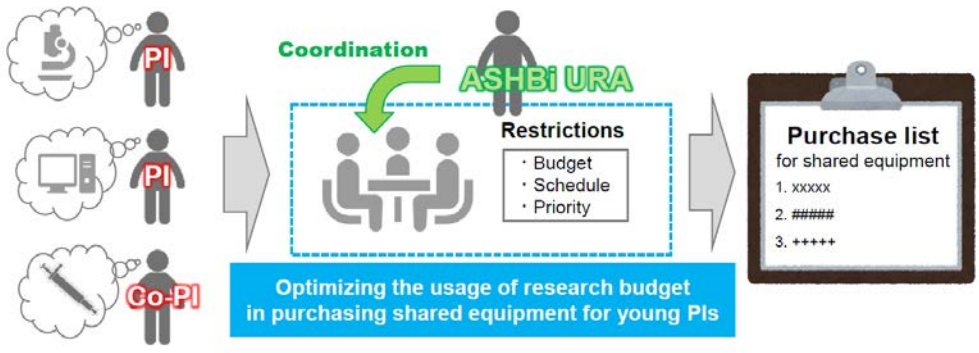


Figure 10. ASHBi URA coordinates the optimization of shared equipment for young PIs.

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.

Reform on Accounting System Allows Multiple-Year Budgeting for Indirect Funds

Kyoto University has created a new organization structure, the "Kyoto University Institute for Advanced Study (KUIAS)", to house its two WPI centers (ASHBi and iCeMS) on a permanent basis. KUIAS was established as a "special zone" for implementing various system reforms to the whole university. As the first testbed at the University, ASHBi was allowed to introduce multiple-year budgeting for indirect funds (Fig. 11). As a benefit, ASHBi will carry over 40 million JPY of indirect funds to FY2020 to greatly increase the flexibility of budget planning in FY2020 and allow us to establish custom-made/high-performance microscope equipment within the Institute.

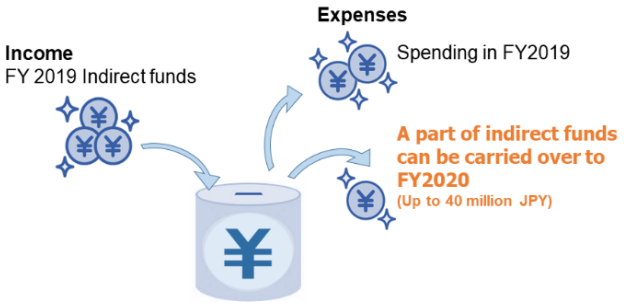


Figure 11. Multiple-year budgeting for indirect funds.

Flexible Funding System to Secure Salary Budget for Young Researchers

As a testbed, the University has also implemented a new salary system to ASHBi to provide flexibility when employing young researchers. In this system, tenure PIs will be allowed to use secured grants or donations as a substitute for part of the University's salary (Fig. 12). By gathering the substitution amount from multiple PIs, the University can open up space in the personnel budget to provide new positions for young researchers. This is the first step of the reform. Although not included as of now, in future steps, the University is considering the possibility of extending this system to provide salary incentives for tenure PIs by allowing them to have some portion added to their salary after opening up the salary budget for young researchers.

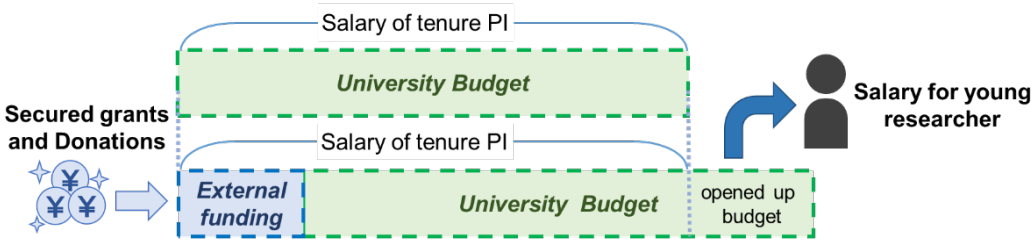


Figure 12. Scheme of the new salary system.

Seminars/Guidebooks for Fostering Young Researchers

The Strategic Research Acceleration Unit (mentioned above) at ASHBi designs and provides seminars and guidebooks for young researchers to assist in the acquisition of knowledge/skills that will permit effective research activity (Fig. 13). For example, (1) we held a seminar on how to prepare good proposals for KAKENHI grants. This seminar was jointly organized with the Kyoto University Research Administrator Office. (2) We also organized a discussion-oriented meeting for ASHBi's young researchers. This meeting was an ideal opportunity for young researchers to interact with researchers from different fields and initiate interdisciplinary research activities. Finally, (3) we issued a guidebook about professional scientific illustrators for our researchers to promote their research. From this guidebook, young researchers can find not only examples of scientific illustrations, but also an estimate of costs, schedules, and important points to be aware of when requesting an illustration from professionals.

Figure 13. ASHBi programs fostering young researchers.

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.

ASHBi has obtained Two Permanent Research Positions

To secure the Institution's long-term development, Kyoto University has provided two permanent positions to ASHBi. By utilizing these positions, ASHBi will be able to employ tenured professor/associate-professor class researchers. This has greatly helped us in our search for excellent early-career researchers around the world and hire them as young PIs. The recruitment of promising young PIs will contribute to securing the next generation researchers who will become the core investigators of ASHBi and lead to the future development of the Institute.

Personnel Support from the Host Institution

Kyoto University takes responsibility for the personnel expenses of seven PIs designated to the University (including the Director and the Vice Directors). The University also takes responsibility for the personnel expenses of the Administrative Director. Furthermore, the University provides three permanent administrative staffs at the KUIAS office to support the administrative management at ASHBi.

Financial Support from the Host Institution

Kyoto University 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 116 million JPY as indirect funds in FY2019. Moreover, KUIAS provided 100 million JPY (43 million JPY in grants and 57 million JPY in loans) in FY2019.

Research Space and Facility Support from the Host Institution

Kyoto University provides 4,910 m^2 of space for ASHBi research activity at its Faculty of Medicine Campus: 2,010 m^2 of space for overseas/young PIs (ASHBi main building, Fig. 5), in addition to the existing 2,900 m^2 of space designated for the eight PIs of Kyoto University. Most research spaces related to the Institute are located closely within a 2-5 minute walk. The ASHBi main building houses the research space for overseas PIs and young PIs, as well as SignAC, meeting rooms, rooms for the director and the administrative director, and the administrative office, as mentioned above.

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.

Cooperation with WPI-iCeMS

In addition to ASHBi, Kyoto University established one more WPI center (iCeMS: Institute for Integrated Cell-Material Sciences) in December 2007. The two WPI centers are closely located and have cooperated in organizing important institutional events. For example, on 16 December 2019, iCeMS and ASHBi received a delegation of professor/PI level researchers from the *National Cheng Kung University College of Medicine* (NCKU) in Taiwan to hold a joint meeting consisting of 8 NCKU, 5 iCeMS, and 3 ASHBi researchers.

At the first ASHBi Retreat, which was held on Awaji island 7-8 February 2020, we invited the two Deputy Directors of iCeMS (Prof. Jun Suzuki and Mineko Kengaku). They introduced iCeMS' research activities and core facilities to ASHBi members. Such cooperation is expected to enhance collaboration between the two institutions (Fig. 14).

Furthermore, we planned to have an international symposium titled "Human development, genetics, and evolution" on 19-20 March 2020 (Fig. 4) in cooperation with iCeMS by inviting iCeMS PI Prof. Ryoichiro Kageyama. However, this symposium was unfortunately postponed due to the outbreak of COVID-19. Nevertheless, the two WPI centers at Kyoto University have progressively cooperated to effectively enhance their research interactions.

Figure 14. ASHBi Retreat 2020 was organized in cooperation with iCeMS.

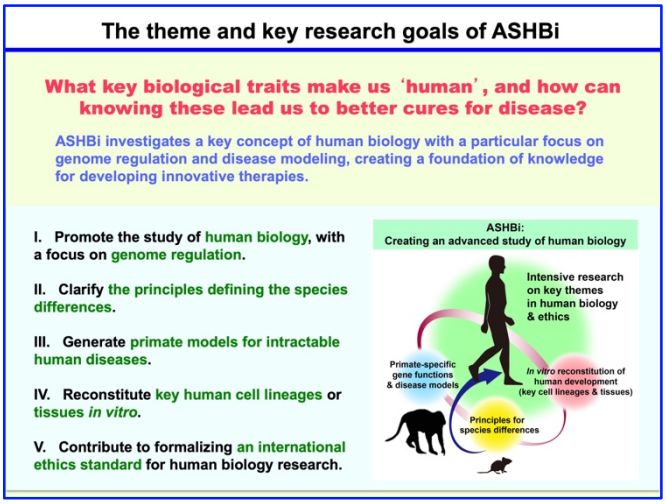
7. Center's Response to Results of Last Year's Follow-up

* 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.

We would like to sincerely thank the WPI Program Committee for their constructive comments, which we have been using as the basis for improving the organization and management of ASHBi.

(1) *The ASHBi's vision, direction and goals should be discussed more deeply and with greater clarity, and shared by all PIs and members of ASHBi in order to establish a unique ASHBi identity. Fusion as whole needs to be emphasized.*

Response 1. The ASHBi's vision is to perform **basic science** that is of the highest quality and is relevant to answering two key questions: What key biological traits make us human? and How can knowing these traits lead us to better cures for disease? Toward this end, we perform five lines of fundamental investigations:



I. Investigations to promote the study of human biology, with a focus on genome regulation. Key PIs: **Ogawa, Ueno, Yanagita, Bourque, Saitou, Yamamoto**

II. Investigations to clarify the principles defining the species differences (Fusion). Key PIs: **Hiraoka, Saitou, Yamamoto, Bourque, Isa, Eiraku, Ueno, Hiiragi, Alev**

III. Investigations to generate primate models for intractable human diseases. Key PIs: **Isa, Yanagita, Ema, Tsukiyama**

IV. Investigations to reconstitute key human cell lineages or tissues in vitro. Key PIs: **Saitou, Eiraku, Alev, Ema**

V. Investigations to contribute to formalizing an international ethics standard for human biology research (Fusion). Key PIs: **Fujita, Saitou, Isa, Yamamoto, Alev, and all other PIs**

Thus, we consider that our vision, direction, goals and fusion are defined clearly. In response to the comments by the WPI Program Committee, we initiated a discussion session that takes place each month as part of the PI meeting, in which PIs share their vision, direction, and goals, and discuss ideas for strengthening interactions and creating collaborations among the ASHBi PIs. The sharing of ideas among ASHBi PIs is further reinforced by the ASHBi colloquium each month, in which two PIs actively discuss key progresses of their research, the periodical ASHBi seminars, and the ASHBi Retreat each year (see **6. others**). We believe that the system for promoting the interactions and sharing ideas among ASHBi PIs and members has now been well instated, and would like to improve it on a continuous basis.

(2) Many researchers have been working on a wide range of issues from embryology to clinical issues in mice, monkeys, and humans. However, it should be made clear what clinical problems are being solved.

Response 2. As stated in **Response 1** and in our original proposal, the ASHBi's vision is to perform **basic science** that is of the highest quality and is relevant to human biology, but not necessarily to directly address clinical problems. Nonetheless, please note that **Ogawa** has been intensively working on the etiology (mutations and tissue remodeling) of various types of cancers and hematologic malignancies in close collaboration with Kyoto University Hospital (e.g., *Nature*, **565**, 312-317, 2019; *Nature*, **577**, 260-265, 2020), **Yanagita** has also been working on the etiology and interventions of various kidney diseases, including chronic kidney diseases, at Kyoto University Hospital as well as at ASHBi (e.g., *Kidney Int.*, **95**, 526-539, 2019; *Kidney Int.*, in press), and **Ueno**, who has been performing human immunology research using patient specimens at Mt. Sinai Hospital, has initiated such research actively at ASHBi and Kyoto University. Thus, in addition to performing basic science, key PIs in ASHBi have clear areas of focus on clinical problems.

Moreover, as part of our initiative on generating primate models for intractable human diseases, especially diseases of the nervous system and the kidney, two typical examples for which rodent models have been largely unsuccessful in recapitulating human phenotypes, **Ema** and **Tsukiyama** have generated a monkey model for autosomal dominant polycystic kidney diseases (ADPKD) with genome editing of *PKD1* (*Nature Communications*, **10**, 5517, 2019), **Yanagita** is generating a monkey model for nephronophthisis type 1 with genome editing of *NPHP1*, and **Isa** is generating a monkey model for a type of schizophrenia with genome editing of *DISC1*. Thus, we believe that

the investigations in ASHBi have clear relevance to clinical problems.

(3) ASHBi needs to strengthen its research related to human evolution and human population genetics.

Response 3. In response to the comments by the WPI Program Committee, **Saitou**, **Bourque** and other ASHBi members have initiated a collaboration with regard to the mechanism and impact of epigenetic reprogramming during evolution to humans based on the *in vitro* system for germ-cell development from iPSCs of humans, chimpanzees, orangutans, and monkeys. **Bourque** has appointed **Fumitaka Inoue** as co-PI of his group and is initiating research on the evolution of enhancer usage, including that of human accelerated regions (HARs), during neural development based on the *in vitro* system for neural development from iPSCs of humans, chimpanzees, orangutans, and monkeys. Moreover, ASHBi has appointed **Yasuhiro Murakawa**, an expert on the architecture and regulation of the human genome, as a new PI (September 2020) who will also work on the evolution of the human genome. We believe that these investigations will reinforce the research on human evolution in ASHBi in the coming years.

We highly appreciate the importance of human population genetics, although such research was not included as a major target of ASHBi in the original proposal. However, given its importance in human biology and because several ASHBi PIs (**Bourque** and **Murakawa**) have already been working in this and related areas, in response to the recommendation by the WPI Program Committee, ASHBi will step into the area of human population genetics at an appropriate time point, e.g., by forging a collaboration with relevant investigators at Kyoto University Hospital.

(4) Collaboration and exchange with clinicians who are seeing patients would be an asset to the center, so that research questions using disease models in animals and cells can be translated into the clinic and benefit patients.

Response 4. Please see **Response 2.**

(5) The center needs to work on its fusion with mathematics more seriously.

Response 5. As we stated during the Site Visit 2019, in order to realize a truly valuable fusion with mathematics, from the outset we adopted a strategy of creating a foundational research group among a relatively small number of ASHBi members, because we consider that the identification of appropriate biological themes and their progressive optimization are time-consuming processes that involve proper concentration and dedication, and because acquisition of the massive datasets appropriate for forefront mathematical analysis requires careful consideration.

Based on this idea, as stated in **2. Generating Fused Disciplines** (page 6), ASHBi has been performing at least four lines of fusion research with mathematics, i.e., 1) noise reduction for scRNA-seq data, 2) topological data analysis (TDA) for cell-fate specification, 3) inference of GRNs by causal discovery, and 4) inference and prediction of dynamic epigenetic regulations. We are currently preparing a manuscript with regard to the outcome of theme 1), which will serve as a basis for further extending the fusion research in 2) and 3). Since research themes 1) to 3) involve highly general biological concepts, we believe that the successful accomplishments of these themes will serve as a foundation for ASHBi's fusion research with mathematics.

Moreover, as stated in **3. Realizing an International Research Environment** (page 9), we appointed **Shohei Shimizu** (Professor, Shiga Univ.) and **Shingo Iwami** (Associate Professor, Kyushu University) as associate investigators at ASHBi, and they are currently performing active collaborations with ASHBi members, broadening the math-biology fusion research at ASHBi. Additionally, at the beginning of FY2020, **Hiraoka** joined the "Cell, Developmental Biology, Systems Biology" course of the Graduate School of Medicine, Kyoto University, as an official member (along with **Alev** and **Yamamoto**), creating a strong link with the Graduate School of

Medicine for expanding math-biology fusion research. We hope that our strategy for establishing and expanding the math-biology fusion research at ASHBi meets with the approval of the WPI Program Committee.

(6) From the aspect of ASHBi's sustainability, moving the primary affiliation of the PIs with home departments in KU to ASHBi should be seriously considered.

Response 6. In order to improve the personnel management at Kyoto University, the University introduced a new system in 2016 to separate the employment and the allocation of the academic staff. The employment is made for 41 research fields. This system removes the boundaries of existing academic departments (education and research organizations) upon forming the screening committee for academic staff recruitment. Since the employment process is independent from the allocation, it enables the University to execute a flexible staff placement for more effective education and research activities from a university-wide perspective. This system allows the PIs from different academic departments to effectively work together beyond the borders of their respective departments under the strong leadership of the ASHBi Director. Thus, this system provides the basis for the ASHBi's sustainability.

(7) There are 13 PIs at present, of which only 2 are not Japanese. Regarding making organizational reforms and advancing internationalization, more international PIs or co-PIs are needed, as well as collaborations with top international institutions.

Response 7. We would like to sincerely thank the WPI Program Committee for this suggestion. We would like to consider **Takashi Hiiragi** (EMBL) and **Hideki Ueno** (Mt. Sinai Hospital) as international PIs, since they have been based in overseas institutes and have been actively performing research in ASHBi. At the same time, we have been seriously taking measures to increase the number of non-Japanese scientists at ASHBi, making it a rule for PIs to hire at least one non-Japanese postdoc among three possible recruitments. With the activity in FY2019, we consider that the framework of ASHBi, including a major renovation of the main building for ASHBi, has been established and we can now aim to advance the internationalization further from FY2020 onward.

Please note that 47 researchers have visited ASHBi from overseas for seminars/discussions in ASHBi during FY2019 (Appendix 5). As a further step toward collaborations with top international institutions, during FY2019, we organized **the ASHBi Symposium 2020 on "Human Development, Genetics, and Evolution"** [organizers: **James Briscoe** (Crick Institute), **Takashi Hiiragi**, **Mitinori Saitou**, and **Barbara Treutlein** (ETH Zurich)], and will present this symposium every other year, alternating with the symposium **"From Stem Cells to Human Development"** organized by the **Company of Biologists, Cambridge, UK**. We have also organized **the EMBO workshop on "Molecular Mechanisms of Developmental and Regenerative Biology"** [organizers: **Ian Chambers** (University of Edinburgh), Mitinori Saitou, **Patrick Tam** (CMRI, Australia), **Elly Tanaka** (IMP, Vienna)] (Kyoto, November 2020), and the **JMUBET Primate Neurobiology School** [organizers: Tadashi Isa; Menno Witter, Criff Kentros (Norwegian University of Science and Technology), Ken-ichiro Tsutsui (Tohoku University)] (Kyoto, September 2020), among other activities. However, due to the COVID19 outbreak, these events were canceled and are currently under re-scheduling. We would like to begin re-scheduling these and other events/activities as well as to initiate further collaborations with top international institutions, when the international situation in regard to the COVID19 outbreak becomes more settled.

Appendix 1 FY 2019 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2019. (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 2020 in blue for reference.

[WPI Papers]

1. Original Articles

1) 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

2) 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. A., 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

3) 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
4) 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
5) 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), 124-129. doi:10.1038/s41586-020-2144-9
6) 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
7) 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
8) 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 Discov***. doi:10.1158/2159-8290.CD-19-0982
9) 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
10) 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†. ***Biol Reprod***, *102*(3), 620-638. doi:10.1093/biolre/ioz205
11) 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

12) 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
13) Arai, H. N., Sato, F., **Yamamoto, T.**, Woltjen, K., Kiyonari, H., Yoshimoto, Y., Shukunami, C., Akiyama, H., Kist, R., & Sehara-Fujisawa, A. (2019). Metalloprotease-Dependent Attenuation of BMP Signaling Restricts Cardiac Neural Crest Cell Fate. ***Cell Reports***, *29*(3), 603-+. doi:10.1016/j.celrep.2019.09.019
14) Asashiba, H., Escolar, E., **Hiraoka, Y**., & Takeuchi, H. (2019). Matrix method for persistence modules on commutative ladders of finite type. ***Japan Journal of Industrial and Applied Mathematics***, *36*(1), 97-130. doi:10.1007/s13160-018-0331-y
15) Azami, T., Bassalert, C., Allegre, N., Estrella, L. V., Pouchin, P., **Ema, M.**, & Chazaud, C. (2019). Regulation of the ERK signalling pathway in the developing mouse blastocyst. ***Development***, *146*(14). doi:10.1242/dev.177139
16) Berger, G., Gerritsen, M., Yi, G. Q., Koorenhof-Scheele, T. N., Kroeze, L. I., Stevens-Kroef, M., Yoshida, K., Shiraishi, Y., van den Berg, E., Schepers, H., Huls, G., Mulder, A. B., **Ogawa, S.**, Martens, J. H. A., Jansen, J. H., & Vellenga, E. (2019). Ring sideroblasts in AML are associated with adverse risk characteristics and have a distinct gene expression pattern. ***Blood Advances***, *3*(20), 3111-3122. doi:10.1182/bloodadvances.2019000518
17) Chan, C. J., Costanzo, M., Ruiz-Herrero, T., Monke, G., Petrie, R. J., Bergert, M., Diz-Munoz, A., Mahadevan, L., & **Hiiragi, T**. (2019). Hydraulic control of mammalian embryo size and cell fate. ***Nature***, *571*(7763), 112-+. doi:10.1038/s41586-019-1309-x
18) Ishida, A., Kobayashi, K., Ueda, Y., Shimizu, T., Tajiri, N., **Isa, T.**, & Hida, H. (2019). Dynamic Interaction between Cortico-Brainstem Pathways during Training-Induced Recovery in Stroke Model Rats. ***Journal of Neuroscience***, *39*(37), 7306-7320. doi:10.1523/jneurosci.0649-19.2019
19) Kinoshita, M., Kato, R., Isa, K., Kobayashi, K., Onoe, H., & **Isa, T.** (2019). Dissecting the circuit for blindsight to reveal the critical role of pulvinar and superior colliculus. ***Nature Communications***, *10*. doi:10.1038/s41467-018-08058-0
20) Kobayashi, K., **Tsukiyama, T.**, Nakaya, M., Kageyama, S., Tomita, K., Murai, R., Yoshida, T., Narita, M., Kawauchi, A., & **Ema, M.** (2019). Generation of an OCT3/4 reporter cynomolgus monkey ES cell line using CRISPR/Cas9. ***Stem Cell Research***, *37*. doi:10.1016/j.scr.2019.101439
21) Komabayashi-Suzuki, M., Yamanishi, E., Watanabe, C., Okamura, M., Tabata, H., Iwai, R., Ajioka, I., Matsushita, J., Kidoya, H., Takakura, N., Okamoto, T., Kinoshita, K., Ichihashi, M., Nagata, K., **Ema, M.**, & Mizutani, K. (2019). Spatiotemporally Dependent Vascularization Is Differently Utilized among Neural Progenitor Subtypes during Neocortical Development. ***Cell Reports***, *29*(5), 1113-+. doi:10.1016/j.celrep.2019.09.048
22) Komura, S., Ito, K., Ohta, S., Ukai, T., Kabata, M., Itakura, F., Semi, K., Matsuda, Y., Hashimoto, K., Shibata, H., Sone, M., Jo, N., Sekiguchi, K., Ohno, T., Akiyama, H., Shimizu, K., Woltjen, K., Ozawa, M., Toguchida, J., **Yamamoto, T.**, & Yamada, Y. (2019). Cell-type dependent enhancer binding of the EWS/ATF1 fusion gene in clear cell sarcomas. ***Nature Communications***, *10*. doi:10.1038/s41467-019-11745-1
23) Mori, S., Sakakura, E., Tsunekawa, Y., Hagiwara, M., Suzuki, T., & **Eiraku, M.** (2019). Self-organized formation of developing appendages from murine pluripotent stem cells. ***Nature Communications***, *10*. doi:10.1038/s41467-019-11702-y
24) Morimoto, H., Kanastu-Shinohara, M., Ogonuki, N., Kamimura, S., Ogura, A., Yabe-Nishimura, C., Mori, Y., Morimoto, T., Watanabe, S., Otsu, K., **Yamamoto, T.**, & Shinohara, T. (2019). ROS amplification drives mouse spermatogonial stem cell self-

renewal. *Life Science Alliance, 2*(2). doi:10.26508/lsa.201900374

25) Niwayama, R., Moghe, P., Liu, Y. J., Fabreges, D., Buchholz, F., Piel, M., & **Hiiragi, T**. (2019). A Tug-of-War between Cell Shape and Polarity Controls Division Orientation to Ensure Robust Patterning in the Mouse Blastocyst. *Developmental Cell, 51*(5), 564-+. doi:10.1016/j.devcel.2019.10.012
26) Onodera, Y., Takimoto, Y., Hijiya, H., Taniguchi, T., Urata, S., Inaba, S., Fujita, S., Obayashi, I., **Hiraoka, Y**., & Kohara, S. (2019). Origin of the mixed alkali effect in silicate glass. *Npg Asia Materials, 11*. doi:10.1038/s41427-019-0180-4
27) Oyama, A., **Hiraoka, Y**., Obayashi, I., Saikawa, Y., Furui, S., Shiraishi, K., Kumagai, S., Hayashi, T., & Kotoku, J. (2019). Hepatic tumor classification using texture and topology analysis of non-contrast-enhanced three-dimensional T1-weighted MR images with a radiomics approach. *Scientific Reports, 9*. doi:10.1038/s41598-019-45283-z
28) Ryan, A. Q., Chan, C. J., Graner, F., & **Hiiragi, T.** (2019). Lumen Expansion Facilitates Epiblast-Primitive Endoderm Fate Specification during Mouse Blastocyst Formation. *Developmental Cell, 51*(6), 684-+. doi:10.1016/j.devcel.2019.10.011
29) Sakakura, M., Ohta, S., Yagi, M., Tanaka, A., Norihide, J., Woltjen, K., **Yamamoto, T.**, & Yamada, Y. (2019). Smarcb1 maintains the cellular identity and the chromatin landscapes of mouse embryonic stem cells. *Biochemical and Biophysical Research Communications, 519*(4), 705-713. doi:10.1016/j.bbrc.2019.09.054
30) Sawai, T., Hatta, T., & **Fujita, M.** (2019). Japan Significantly Relaxes Its Human-Animal Chimeric Embryo Research Regulations. *Cell Stem Cell, 24*(4), 513-514. doi:10.1016/j.stem.2019.03.015
31) Sawai, T., Sakaguchi, H., Thomas, E., Takahashi, J., & **Fujita, M.** (2019). The Ethics of Cerebral Organoid Research: Being Conscious of Consciousness. *Stem Cell Reports, 13*(3), 440-447. doi:10.1016/j.stemcr.2019.08.003
32) Seita, Y., Iwatani, C., Tsuchiya, H., Nakamura, S., Kimura, F., Murakami, T., & **Ema, M.** (2019). Poor second ovarian stimulation in cynomolgus monkeys (Macaca fascicularis) is associated with the production of antibodies against human follicle-stimulating hormone. *Journal of Reproduction and Development, 65*(3), 267-273. doi:10.1262/jrd.2018-156
33) Seita, Y., **Tsukiyama, T.**, Azami, T., Kobayashi, K., Iwatani, C., Tsuchiya, H., Nakaya, M., Tanabe, H., Hitoshi, S., Miyoshi, H., Nakamura, S., Kawauchi, A., & **Ema, M.** (2019). Comprehensive evaluation of ubiquitous promoters suitable for the generation of transgenic cynomolgus monkeys. *Biology of Reproduction, 100*(6), 1440-1452. doi:10.1093/biolre/ioz040
34) Shiba, N., Yoshida, K., Hara, Y., Yamato, G., Shiraishi, Y., Matsuo, H., Okuno, Y., Chiba, K., Tanaka, H., Kaburagi, T., Takeuchi, M., Ohki, K., Sanada, M., Okubo, J., Tomizawa, D., Taki, T., Shimada, A., Sotomatsu, M., Horibe, K., Taga, T., Adachi, S., Tawa, A., Miyano, S., **Ogawa, S.**, & Hayashi, Y. (2019). Transcriptome analysis offers a comprehensive illustration of the genetic background of pediatric acute myeloid leukemia. *Blood Advances, 3*(20), 3157-3169. doi:10.1182/bloodadvances.2019000404
35) Shinzawa, M., Tanaka, S., Tokumasu, H., Takada, D., Tsukamoto, T., **Yanagita, M.**, & Kawakami, K. (2019). Association of Low Birth Weight With Childhood Proteinuria at Age 3 Years: A Population-Based Retrospective Cohort Study. *American Journal of Kidney Diseases, 74*(1), 141-143. doi:10.1053/j.ajkd.2019.02.018
36) Sugiyama, Y., Oishi, T., Yamashita, A., Murata, Y., Yamamoto, T., Takashima, I., **Isa, T.**, & Higo, N. (2019). Neuronal and microglial localization of secreted phosphoprotein 1 (osteopontin) in intact and damaged motor cortex of macaques. *Brain Research, 1714*, 52-64. doi:10.1016/j.brainres.2019.02.021
37) Suzuki, M., Onoe, K., Sawada, M., Takahashi, N., Higo, N., Murata, Y., Tsukada, H., **Isa, T.**, Onoe, H., & Nishimura, Y. (2019). The Ventral Striatum is a Key Node for Functional

Recovery of Finger Dexterity After Spinal Cord Injury in Monkeys. ***Cereb Cortex***. doi:10.1093/cercor/bhz307

38) Terada, Y., Jo, N., Arakawa, Y., Sakakura, M., Yamada, Y., Ukai, T., Kabata, M., Mitsunaga, K., Mineharu, Y., Ohta, S., Nakagawa, M., Miyamoto, S., **Yamamoto, T.** & Yamada Y. (2019). Human Pluripotent Stem Cell-Derived Tumor Model Uncovers the Embryonic Stem Cell Signature as a Key Driver in Atypical Teratoid/Rhabdoid Tumor. ***Cell Reports***, *26*(10), 2608-+. doi:10.1016/j.celrep.2019.02.009
39) **Tsukiyama, T.**, Kobayashi, K., Nakaya, M., Iwatani, C., Seita, Y., Tsuchiya, H., Matsushita, J., Kitajima, K., Kawamoto, I., Nakagawa, T., Fukuda, K., Iwakiri, T., Izumi, H., Itagaki, I., Kume, S., Maegawa, H., Nishinakamura, R., Nishio, S., Nakamura, S., Kawauchi, A., & **Ema, M.** (2019). Monkeys mutant for PKD1 recapitulate human autosomal dominant polycystic kidney disease. ***Nature Communications***, *10*. doi:10.1038/s41467-019-13398-6
40) Umeda, T., **Isa, T.**, & Nishimura, Y. (2019). The somatosensory cortex receives information about motor output. ***Science Advances***, *5*(7). doi:10.1126/sciadv.aaw5388
41) Wu, H. C., Witzl, A., & **Ueno, H.** (2019). Assessment of TCR signal strength of antigen-specific memory CD8(+) T cells in human blood. ***Blood Advances***, *3*(14), 2153-2163. doi:10.1182/bloodadvances.2019000292
42) Yagi, M., Kabata, M., Ukai, T., Ohta, S., Tanaka, A., Shimada, Y., Sugimoto, M., Araki, K., Okita, K., Woltjen, K., Hochedlinger, K., **Yamamoto, T.**, & Yamada, Y. (2019). De Novo DNA Methylation at Imprinted Loci during Reprogramming into Naive and Primed Pluripotency. ***Stem Cell Reports***, *12*(5), 1113-1128. doi:10.1016/j.stemcr.2019.04.008

2. Review articles

43) Chan, C. J., & **Hiiragi, T**. (2020). Integration of luminal pressure and signalling in tissue self-organization. ***Development***, *147*(5). doi:10.1242/dev.181297
44) **Ogawa, S**. (2020). Genetic basis of myelodysplastic syndromes. ***Proceedings of the Japan Academy, Series B***, *96*(3), 107-121. doi:https://doi.org/10.2183/pjab.96.009
45) **Ueno, H**. (2020). The IL-12-STAT4 axis in the pathogenesis of human systemic lupus erythematosus. ***European Journal of Immunology***, *50*(1), 10-16. doi:10.1002/eji.201948134
46) Hamidi, S., Nakaya, Y., Nagai, H., **Alev, C.**, Shibata, T., & Sheng, G. J. (2019). Biomechanical regulation of EMT and epithelial morphogenesis in amniote epiblast. ***Physical Biology***, *16*(4). doi:10.1088/1478-3975/ab1048
47) **Isa, T.** (2019). Dexterous Hand Movements and Their Recovery After Central Nervous System Injury. ***Annu Rev Neurosci***, *42*, 315-335. doi:10.1146/annurev-neuro-070918-050436
48) **Isa, T**., Mitsuhashi, M., & Yamaguchi, R. (2019). Alternative routes for recovery of hand functions after corticospinal tract injury in primates and rodents. ***Current Opinion in Neurology***, *32*(6), 836-843. doi:10.1097/wco.0000000000000749
49) Kurimoto, K., & **Saitou, M.** (2019). Germ cell reprogramming. In R. Lehmann (Ed.), ***Immortal Germline*** (Vol. 135, pp. 91-125).
50) Sato, Y., & **Yanagita, M**. (2019). Functional heterogeneity of resident fibroblasts in the kidney. ***Proceedings of the Japan Academy Series B-Physical and Biological Sciences***, *95*(8), 468-478. doi:10.2183/pjab.95.033
51) Sato, Y., & **Yanagita, M**. (2019). Immunology of the ageing kidney. ***Nature Reviews Nephrology***, *15*(10), 625-640. doi:10.1038/s41581-019-0185-9
52) Sato, Y., & **Yanagita, M**. (2019). The unprecedented era of aging. ***Inflammation and Regeneration***, *39*. doi:10.1186/s41232-019-0104-2
53) **Ueno, H**. (2019). Tfh cell response in influenza vaccines in humans: what is visible and

what is invisible. ***Current Opinion in Immunology***, *59*, 9-14. doi:10.1016/j.coi.2019.02.007

54) **Yoshitomi, H.** (2019). Regulation of Immune Responses and Chronic Inflammation by Fibroblast-Like Synoviocytes. ***Frontiers in Immunology***, *10*. doi:10.3389/fimmu.2019.01395

3. Proceedings

4. Other articles

55) McIntyre, Brendan, Asahara, Takayuki, & **Alev, Cantas.** (2020). Overview of basic mechanisms of Notch signaling in development and disease. In ***Notch Signaling in Embryology and Cancer*** (pp. 9-27): Springer.

[WPI related Papers]

1. Original Articles

56) 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

57) 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

58) 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

59) Madan, V., Li, J., Zhou, S. Q., Teoh, W. W., Han, L., Meggendorfer, M., Malcovati, L., Cazzola, M., **Ogawa, S.**, Haferlach, T., Yang, H., & Koeffler, H. P. (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

60) 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. ***Intern Med***, *59*(8), 1081-1086. doi:10.2169/internalmedicine.3770-19

61) 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

62) 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 Res***. doi:10.1158/0008-5472.CAN-19-2787

63) 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. C.R, & Plo, I. (2020). TET2 haploinsufficiency alters reprogramming into induced pluripotent stem cells. ***Stem Cell Res***, *44*, 101755. doi:10.1016/j.scr.2020.101755

64) 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

65) Adachi, M, Yoshida, K, Shiraishi, Y, Chiba, K, Miyano, S, & **Ogawa, S**. (2019). Successful treatment of pure red cell aplasia with cyclosporin in a patient with T-cell large granular lymphocytic leukemia harboring the STAT3 D661V mutation. ***[Rinsho ketsueki] The Japanese journal of clinical hematology***, *60*(1), 39-45. doi:10.11406/rinketsu.60.39

66) Ahn, J. S., Kim, T., Kim, Y. K., Cho, Y. C., Cho, S., Jung, S. N., Ahn, S. Y., Jung, S. Y., Yang, D. H., Lee, J. J., Choi, S., Lee, J. Y., Shin, M. G., Yoshida, K., **Ogawa, S.**, Kim, I. C., Zhang, Z. L., Kim, H. J., & Kim, D. D. H. (2019). Remission clone in acute myeloid leukemia shows growth advantage after chemotherapy but is distinct from leukemic clone. ***Experimental Hematology***, *75*, 26-30. doi:10.1016/j.exphem.2019.06.001

67) Becker, H., Greve, G., Kataoka, K., Mallm, J. P., Duque-Afonso, J., Ma, T., Niemoller, C., Pantic, M., Duyster, J., Cleary, M. L., Schuler, J., Rippe, K., **Ogawa, S.**, & Lubbert, M. (2019). Identification of enhancer of mRNA decapping 4 as a novel fusion partner of MLL in acute myeloid leukemia. ***Blood Advances***, *3*(5), 761-765. doi:10.1182/bloodadvances.2018023879

68) Bourgey, M., Dali, R., Eveleigh, R., Chen, K. C., Letourneau, L., Fillon, J., Michaud, M., Caron, M., Sandoval, J., Lefebvre, F., Leveque, G., Mercier, E., Bujold, D., Marquis, P., Van, P. T., Morais, D. A. D., Tremblay, J., Shao, X. J., Henrion, E., Gonzalez, E., Quirion, P. O., Caron, B., & **Bourque, G.** (2019). GenPipes: an open-source framework for distributed and scalable genomic analyses. ***Gigascience***, *8*(6). doi:10.1093/gigascience/giz037

69) Breeze, C. E., Reynolds, A. P., van Dongen, J., Dunham, I., Lazar, J., Neph, S., Vierstra, J., **Bourque, G.**, Teschendorff, A. E., Stamatoyannopoulos, J. A., & Beck, S. (2019). eFORGE v2.0: updated analysis of cell type-specific signal in epigenomic data. ***Bioinformatics***, *35*(22), 4767-4769. doi:10.1093/bioinformatics/btz456

70) Caielli, S., Veiga, D. T., Balasubramanian, P., Athale, S., Domic, B., Murat, E., Banchereau, R., Xu, Z. H., Chandra, M., Chung, C. H., Walters, L., Baisch, J., Wright, T., Punaro, M., Nassi, L., Stewart, K., Fuller, J., Ucar, D., **Ueno, H.**, Zhou, J., Banchereau, J., & Pascual, V. (2019). A CD4(+) T cell population expanded in lupus blood provides B cell help through interleukin-10 and succinate. ***Nature Medicine***, *25*(1), 75-+. doi:10.1038/s41591-018-0254-9

71) Cao-Sy, L., Obara, N., Sakamoto, T., Kato, T., Hattori, K., Sakashita, S., Nannya, Y., **Ogawa, S.**, Harada, H., Sakata-Yanagimoto, M., Nishikii, H., & Chiba, S. (2019). Prominence of nestin-expressing Schwann cells in bone marrow of patients with myelodysplastic syndromes with severe fibrosis. ***International Journal of Hematology***, *109*(3), 309-318. doi:10.1007/s12185-018-02576-9

72) Chan, D., Shao, X. J., Dumargne, M. C., Aarabi, M., Simon, M. M., Kwan, T., Bailey, J. L., Robaire, B., Kimmins, S., San Gabriel, M. C., Zini, A., Librach, C., Moskowtsev, S., Grundberg, E., **Bourque, G.**, Pastinen, T., & Trasler, J. M. (2019). Customized MethylC-Capture Sequencing to Evaluate Variation in the Human Sperm DNA Methylome

Representative of Altered Folate Metabolism. *Environmental Health Perspectives, 127*(8). doi:10.1289/ehp4812

73) Chang, S. H., Mori, D., Kobayashi, H., Mori, Y., Nakamoto, H., Okada, K., Taniguchi, Y., Sugita, S., Yano, F., Chung, U., Kim-Kaneyama, J., **Yanagita, M.**, Economides, A., Canalis, E., Chen, D., Tanaka, S., & Saito, T. (2019). Excessive mechanical loading promotes osteoarthritis through the gremlin-1-NF-kappa B pathway. *Nature Communications, 10*. doi:10.1038/s41467-019-09491-5
74) Chao, Z. C., Sawada, M., **Isa, T.**, & Nishimura, Y. (2019). Dynamic Reorganization of Motor Networks During Recovery from Partial Spinal Cord Injury in Monkeys. *Cerebral Cortex, 29*(7), 3059-3073. doi:10.1093/cercor/bhy172
75) Chehboun, S., Leiva-Torres, G. A., Charbonneau, B., Eveleigh, R., **Bourque, G.**, & Vidal, S. M. (2020). A point mutation in the linker domain of mouse STAT5A is associated with impaired NK-cell regulation. *Genes Immun, 21*(2), 136-141. doi:10.1038/s41435-019-0088-6
76) Chonabayashi, K., Yoshida, Y., Kitawaki, T., Nannya, Y., Nakamura, M., Oshima, S., Hishizawa, M., Yamashita, K., **Ogawa, S.**, & Takaori-Kondo, A. (2019). Acute myeloid leukemia with a cryptic NUP98/PRRX2 rearrangement developing after low-dose methotrexate therapy for rheumatoid arthritis. *Annals of Hematology, 98*(12), 2841-2843. doi:10.1007/s00277-019-03838-0
77) Christen, F., Hoyer, K., Yoshida, K., Hou, H. A., Waldhueter, N., Heuser, M., Hills, R. K., Chan, W., Hablesreiter, R., Blau, O., Ochi, Y., Klement, P., Chou, W. C., Blau, I. W., Tang, J. L., Zemojtel, T., Shiraishi, Y., Shiozawa, Y., Thol, F., Ganser, A., Lowenberg, B., Linch, D. C., Bullinger, L., Valk, P. J. M., Tien, H. F., Gale, R. E., **Ogawa, S.**, & Damm, F. (2019). Genomic landscape and clonal evolution of acute myeloid leukemia with t(8;21): an international study on 331 patients. *Blood, 133*(10), 1140-1151. doi:10.1182/blood-2018-05-852822
78) Chung, E. Y., Mai, Y., Shah, U. A., Wei, Y. Q., Ishida, E., Kataoka, K., Ren, X. X., Pradhan, K., Bartholdy, B., Wei, X. L., Zou, Y. Y., Zhang, J. H., **Ogawa, S.**, Steidl, U., Zang, X. X., Verma, A., Janakiram, M., & Ye, B. H. (2019). PAK Kinase Inhibition Has Therapeutic Activity in Novel Preclinical Models of Adult T-Cell Leukemia/Lymphoma. *Clinical Cancer Research, 25*(12), 3589-3601. doi:10.1158/1078-0432.ccr-18-3033
79) Elbadry, M. I., Mizumaki, H., Hosokawa, K., Espinoza, J. L., Nakagawa, N., Chonabayashi, K., Yoshida, Y., Katagiri, T., Hosomichi, K., Zaimoku, Y., Imi, T., Nguyen, M. A. T., Fujii, Y., Tajima, A., **Ogawa, S.**, Takenaka, K., Akashi, K., & Nakao, S. (2019). Escape hematopoiesis by HLA-B5401-lacking hematopoietic stem progenitor cells in men with acquired aplastic anemia. *Haematologica, 104*(10), E447-E450. doi:10.3324/haematol.2018.210856
80) Frick, M., Chan, W., Arends, C. M., Hablesreiter, R., Halik, A., Heuser, M., Michonneau, D., Blau, O., Hoyer, K., Christen, F., Galan-Sousa, J., Noerenberg, D., Wais, V., Stadler, M., Yoshida, K., Schetelig, J., Schuler, E., Thol, F., Clappier, E., Christopeit, M., Ayuk, F., Bornhauser, M., Blau, I. W., **Ogawa, S.**, Zemojtel, T., Gerbitz, A., Wagner, E. M., Spriewald, B. M., Schrezenmeier, H., Kuchenbauer, F., Kobbe, G., Wiesneth, M., Koldehoff, M., Socie, G., Kroeger, N., Bullinger, L., Thiede, C., & Damm, F. (2019). Role of Donor Clonal Hematopoiesis in Allogeneic Hematopoietic Stem-Cell Transplantation. *Journal of Clinical Oncology, 37*(5), 375-+. doi:10.1200/jco.2018.79.2184
81) Funakoshi, T., Miyamoto, S., Kakiuchi, N., Nikaido, M., Setoyama, T., Yokoyama, A., Horimatsu, T., Yamada, A., Torishima, M., Kosugi, S., Yamada, H., Sugimura, H., Haga, H., Sakai, Y., **Ogawa, S.**, Seno, H., Muto, M., & Chiba, T. (2019). Genetic analysis of a case of Helicobacter pylori-uninfected intramucosal gastric cancer in a family with hereditary diffuse gastric cancer. *Gastric Cancer, 22*(4), 892-898. doi:10.1007/s10120-018-00912-w

82) Grajcarek, J., Monlong, J., Nishinaka-Arai, Y., Nakamura, M., Nagai, M., Matsuo, S., Lougheed, D., Sakurai, H., Saito, M. K., **Bourque, G.**, & Woltjen, K. (2019). Genome-wide microhomologies enable precise template-free editing of biologically relevant deletion mutations. ***Nature Communications**, 10*. doi:10.1038/s41467-019-12829-8

83) Gu, M., 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. (2019). RNAmut: robust identification of somatic mutations in acute myeloid leukemia using RNA-seq. ***Haematologica***. doi:10.3324/haematol.2019.230821

84) Haase, D., Stevenson, K. E., Neuberg, D., Maciejewski, J. P., Nazha, A., Sekeres, M. A., Ebert, B. L., Garcia-Manero, G., Haferlach, C., Haferlach, T., Kern, W., **Ogawa, S.,** Nagata, Y., Yoshida, K., Graubert, T. A., Walter, M. J., List, A. F., Komrokji, R. S., Padron, E., Sallman, D., Papaemmanuil, E., Campbell, P. J., Savona, M. R., Seegmiller, A., Ades, L., Fenaux, P., Shih, L. Y., Bowen, D., Groves, M. J., Tauro, S., Fontenay, M., Kosmider, O., Bar-Natan, M., Steensma, D., Stone, R., Heuser, M., Thol, F., Cazzola, M., Malcovati, L., Karsan, A., Ganster, C., Hellstrom-Lindberg, E., Boultwood, J., Pellagatti, A., Santini, V., Quek, L., Vyas, P., Tuchler, H., Greenberg, P. L., Bejar, R., & Int Working Grp, M. D. S. Mol Progno. (2019). TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. ***Leukemia**, 33*(7), 1747-1758. doi:10.1038/s41375-018-0351-2

85) Hirano, K., Kobayashi, D., Kohtani, N., Uemura, Y., Ohashi, Y., Komatsu, Y., **Yanagita, M.**, & Hishida, A. (2019). Optimal follow-up intervals for different stages of chronic kidney disease: a prospective observational study. ***Clinical and Experimental Nephrology**, 23*(5), 613-620. doi:10.1007/s10157-018-01684-4

86) Hirata, K., Kodama, S., Nakano, Y., Minaki-Nakagawa, Y., Aoyama, Y., Sakikubo, M., Goto, T., Yoshida, M., Masui, T., **Yamamoto, T.**, Uemoto, S., & Kawaguchi, Y. (2019). Exocrine tissue-driven TFF2 prevents apoptotic cell death of endocrine lineage during pancreas organogenesis. ***Scientific Reports**, 9*. doi:10.1038/s41598-018-38062-9

87) Hoshino, A., Yang, X., Tanita, K., Yoshida, K., Ono, T., Nishida, N., Okuno, Y., Kanzaki, T., Goi, K., Fujino, H., Ohshima, K., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., **Ogawa, S.**, Kojima, S., Morio, T., & Kanegane, H. (2019). Modification of cellular and humoral immunity by somatically reverted T cells in X-linked lymphoproliferative syndrome type 1. ***Journal of Allergy and Clinical Immunology**, 143*(1), 421-+. doi:10.1016/j.jaci.2018.07.044

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

89) Jessa, S., Blanchet-Cohen, A., Krug, B., Vladoiu, M., Coutelier, M., Faury, D., Poreau, B., De Jay, N., Hebert, S., Monlong, J., Farmer, W. T., Donovan, L. K., Hu, Y. X., McConechy, M. K., Cavalli, F. M. G., Mikael, L. G., Ellezam, B., Richer, M., Allaire, A., Weil, A. G., Atkinson, J., Farmer, J. P., Dudley, R. W. R., Larouche, V., Crevier, L., Albrecht, S., Filbin, M. G., Sartelet, H., Lutz, P. E., Nagy, C., Turecki, G., Costantino, S., Dirks, P. B., Murai, K. K., **Bourque, G.**, Ragoussis, J., Garzia, L., Taylor, M. D., Jabado, N., & Kleinman, C. L. (2019). Stalled developmental programs at the root of pediatric brain tumors. ***Nature Genetics**, 51*(12), 1702-+. doi:10.1038/s41588-019-0531-7

90) Kagawa, H., Shimamoto, R., Kim, S. I., Oceguera-Yanez, F., **Yamamoto, T.**, Schroeder, T., & Woltjen, K. (2019). OVOL1 Influences the Determination and Expansion of iPSC Reprogramming Intermediates. ***Stem Cell Reports**, 12*(2), 319-332.

doi:10.1016/j.stemcr.2018.12.008

91) Kanatsu-Shinohara, M., **Yamamoto, T.**, Toh, H., Kazuki, Y., Kazuki, K., Imoto, J., Ikeo, K., Oshima, M., Shirahige, K., Iwama, A., Nabeshima, Y., Sasaki, H., & Shinohara, T. (2019). Aging of spermatogonial stem cells by Jnk-mediated glycolysis activation. ***Proceedings of the National Academy of Sciences of the United States of America***, *116*(33), 16404-16409. doi:10.1073/pnas.1904980116

92) 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. (2019). Predisposed genomic instability in pre-treatment bone marrow evolves to therapy-related myeloid neoplasms in malignant lymphoma. ***Haematologica***. doi:10.3324/haematol.2019.229856

93) Kataoka, K., Miyoshi, H., Sakata, S., Dobashi, A., Couronne, L., Kogure, Y., Sato, Y., Nishida, K., Gion, Y., Shiraishi, Y., Tanaka, H., Chiba, K., Watatani, Y., Kakiuchi, N., Shiozawa, Y., Yoshizato, T., Yoshida, K., Makishima, H., Sanada, M., Onozawa, M., Teshima, T., Yoshiki, Y., Ishida, T., Suzuki, K., Shimada, K., Tomita, A., Kato, M., Ota, Y., Izutsu, K., Demachi-Okamura, A., Akatsuka, Y., Miyano, S., Yoshino, T., Gaulard, P., Hermine, O., Takeuchi, K., Ohshima, K., & **Ogawa, S.** (2019). Frequent structural variations involving programmed death ligands in Epstein-Barr virus-associated lymphomas. ***Leukemia***, *33*(7), 1687-1699. doi:10.1038/s41375-019-0380-5

94) Kataoka, S., Nishikawa, Y., Funakoshi, T., Horimatsu, T., Kondo, N., Matsubara, T., **Yanagita, M.**, Matsumoto, S., & Muto, M. Long-term survival and renal dysfunction in a patient with recurrent colorectal cancer treated with Bevacizumab. ***Clinical Journal of Gastroenterology***. doi:10.1007/s12328-019-01060-z

95) Kawai, S., Yoshitomi, H., Sunaga, J., **Alev, C.**, Nagata, S., Nishio, M., Hada, M., Koyama, Y., Uemura, M., Sekiguchi, K., Maekawa, H., Ikeya, M., Tamaki, S., Jin, Y., Harada, Y., Fukiage, K., Adachi, T., Matsuda, S., & Toguchida, J. (2019). In vitro bone-like nodules generated from patient-derived iPSCs recapitulate pathological bone phenotypes. ***Nat Biomed Eng***, *3*(7), 558-570. doi:10.1038/s41551-019-0410-7

96) Kawashima, N., Akashi, A., Nagata, Y., Kihara, R., Ishikawa, Y., Asou, N., Ohtake, S., Miyawaki, S., Sakura, T., Ozawa, Y., Usui, N., Kanamori, H., Ito, Y., Imai, K., Suehiro, Y., Kitamura, K., Sakaida, E., Takeshita, A., Suzushima, H., Naoe, T., Matsumura, I., Miyazaki, Y., **Ogawa, S.**, Kiyoi, H., & Japan Adult Leukemia Study, Grp. (2019). Clinical significance of ASXL2 and ZBTB7A mutations and C-terminally truncated RUNX1-RUNX1T1 expression in AML patients with t(8;21) enrolled in the JALSG AML201 study. ***Annals of Hematology***, *98*(1), 83-91. doi:10.1007/s00277-018-3492-5

97) Kim, S. K., Takeda, H., Takai, A., Matsumoto, T., Kakiuchi, N., Yokoyama, A., Yoshida, K., Kaido, T., Uemoto, S., Minamiguchi, S., Haga, H., Shiraishi, Y., Miyano, S., Seno, H., **Ogawa, S.**, & Marusawa, H. (2019). Comprehensive analysis of genetic aberrations linked to tumorigenesis in regenerative nodules of liver cirrhosis. ***Journal of Gastroenterology***, *54*(7), 628-640. doi:10.1007/s00535-019-01555-z

98) Kimura, S., Hasegawa, D., Yoshimoto, Y., Seki, M., Daida, A., Sekiguchi, M., Hirabayashi, S., Hosoya, Y., Kobayashi, M., Miyano, S., **Ogawa, S.**, Takita, J., & Manabe, A. (2019). Duplication of ALK F1245 missense mutation due to acquired uniparental disomy associated with aggressive progression in a patient with relapsed neuroblastoma. ***Oncology Letters***, *17*(3), 3323-3329. doi:10.3892/ol.2019.9985

99) Kimura, S., Seki, M., Yoshida, K., Shiraishi, Y., Akiyama, M., Koh, K., Imamura, T., Manabe, A., Hayashi, Y., Kobayashi, M., Oka, A., Miyano, S., **Ogawa, S.**, & Takita, J. (2019). NOTCH1 pathway activating mutations and clonal evolution in pediatric T-cell acute lymphoblastic leukemia. ***Cancer Science***, *110*(2), 784-794. doi:10.1111/cas.13859

100) Kinashi, H., Toda, N., Sun, T., Nguyen, T. Q., Suzuki, Y., Katsuno, T., Yokoi, H., Aten, J.,

Mizuno, M., Maruyama, S., **Yanagita, M.**, Goldschmeding, R., & Ito, Y. (2019). Connective tissue growth factor is correlated with peritoneal lymphangiogenesis. *Scientific Reports, 9*. doi:10.1038/s41598-019-48699-9

101) Kitadate, Y., Jorg, D. J., Tokue, M., Maruyama, A., Ichikawa, R., Tsuchiya, S., Segi-Nishida, E., Nakagawa, T., Uchida, A., Kimura-Yoshida, C., Mizuno, S., Sugiyama, F., Azami, T., **Ema, M.**, Noda, C., Kobayashi, S., Matsuo, I., Kanai, Y., Nagasawa, T., Sugimoto, Y., Takahashi, S., Simons, B. D., & Yoshida, S. (2019). Competition for Mitogens Regulates Spermatogenic Stem Cell Homeostasis in an Open Niche. *Cell Stem Cell, 24*(1), 79-+. doi:10.1016/j.stem.2018.11.013

102) Kobayashi, K., Mizuta, S., Yamane, N., Ueno, H., Yoshida, K., Kato, I., Umeda, K., Hiramatsu, H., Suehiro, M., Maihara, T., Usami, I., Shiraishi, Y., Chiba, K., Miyano, S., Adachi, S., **Ogawa, S.**, Kiyokawa, N., & Heike, T. (2019). Paraneoplastic hypereosinophilic syndrome associated with IL3-IgH positive acute lymphoblastic leukemia. *Pediatric Blood & Cancer, 66*(1). doi:10.1002/pbc.27449

103) Kohara, H., Utsugisawa, T., Sakamoto, C., Hirose, L., Ogawa, Y., Ogura, H., Sugawara, A., Liao, J. Y., Aoki, T., Iwasaki, T., Asai, T., Doisaki, S., Okuno, Y., Muramatsu, H., Abe, T., Kurita, R., Miyamoto, S., Sakuma, T., Shiba, M., Yamamoto, T., Ohga, S., Yoshida, K., **Ogawa, S.**, Ito, E., Kojima, S., Kanno, H., & Tani, K. (2019). KLF1 mutation E325K induces cell cycle arrest in erythroid cells differentiated from congenital dyserythropoietic anemia patient-specific induced pluripotent stem cells. *Experimental Hematology, 73*, 25-37. doi:10.1016/j.exphem.2019.03.001

104) Koizumi, M., Ueda, K., Niimura, F., Nishiyama, A., **Yanagita, M.**, Saito, A., Pastan, I., Fujita, T., Fukagawa, M., & Matsusaka, T. (2019). Podocyte Injury Augments Intrarenal Angiotensin II Generation and Sodium Retention in a Megalin-Dependent Manner. *Hypertension, 74*(3), 509-517. doi:10.1161/hypertensionaha.118.12352

105) Kotani, S., Yoda, A., Kon, A., Kataoka, K., Ochi, Y., Shiozawa, Y., Hirsch, C., Takeda, J., Ueno, H., Yoshizato, T., Yoshida, K., Nakagawa, M. M., Nannya, Y., Kakiuchi, N., Yamauchi, T., Aoki, K., Shiraishi, Y., Miyano, S., Maeda, T., Maciejewski, J. P., Takaori-Kondo, A., **Ogawa, S.**, & Makishima, H. (2019). Molecular pathogenesis of disease progression in MLL-rearranged AML. *Leukemia, 33*(3), 612-624. doi:10.1038/s41375-018-0253-3

106) Kubota, Y., Arakawa, Y., Sekiguchi, M., Watanabe, K., Hiwatari, M., Kishimoto, H., Nakazawa, A., Yoshida, A., **Ogawa, S.**, Hanada, R., Oka, A., Takita, J., & Koh, K. (2019). A case of malignant rhabdoid tumor mimicking yolk sac tumor. *Pediatric Blood & Cancer, 66*(8). doi:10.1002/pbc.27784

107) Kubota, Y., Uryu, K., Ito, T., Seki, M., Kawai, T., Isobe, T., Kumagai, T., Toki, T., Yoshida, K., Suzuki, H., Kataoka, K., Shiraishi, Y., Chiba, K., Tanaka, H., Ohki, K., Kiyokawa, N., Kagawa, J., Miyano, S., Oka, A., Hayashi, Y., **Ogawa, S.**, Terui, K., Sato, A., Hata, K., Ito, E., & Takita, J. (2019). Integrated genetic and epigenetic analysis revealed heterogeneity of acute lymphoblastic leukemia in Down syndrome. *Cancer Science, 110*(10), 3358-3367. doi:10.1111/cas.14160

108) Labuhn, M., Perkins, K., Matzk, S., Varghese, L., Garnett, C., Papaemmanuil, E., Metzner, M., Kennedy, A., Amstislavskiy, V., Risch, T., Bhayadia, R., Samulowski, D., Hernandez, D. C., Stoilova, B., Lotchkova, V., Oppermann, U., Scheer, C., Yoshida, K., Schwarzer, A., Taub, J., Crispino, J. D., Weiss, M. J., Hayashi, A., Taga, T., Ito, E., **Ogawa, S.**, Reinhardt, D., Yaspo, M. L., Campbell, P. J., Roberts, I., Constantinescu, S., Vyas, P., Heckl, D., & Klusmann, J. H. (2019). Mechanisms of Progression of Myeloid Preleukemia to Transformed Myeloid Leukemia in Children with Down Syndrome. *Cancer Cell, 36*(2), 123-+. doi:10.1016/j.ccell.2019.06.007

109) Laperle, J., Hebert-Deschamps, S., Raby, J., Morais, D. A. D., Barrette, M., Bujold, D.,

Bastin, C., Robert, M. A., Nadeau, J. F., Harel, M., Nordell-Markovits, A., Veilleux, A., **Bourque, G.**, & Jacques, P. E. (2019). The epiGenomic Efficient Correlator (epiGeEC) tool allows fast comparison of user datasets with thousands of public epigenomic datasets. ***Bioinformatics**, 35*(4), 674-676. doi:10.1093/bioinformatics/bty655

110) Masaki, S., Ikeda, S., Hata, A., Shiozawa, Y., Kona, A., **Ogawa, S.**, Suzuki, K., Hakuno, F., Takahashi, S. I., & Kataoka, N. (2019). Myelodysplastic Syndrome-Associated SRSF2 Mutations Cause Splicing Changes by Altering Binding Motif Sequences. ***Frontiers in Genetics**, 10*. doi:10.3389/fgene.2019.00338

111) Matsui, S., Ochiai, M., Yasuda, K., Mae, S., Kotaka, M., Toyoda, T., **Yamamoto, T.**, & Osafune, K. (2019). Differentiation and isolation of iPSC-derived remodeling ductal plate-like cells by use of an AQP1-GFP reporter human iPSC line. ***Stem Cell Research**, 35*. doi:10.1016/j.scr.2019.101400

112) 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. (2019). Pathogenic mutations identified by a multimodality approach in 117 Japanese Fanconi anemia patients. ***Haematologica**, 104*(10), 1962-1973. doi:10.3324/haematol.2018.207241

113) Mori, T., Takaoka, H., Yamane, J., **Alev, C**., & Fujibuchi, W. (2019). Novel computational model of gastrula morphogenesis to identify spatial discriminator genes by self-organizing map (SOM) clustering. ***Scientific Reports**, 9*. doi:10.1038/s41598-019-49031-1

114) Murakami, M, Kohara, S, Kitamura, N, Akola, J, Inoue, H, Hirata, A, **Hiraoka, Y**, Onodera, Y, Obayashi, I, Kalikka, J, Hirao, N, Musso, T, Foster, AS, Idemoto, Y, Sakata, O, & Ohishi, Y. (2019). Ultrahigh-pressure form of Si O 2 glass with dense pyrite-type crystalline homology. ***Physical Review B**, 99*(4), 045153. doi:https://doi.org/10.1103/PhysRevB.99.045153

115) Mutzel, V., Okamoto, I., Dunkel, I., **Saitou, M.**, Giorgetti, L., Heard, E., & Schulz, E. G. (2019). A symmetric toggle switch explains the onset of random X inactivation in different mammals. ***Nature Structural & Molecular Biology**, 26*(5), 350-+. doi:10.1038/s41594-019-0214-1

116) Nagao, Y., Mimura, N., Takeda, J., Yoshida, K., Shiozawa, Y., Oshima, M., Aoyama, K., Saraya, A., Koide, S., Rizq, O., Hasegawa, Y., Shiraishi, Y., Chiba, K., Tanaka, H., Nishijima, D., Isshiki, Y., Kayamori, K., Kawajiri-Manako, C., Oshima-Hasegawa, N., Tsukamoto, S., Mitsukawa, S., Takeda, Y., Ohwada, C., Takeuchi, M., Iseki, T., Misawa, S., Miyano, S., Ohara, O., Yokote, K., Sakaida, E., Kuwabara, S., Sanada, M., Iwama, A., **Ogawa, S.**, & Nakaseko, C. (2019). Genetic and transcriptional landscape of plasma cells in POEMS syndrome. ***Leukemia**, 33*(7), 1723-1735. doi:10.1038/s41375-018-0348-x

117) Nagata, Y., Makishima, H., Kerr, C. M., Przychodzen, B. P., Aly, M., Goyal, A., Awada, H., Asad, M. F., Kuzmanovic, T., Suzuki, H., Yoshizato, T., Yoshida, K., Chiba, K., Tanaka, H., Shiraishi, Y., Miyano, S., Mukherjee, S., LaFramboise, T., Nazha, A., Sekeres, M. A., Radivoyevitch, T., Haferlach, T., **Ogawa, S.**, & Maciejewski, J. P. (2019). Invariant patterns of clonal succession determine specific clinical features of myelodysplastic syndromes. ***Nature Communications**, 10*. doi:10.1038/s41467-019-13001-y

118) Nakamura, J., Sato, Y., Kitai, Y., Wajima, S., Yamamoto, S., Oguchi, A., Yamada, R., Kaneko, K., Kondo, M., Uchino, E., Tsuchida, J., Hirano, K., Sharma, K., Kohno, K., & **Yanagita, M.** (2019). Myofibroblasts acquire retinoic acid-producing ability during fibroblast-to-myofibroblast transition following kidney injury. ***Kidney International**, 95*(3), 526-539. doi:10.1016/j.kint.2018.10.017

119) Nakano, D., Kitada, K., Wan, N., Zhang, Y., Wiig, H., Wararat, K., **Yanagita, M.**, Lee, S.,

Jia, L., Titze, J. M., & Nishiyama, A. (2020). Lipopolysaccharide induces filtrate leakage from renal tubular lumina into the interstitial space via a proximal tubular Toll-like receptor 4-dependent pathway and limits sensitivity to fluid therapy in mice. *Kidney Int, 97*(5), 904-912. doi:10.1016/j.kint.2019.11.024

120) Okano, T., Imai, K., Tsujita, Y., Mitsuiki, N., Yoshida, K., Kamae, C., Honma, K., Mitsui-Sekinaka, K., Sekinaka, Y., Kato, T., Hanabusa, K., Endo, E., Takashima, T., Hiroki, H., Yeh, T. W., Tanaka, K., Nagahori, M., Tsuge, I., Bando, Y., Iwasaki, F., Shikama, Y., Inoue, M., Kimoto, T., Moriguchi, N., Yuza, Y., Kaneko, T., Suzuki, K., Matsubara, T., Maruo, Y., Kunitsu, T., Waragai, T., Sano, H., Hashimoto, Y., Tasaki, K., Suzuki, O., Shirakawa, T., Kato, M., Uchiyama, T., Ishimura, M., Tauchi, T., Yagasaki, H., Jou, S. T., Yu, H. H., Kanegane, H., Kracker, S., Durandy, A., Kojima, D., Muramatsu, H., Wada, T., Inoue, Y., Takada, H., Kojima, S., **Ogawa, S.**, Ohara, O., Nonoyama, S., & Morio, T. (2019). Hematopoietic stem cell transplantation for progressive combined immunodeficiency and lymphoproliferation in patients with activated phosphatidylinositol-3-OH kinase delta syndrome type 1. *Journal of Allergy and Clinical Immunology, 143*(1), 266-275. doi:10.1016/j.jaci.2018.04.032

121) Okuno, Y., Murata, T., Sato, Y., Muramatsu, H., Ito, Y., Watanabe, T., Okuno, T., Murakami, N., Yoshida, K., Sawada, A., Inoue, M., Kawa, K., Seto, M., Ohshima, K., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., Narita, Y., Yoshida, M., Goshima, F., Kawada, J. I., Nishida, T., Kiyoi, H., Kato, S., Nakamura, S., Morishima, S., Yoshikawa, T., Fujiwara, S., Shimizu, N., Isobe, Y., Noguchi, M., Kikuta, A., Iwatsuki, K., Takahashi, Y., Kojima, S., **Ogawa, S.**, & Kimura, H. (2019). Defective Epstein-Barr virus in chronic active infection and haematological malignancy (vol 4, pg 404, 2019). *Nature Microbiology, 4*(3), 544-544. doi:10.1038/s41564-019-0387-8

122) Ono, S., Matsuda, J., Watanabe, E., Akaike, H., Teranishi, H., Miyata, I., Otomo, T., Sadahira, Y., Mizuochi, T., Kusano, H., Kage, M., Ueno, H., Yoshida, K., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., **Ogawa, S.**, Hayashi, Y., Kanegane, H., & Ouchi, K. (2019). Novel neuroblastoma amplified sequence (NBAS) mutations in a Japanese boy with fever-triggered recurrent acute liver failure. *Human Genome Variation, 6*. doi:10.1038/s41439-018-0035-5

123) Onodera, Y., Kohara, S., Tahara, S., Masuno, A., Inoue, H., Shiga, M., Hirata, A., Tsuchiya, K., **Hiraoka, Y.**, Obayashi, I., Ohara, K., Mizuno, A., & Sakata, O. (2019). Understanding diffraction patterns of glassy, liquid and amorphous materials via persistent homology analyses. *Journal of the Ceramic Society of Japan, 127*(12), 853-863. doi:10.2109/jcersj2.19143

124) Otomo, N., Takeda, K., Kawai, S., Kou, I., Guo, L., Osawa, M., **Alev, C.**, Kawakami, N., Miyake, N., Matsumoto, N., Yasuhiko, Y., Kotani, T., Suzuki, T., Uno, K., Sudo, H., Inami, S., Taneichi, H., Shigematsu, H., Watanabe, K., Yonezawa, I., Sugawara, R., Taniguchi, Y., Minami, S., Kaneko, K., Nakamura, M., Matsumoto, M., Toguchida, J., & Ikegawa, S. (2019). Bi-allelic loss of function variants of. *J Med Genet, 56*(9), 622-628. doi:10.1136/jmedgenet-2018-105920

125) Ozeki-Hayashi, R., **Fujita, M.**, Tsuchiya, A., Hatta, T., Nakazawa, E., Takimoto, Y., & Akabayashi, A. (2019). Beliefs held by breast surgeons that impact the treatment decision process for advanced breast cancer patients: a qualitative study. *Breast Cancer-Targets and Therapy, 11*, 221-229. doi:10.2147/bctt.s208910

126) Page, D. J., Miossec, M. J., Williams, S. G., Monaghan, R. M., Fotiou, E., Cordell, H. J., Sutcliffe, L., Topf, A., Bourgey, M., **Bourque, G.**, Eveleigh, R., Dunwoodie, S. L., Winlaw, D. S., Bhattacharya, S., Breckpot, J., Devriendt, K., Gewillig, M., Brook, J. D., Setchfield, K. J., Bu'Lock, F. A., O'Sullivan, J., Stuart, G., Bezzina, C. R., Mulder, B. J. M., Postma, A. V., Bentham, J. R., Baron, M., Bhaskar, S. S., Black, G. C., Newman, W. G., Hentges, K.

E., Lathrop, G. M., Santibanez-Koref, M., & Keavney, B. D. (2019). Whole Exome Sequencing Reveals the Major Genetic Contributors to Nonsyndromic Tetralogy of Fallot. *Circulation Research, 124*(4), 553-563. doi:10.1161/circresaha.118.313250

127) Polprasert, C., Takeuchi, Y., Kakiuchi, N., Yoshida, K., Assanasen, T., Sitthi, W., Bunworasate, U., Pirunsarn, A., Wudhikarn, K., Lawasut, P., Uaprasert, N., Kongkiatkamon, S., Moonla, C., Sanada, M., Akita, N., Takeda, J., Fujii, Y., Suzuki, H., Nannya, Y., Shiraishi, Y., Chiba, K., Tanaka, H., Miyano, S., Rojnuckarin, P., **Ogawa, S.**, & Makishima, H. (2019). Frequent germline mutations of HAVCR2 in sporadic subcutaneous panniculitis-like T-cell lymphoma. *Blood Advances, 3*(4), 588-595. doi:10.1182/bloodadvances.2018028340

128) Qin, Z. T., Hoh, C. K., Olson, E. S., Jahromi, A. H., Hall, D. J., Barback, C. V., You, Y. H., **Yanagita, M.**, Sharma, K., & Vera, D. R. (2019). Molecular Imaging of the Glomerulus via Mesangial Cell Uptake of Radiolabeled Tilmanocept. *Journal of Nuclear Medicine, 60*(9), 1325-1332. doi:10.2967/jnumed.118.223727

129) Sakai, S., Yamamoto, T., Takabatake, Y., Takahashi, A., Namba-Hamano, T., Minami, S., Fujimura, R., Yonishi, H., Matsuda, J., Hesaka, A., Matsui, I., Matsusaka, T., Niimura, F., **Yanagita, M.**, & Isaka, Y. (2019). Proximal Tubule Autophagy Differs in Type 1 and 2 Diabetes. *Journal of the American Society of Nephrology, 30*(6), 929-945. doi:10.1681/asn.2018100983

130) Sato, T., Higashioka, K., Sakurai, H., **Yamamoto, T.**, Goshima, N., Ueno, M., & Sotozono, C. (2019). Core Transcription Factors Promote Induction of PAX3-Positive Skeletal Muscle Stem Cells. *Stem Cell Reports, 13*(2), 352-365. doi:10.1016/j.stemcr.2019.06.006

131) Saulnier, K. M., Bujold, D., Dyke, S. O. M., Dupras, C., Beck, S., **Bourque, G.**, & Joly, Y. (2019). Benefits and barriers in the design of harmonized access agreements for international data sharing. *Scientific Data, 6*. doi:10.1038/s41597-019-0310-4

132) Seto, Y., & **Eiraku, M.** (2019). Human brain development and its in vitro recapitulation. *Neuroscience Research, 138*, 33-42. doi:10.1016/j.neures.2018.09.011

133) Seto, Y., & **Eiraku, M.** (2019). Toward the formation of neural circuits in human brain organoids. *Current Opinion in Cell Biology, 61*, 86-91. doi:10.1016/j.ceb.2019.07.010

134) Shibata, S, Kitano, T, Okamoto, Y, Takiuchi, Y, Yamamoto, K, Tabata, S, Aiba, A, Yoshida, Y, Nannya, Y, **Ogawa, S**, & Arima, N. (2019). Essential thrombocythemia correctly diagnosed through the guidance of comprehensive genomic profiling. *[Rinsho ketsueki] The Japanese journal of clinical hematology, 60*(12), 1630-1634. doi:10.11406/rinketsu.60.1630

135) Shokoohi, F., Stephens, D. A., **Bourque, G.**, Pastinen, T., Greenwood, C. M. T., & Labbe, A. (2019). A hidden markov model for identifying differentially methylated sites in bisulfite sequencing data. *Biometrics, 75*(1), 210-221. doi:10.1111/biom.12965

136) Subramanian, K., Dierckx, T., Khouri, R., Menezes, S. M., Kagdi, H., Taylor, G. P., Farre, L., Bittencourt, A., Kataoka, K., **Ogawa, S.**, & Van Weyenbergh, J. (2019). Decreased RORC expression and downstream signaling in HTLV-1-associated adult T-cell lymphoma/leukemia uncovers an antiproliferative IL17 link: A potential target for immunotherapy? *International Journal of Cancer, 144*(7), 1664-1675. doi:10.1002/ijc.31922

137) Sugahara, S., Kume, S., Chin-Kanasaki, M., Tomita, I., Yasuda-Yamahara, M., Yamahara, K., Takeda, N., Osawa, N., **Yanagita, M.**, Araki, S., & Maegawa, H. (2019). Protein O-GlcNAcylation Is Essential for the Maintenance of Renal Energy Homeostasis and Function via Lipolysis during Fasting and Diabetes. *Journal of the American Society of Nephrology, 30*(6), 962-978. doi:10.1681/asn.2018090950

138) Takashima, Y., Kawaguchi, A., Sato, R., Yoshida, K., Hayano, A., Homma, J., Fukai, J.,

Iwadate, Y., Kajiwara, K., Ishizawa, S., Hondoh, H., Nakano, M., **Ogawa, S.**, Tashiro, K., & Yamanaka, R. (2019). Differential expression of individual transcript variants of PD-1 and PD-L2 genes on Th-1/Th-2 status is guaranteed for prognosis prediction in PCNSL. *Scientific Reports, 9*. doi:10.1038/s41598-019-46473-5

139) Tan, L., Sato, N., Shiraki, A., **Yanagita, M.**, Yoshida, Y., Takemura, Y., & Shiraki, K. (2019). Everolimus delayed and suppressed cytomegalovirus DNA synthesis, spread of the infection, and alleviated cytomegalovirus infection. *Antiviral Research, 162*, 30-38. doi:10.1016/j.antiviral.2018.12.004

140) Tu, H. Y., Watanabe, T., Shirai, H., Yamasaki, S., Kinoshita, M., Matsushita, K., Hashiguchi, T., Onoe, H., Matsuyama, T., Kuwahara, A., Kishino, A., Kimura, T., **Eiraku, M.**, Suzuma, K., Kitaoka, T., Takahashi, M., & Mandai, M. (2019). Medium- to long-term survival and functional examination of human iPSC-derived retinas in rat and primate models of retinal degeneration. *Ebiomedicine, 39*, 562-574. doi:10.1016/j.ebiom.2018.11.028

141) Watanabe, C., Matsushita, J., Azami, T., Tsukiyama-Fujii, S., **Tsukiyama, T.**, Mizuno, S., Takahashi, S., & **Ema, M.** (2019). Generating Vegfr3 reporter transgenic mouse expressing membrane-tagged Venus for visualization of VEGFR3 expression in vascular and lymphatic endothelial cells. *Plos One, 14*(1). doi:10.1371/journal.pone.0210060

142) Watanabe, T., Yamazaki, S., Yoneda, N., Shinohara, H., Tomioka, I., Higuchi, Y., Yagoto, M., **Ema, M.**, Suemizu, H., Kawai, K., & Sasaki, E. (2019). Highly efficient induction of primate iPS cells by combining RNA transfection and chemical compounds. *Genes to Cells, 24*(7), 473-484. doi:10.1111/gtc.12702

143) Watatani, Y., Sato, Y., Miyoshi, H., Sakamoto, K., Nishida, K., Gion, Y., Nagata, Y., Shiraishi, Y., Chiba, K., Tanaka, H., Zhao, L. Y., Ochi, Y., Takeuchi, Y., Takeda, J., **Ueno, H.**, Kogure, Y., Shiozawa, Y., Kakiuchi, N., Yoshizato, T., Nakagawa, M. M., Nanya, Y., Yoshida, K., Makishima, H., Sanada, M., Sakata-Yanagimoto, M., Chiba, S., Matsuoka, R., Noguchi, M., Hiramoto, N., Ishikawa, T., Kitagawa, J., Nakamura, N., Tsurumi, H., Miyazaki, T., Kito, Y., Miyano, S., Shimoda, K., Takeuchi, K., Ohshima, K., Yoshino, T., **Ogawa, S.**, & Kataoka, K. (2019). Molecular heterogeneity in peripheral T-cell lymphoma, not otherwise specified revealed by comprehensive genetic profiling. *Leukemia, 33*(12), 2867-2883. doi:10.1038/s41375-019-0473-1

144) Yabe, M., Koike, T., Ohtsubo, K., Imai, E., Morimoto, T., Takakura, H., Koh, K., Yoshida, K., **Ogawa, S.**, Ito, E., Okuno, Y., Muramatsu, H., Kojima, S., Matsuo, K., Mori, M., Hira, A., Takata, M., & Yabe, H. (2019). Associations of complementation group, ALDH2 genotype, and clonal abnormalities with hematological outcome in Japanese patients with Fanconi anemia. *Annals of Hematology, 98*(2), 271-280. doi:10.1007/s00277-018-3517-0

145) Yamada, H., Doi, K., Tsukamoto, T., Kiyomoto, H., Yamashita, K., **Yanagita, M.**, Terada, Y., & Mori, K. (2019). Low-dose atrial natriuretic peptide for prevention or treatment of acute kidney injury: a systematic review andmeta-analysis. *Critical Care, 23*. doi:10.1186/s13054-019-2330-z

146) Yokoyama, A., Kakiuchi, N., Yoshizato, T., Nannya, Y., Suzuki, H., Takeuchi, Y., Shiozawa, Y., Sato, Y., Aoki, K., Kim, S. K., Fujii, Y., Yoshida, K., Kataoka, K., Nakagawa, M. M., Inoue, Y., Hirano, T., Shiraishi, Y., Chiba, K., Tanaka, H., Sanada, M., Nishikawa, Y., Amanuma, Y., Ohashi, S., Aoyama, I., Horimatsu, T., Miyamoto, S., Tsunoda, S., Sakai, Y., Narahara, M., Brown, J. B., Sawada, G., Mimori, K., Minamiguchi, S., Haga, H., Seno, H., Miyano, S., Makishima, H., Muto, M., & **Ogawa, S.** (2019). Age-related remodelling of oesophageal epithelia by mutated cancer drivers. *Nature, 565*(7739), 312-+. doi:10.1038/s41586-018-0811-x

2. Review articles

147) **Ogawa, S.** (2019). Genetics of MDS. ***Blood****, 133*(10), 1049-1059. doi:10.1182/blood-2018-10-844621

3. Proceedings

4. Other articles

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

- List up to 10 main presentations during FY 2019 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
12th Mar 2020 *cancelled*	Takuya Yamamoto	Post-transcriptional regulation during somatic cell reprogramming	The 19th Congress of the Japanese Society for Regenerative Medicine, Yokohama
3rd Feb 2020	Tadashi Isa	Neurobiology of recovery after brain and spinal cord injury in macaque models	NIH, Neuroscience Seminar Series, NIH, Bethesda, USA
6th Dec 2019	Masatsugu Ema	Genetically Modified Cynomolgus Monkeys for Human Autosomal Dominant Polycystic Kidney Disease Modeling	Annual meeting for Molecular Biology Society of Japan, Hakata
7th Nov 2019	Motoko Yanagita	Erythropoietin-Producing Cells in Kidney Fibrosis	Kidney Week 2019, American Society of Nephrology, Washington DC, USA
1st Nov 2019	Cantas Alev	Recapitulating Human Mesoderm Development in vitro	2nd Annual Meeting of the Organoid Society, Seoul, Korea
24th Jun 2019	Hideki Ueno	Why is the efficacy of seasonal influenza vaccine limited? Blame on Tfh1.	The Riken IMS-JSI International Symposium on Immunology 2019, Tokyo
21st Jun 2019	Misao Fujita	The ethics of stem cell research and application	2019 Nano-Gene Therapy and Regenerative Medicine Summit, Taipei, Taiwan
15th Jun 2019	Seishi Ogawa	Clonal hematopoiesis in Aplastic anemia	24th Congress of European Hematology Association, Amsterdam, Nethrelands
31st May 2019	Takashi Hiiragi	Self-organisation in mouse development	Sammy Lee Memorial Keynote lecture for the Young Embryologist Network conference 2019, London, UK
22nd May 2019	Mitinori Saitou	Mechanism and Reconstitution In Vitro of Human Germ Cell Development	Gordon Research Conference, Hong Kong
13th May 2019	Guillaume Bourque	Unmasking transposable elements in regulation and disease	Royal Society: Crossroads between transposons and gene regulation, London, UK
19th Apr 2019	Mototsugu Eiraku	Functional 3D tissue formation by in vitro manipulation and cell autonomy	The State-of-the-Art 3D Tissue Culture & Organoids, OIST

15th Apr 2019	Yasuaki Hiraoka	Topological data analysis in materials science.	Workshop “Data Driven Dynamics: Algebraic Topology, Combinatorics and Analysis”, Montreal, Canada

3. Major Awards

- List up to 10 main awards received during FY 2019 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
11th Mar 2020	Mitinori Saitou	Uehara Prize 2019
29th Jan 2020	Mitinori Saitou	Asashi Prize 2019
28th Nov 2019	Seishi Ogawa	Erwin von Bälz Prize
23rd Jun 2019	Hiroyuki Yoshitomi	Novartis medical award in rheumatoid arthritis

Appendix 2　FY 2019 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 or, for centers selected in FY2012 in the progress report for Extension application screening, attach a “Biographical Sketch of a New Principal Investigator” (Appendix 2a).

<Results at the end of FY2019>　　**Principal Investigators Total: 14**

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	49	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	
Vice director Tadashi Isa	59	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	
Vice director Yasuaki Hiraoka	42	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	
Head of the Single-cell Genome Information Analysis Core Takuya Yamamoto	42	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	
Cantas Alev	45	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	
Guillaume Bourque	43	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

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
Mototsugu Eiraku	45	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	52	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	50	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	52	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
Seishi Ogawa	57	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	36	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	52	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
Motoko Yanagita	50	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 2019

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

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)

Cantas Alev (45)

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

Associate Professor

Institute for the Advanced Study of Human Biology (ASHBi)

Kyoto University

Academic degree and specialty

M.D., Ph.D., Developmental Biology

Effort 100 **%**

Research and education history

Dr. Alev obtained his Ph.D. and Doctor of Medicine (Dr.med.) from the Ruhr University Bochum in Germany, where he studied medicine and biochemistry. He did his post-doctoral work on early embryonic development with a focus on mesoderm induction and patterning in the laboratory of Dr. Guojun Sheng at the RIKEN Center for Developmental Biology (CDB) in Kobe, Japan, before moving to the Center for iPS Cell Research and Application (CiRA). At CiRA he worked on pluripotent stem cell (PSC)-based *in vitro* model systems of human mesoderm development, successfully establishing the first *in vitro* model of the human segmentation clock (Matsuda, Yamanaka et al., *Nature* 2020). In his new lab at the Institute for the Advanced Study of Human Biology (ASHBi) at Kyoto University he is working on the *in vitro* reconstitution of human and non-human amniote embryonic development. His lab focuses foremost on the *in vitro* recapitulation of mesendodermal organogenesis and complex mesoderm-driven morphogenetic processes, including endodermal and ectodermal tissue formation and maturation from PSCs. His lab aims to establish novel scientific concepts and disruptive technologies in the field of synthetic embryology and *in vitro* organogenesis, with the overall goal to increase our still limited understanding of human evolution, development and diseases.

Selected Publications

1. *Recapitulating the human segmentation clock with pluripotent stem cells*.
   Matsuda M, Yamanaka Y, Uemura M, Osawa M, Saito K. M, Nagahashi A, Nishio M, Guo L, Ikegawa S, Sakurai S, Kihara S, Maurissen L. T, Nakamura M, Matsumoto T, Yoshitomi H, Ikeya M, Kawakami N, Yamamoto T, Woltjen K, Ebisuya M, Toguchida J, **Alev C*** .
   Nature, 2020 Apr 1; 580(7801):124-129. DOI:10.1038/s41586-020-2144-9 [*****Corresponding author & Lead contact]

2. *Species-specific oscillation periods of human and mouse segmentation clocks are due to cell autonomous differences in biochemical reaction parameters*.
   Matsuda M, Hayashi H, Garcia-Ojalvo J, Yoshioka-Kobayashi K, Kageyama R, Yamanaka Y, Ikeya M, Toguchida J, **Alev C**, Ebisuya M.
   bioRxiv*.* 2019 May 26; DOI:10.1101/650648 650648 [in revision at **Science**]

3. *Overview of Basic Mechanisms of Notch Signaling in Development and Disease.*
   McIntyre B, Asahara T, **Alev C*** .
   Advances in Experimental Medicine & Biology. 2020;1227:9-27. DOI:10.1007/978-3-030-36422-9_2 [*****Corresponding author & Lead contact] [book chapter]

4. *Mesenchymal-epithelial transition regulates initiation of pluripotency exit before gastrulation.*
Hamidi S, Nakaya Y, Nagai H, **Alev C**, Kasukawa T, Lee A, Niwa H, Warmflash A, Shibata T, Sheng G.
Development. 2020 Feb 3;147(3). pii: dev184960. DOI:10.1242/dev.184960

5. *Engineering bone-like nodules from human iPS cells as a research platform for bone*.
Kawai S, Yoshitomi H, Sunaga J, **Alev C**, Nishio M, Hada M, Koyama Y, Uemura M, Sekiguchi K, Maekawa H, Ikeya M, Tamaki S, Jin Y, Harada Y, Fukiage K, Adachi T, Shuichi M, Toguchida J.
Nature Biomedical Engineering. 2019 Jul; 3(7):558-570. DOI:10.1038/s41551-019-0410-7.

6. *Biomechanical regulation of EMT and epithelial morphogenesis in amniote epiblast.*
Hamidi S, Nakaya Y, Nagai H, **Alev C**, Shibata T, Sheng G.
Physical Biology. 2019 Apr 23;16(4):041002. DOI:10.1088/1478-3975/ab1048. [review]

7. *The role of VEGF in extremities.*
McIntyre BA, Asahara T, **Alev C***.
Therapeutic Angiogenesis. 2017 Jul 12; Higashi Y., Murohara T. (eds) Springer, Singapore 111-131. DOI:10.1007/978-981-10-2744-4_8 [*****Corresponding author & Lead contact] [book chapter]

8. *Expansive generation of functional airway epithelium from human embryonic stem cells.*
McIntyre BA, **Alev C**, Mechael R, Salci KR, Lee JB, Fiebig-Comyn A, Guezguez B, Wu Y, Sheng G, Bhatia M.
Stem Cells Translational Medicine. 2014 Jan;3(1):7-17. DOI:10.5966/sctm.2013-0119.

9. *Manipulating the avian epiblast and epiblast-derived stem cells.*
Alev C, Nakano M, Wu Y, Horiuchi H, Sheng G.
Methods Mol Biol. 2013;1074:151-73. DOI:10.1007/978-1-62703-628-3_12. [book chapter]

10. *Decoupling of amniote gastrulation and streak formation reveals a morphogenetic unity in vertebrate mesoderm induction.*
Alev C, Wu Y, Nakaya Y, Sheng G.
Development. 2013 Jul;140(13):2691-6. DOI:10.1242/dev.094318.

11. *Transcriptomic landscape of the primitive streak.*
Alev C, Wu Y, Kasukawa T, Jakt LM, Ueda HR, Sheng G.
Development. 2010 Sep 1;137(17):2863-74. DOI:10.1242/dev.053462.

12. *Dynamic expression of Endoglin, a TGF-beta co-receptor, during pre-circulation vascular development in chick.*
Alev C, McIntyre BA, Ota K, Sheng G.
Int J Dev Biol. 2010;54(4):737-42. DOI:10.1387/ijdb.092962ca. [selected for cover]

13. *The neuronal connexin36 interacts with and is phosphorylated by CaMKII in a way similar to CaMKII interaction with glutamate receptors.*
Alev C, Urschel S, Sonntag S, Fort AG, Höher T, Matsubara M, Willecke K, Spray DC, Dermietzel R.
Proc. Nat. Acad. Scien. USA (PNAS). 2008 Dec 30;105(52):20964-9. DOI:10.1073/pnas.0805408105.

Achievements and highlights of past research activities

Dr. Alev is an established developmental biologist and expert on early embryonic development of amniotes. During his research and post-doc fellowship in the Sheng-lab at the RIKEN Center for Developmental Biology he published more than 22 papers on gastrulation, mesendoderm induction, patterning and differentiation. He was the first to analyze the transcriptome of a primitive streak (Alev et al., *Development* 2010) and further succeeded to reveal an evolutionary conserved mode of ancestral mesoderm induction in amniotes (Alev et al., *Development* 2013). He also successfully established a pluripotent stem cell-based *in vitro* model of the human segmentation clock and diseases of the spine (Matsuda, Yamanaka et al., *Nature* 2020), while working as an Assistant Professor at the Center for iPS Cell Research and Application (CiRA). He continues to work at ASHBi on novel concepts and disruptive technologies for synthetic embryology and *in vitro* organogenesis.

Achievements

(1) International influence

a) Dr. Alev is the recipient of multiple awards (ISSCR, GSCN, EMBL, Kahenara Foundation), fellowships and scholarships (JSPS, JSDB, Yokochi Fund of the Ichiro Kanehara Foundation, German National Merit Foundation – Studienstiftung des Deutschen Volkes).

b) Dr. Alev is an active member of Japanese Society for Developmental Biology (JSDB), German Society for Developmental Biology (GfE), International Society for Stem Cell Research (ISSCR), German Stem Cell Network (GSCN) & Molecular Biology Society of Japan (MBSJ).

c) Dr. Alev was an invited speaker/lecturer at meetings organized by the JSDB, GSCN, ISSCR, NCKU, JBS, CCHMC, OIST, IMBA/IMP, MCRI and is one of the organizers & coordinators of the annual exchange meetings for young scientists between the Japanese and German Societies of Developmental Biology (JSDB-GfE). He is also co-organizer of an upcoming CSHA meeting on Human Embryology (2021).

d) Dr. Alev is currently editing a special issue on Organoid Research at the Springer journal JMM (*Journal of Molecular Medicine*) and is invited to contribute to a special issue on "*In vitro* Human Embryology & Organogenesis" in *Stem Cell Reports*.

e) Dr. Alev was a peer reviewer for Stem Cells, Stem Cells Translational Medicine, Cells Tissues & Organs, Genes to Cells, Acta Biomaterialia, Tissue Engineering, Cell Transplantation, Cellular Signaling, Scientific Data, Nature Experimental and Molecular Medicine, eLife and is an active reviewer of the FWO Granting Program (Research Foundation Flanders).

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

2018-2019 Naito Foundation Scientific Research Grant; Principal Investigator (PI) of project titled "*Establishment of iPSC-based models of human organogenesis*"; 3,000,000¥

2017-2018 CiRA Fellowship Program of Challenge; Principal Investigator (PI) of project titled "*Establishment of advanced tools for guided 3D organogenesis and reproducible in vitro construction of complex tissues from human induced pluripotent stem cells (iPSCs)*"; 3,000,000¥

2016-2018 Grant-in-Aid (*KAKENHI)* for Challenging Exploratory Research; Principal Investigator (PI) of project titled "*Establishment of tendon/ligament progenitor cells from human induced pluripotent stem cells (iPSCs)*"; #16K15664; 3,510,000¥

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

1. *Recapitulating the human segmentation clock with pluripotent stem cells*.
   Matsuda M, Yamanaka Y, Uemura M, Osawa M, Saito K. M, Nagahashi A, Nishio M, Guo L, Ikegawa S, Sakurai S, Kihara S, Maurissen L. T, Nakamura M, Matsumoto T, Yoshitomi H, Ikeya M, Kawakami N, Yamamoto T, Woltjen K, Ebisuya M, Toguchida J, **Alev C***.
   Nature, 2020 Apr 1; 580(7801):124-129. [4 citations]

2. *Decoupling of amniote gastrulation and streak formation reveals a morphogenetic unity in vertebrate mesoderm induction.*
   Alev C, Wu Y, Nakaya Y, Sheng G.
   Development. 2013 Jul;140(13):2691-6. [21 citations]

3. *Transcriptomic landscape of the primitive streak.*
   Alev C, Wu Y, Kasukawa T, Jakt LM, Ueda HR, Sheng G.
   Development. 2010 Sep 1;137(17):2863-74. [40 citations]

(4) Others (Other achievements indicative of the PI's qualifications)

Methods of Prognosing Preeclampsia
(International Patent Application PCT/US2014/26124)
Inventors: B. Ling, T. Yang, A. Butte, L. Miller, Q. Wen, G. Sheng, C. Alev

Novel Bone Differentiation Induction Medium
(Japanese Patent Application No. 2017-243241)
Inventors: J. Toguchida, S. Kawai, H. Yoshitomi, C. Alev

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)

Tomoyuki Tsukiyama (36)

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

Program-Specific Associate Professor,

Research Center for Animal Life Science,

Shiga University of Medical Science

Academic degree and specialty

PhD

Developmental Engineering, Reproductive and Stem Cell 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

2002 Rakunan High School, Kyoto, Japan

2006 B.S. (Agriculture) Kyoto University, Faculty of Agriculture, Kyoto, Japan

2008 M.S. (Agriculture) Kyoto University, Graduate School of Agriculture, Kyoto, Japan

2011 Ph.D. (Agriculture) Kyoto University, Graduate School of Agriculture, Kyoto, Japan

2011-2014 Research Scientist RIKEN, Center for Developmental Biology (CDB), Kobe, Japan (Dr. Hitoshi Niwa)

2014-2019 Assistant Professor Shiga University of Medical Science, Research Center for Animal Life Science (Dr. Masatsugu Ema)

2019-present Program-Specific Associate Professor Shiga University of Medical Science, Research Center for Animal Life Science

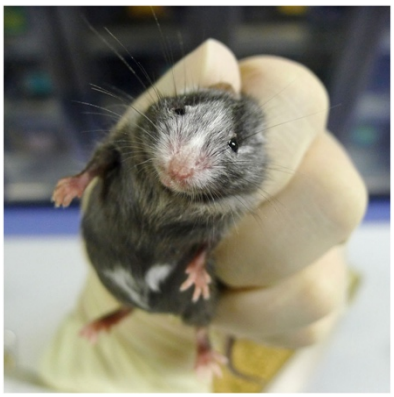
Achievements and highlights of past research activities

Germ cells are responsible for the continuity of life. I am interested in germ cells, and have consistently studied germ cells or their derivatives, fertilized eggs and pluripotent stem cells, and applied them to animal production. First, we focused on small RNAs that exist specifically in the testis and ovary, and identified them. Later, it was revealed that the small RNAs identified in the testes interacted with Piwi and were involved in retrotransposon suppression. This small RNA is now known as Piwi-interacting RNA (piRNA) and is now attracting attention as it forms a research area. (Watanabe T. et al., 2006, *Genes and Development*)

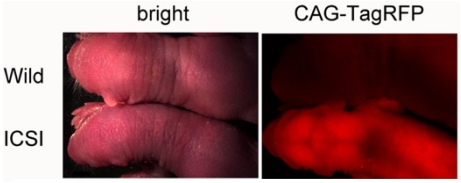
Next, we have developed a system for evaluating culture conditions that is universal regardless of animal species. In this system, we applied piggyBac transposon to introduce a polycistronic cassette and fluorescent reporters into somatic cells. The polycistronic cassette contains TET-ON reprogramming factors that can control the expression of exogenous reprogramming factors with or without the addition of doxycycline. The fluorescent reporters were used to evaluate the pluripotency, chimera-contributing ability, and germ cell-contributing

ability of established cells. (Tsukiyama T. et al., 2011, *Genes to Cells;* Tsukiyama T. et al., 2014, *PLoS ONE*)

By using the system, we showed that iPS cells could be established from NOD strain, which was known to be difficult to obtain ES cells, in addition to 129B6F1 strain. Moreover, we established rat iPS cells from rat fetal fibroblasts using a conventional culture condition. We showed that the mouse iPS cells and rat iPS cells were able to contribute to germ cells. The rat iPS cells were able to contribute to mouse-rat interspecific chimeras. We found that the rat iPS cells were able to generate functional germ cells, which were able to produce reporter-positive rats, in the mouse-rat interspecific chimeras for the first time in the world. The results showed the usefulness of our system to evaluate the ability to contribute to chimeras and germ cells by expression of fluorescent reporters non-invasively. (Tsukiyama T. et al., 2014, *PLoS ONE*)

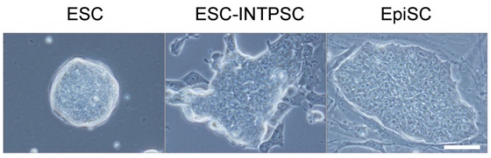


A mouse-rat interspecific chimera



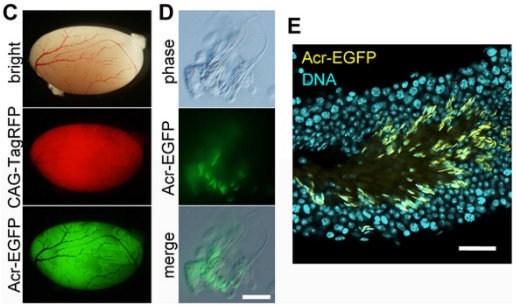
A reporter-positive rats from rat-iPS-derived sperm generated in a mouse-rat chimera

Furthermore, we found that culturing ES cells under the EpiS cell culture condition containing a GSK3 inhibitor stabilized the cells into a novel pluripotent state that exhibited properties intermediate between those of ES cells and those of EpiS cells. We named the cells Intermediate Pluripotent Stem Cells (INTPS cells).



The morphology of INTPSCs

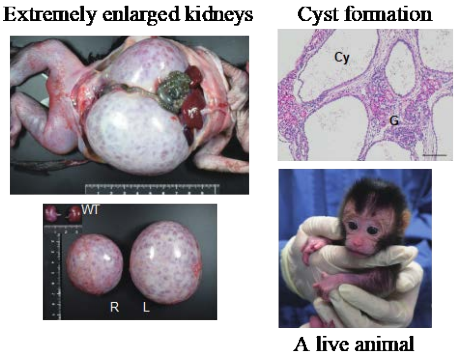
In addition, by using the above-described system, we showed that these cells have chimeric and germ cell-contributing ability. This culture condition may be useful for maintaining pluripotency in a manner independent on LIF signaling, and may be useful in establishing new pluripotent stem cell lines in non-rodents. (Tsukiyama T. et al., 2014, *PLoS ONE*)



INTPSC-derived sperm

Since assigning as an assistant professor to Shiga University of Medical Science, we engage in the creation of transgenic cynomolgus monkeys and genome-edited cynomolgus monkeys by CRISPR/Cas9. I have been responsible for launching the projects using lentiviral vectors and cynomolgus monkey ES cells. (Seita Y., Tsukiyama T., et al., 2016, *Scientific Reports*; Seita Y., Tsukiyama T., et al., 2019, *Biology of Reproduction*; Kobayashi K., Tsukiyama T., et al., 2019, *Stem Cell Research*)

In the genome editing cynomolgus monkey project, we have generated knock out monkeys. Among them, we showed that CRISPR/Cas9-induced mutagenesis of the *PKD1* gene can recapitulate the pathology of human autosomal dominant polycystic kidney disease (ADPKD), which is difficult to reproduce in small animals. Although



ADPKD Monkeys

ADPKD is the most common genetic kidney disease, there is no definitive treatment. Based on the results obtained in this study, we propose that our models elucidate the onset and progression of ADPKD, which will serve as a critical basis for establishing new therapeutic strategies, including drug treatments, and demonstrate that monkey disease models are useful for elucidation of human diseases. (Tsukiyama T. et al., 2019, *Nature Communications*)

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

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)

2017-2019 Grant-in-Aid for Scientific Research (C)

2015-2016 Grant-in-Aid for Young Scientists (B)

2013-2014 Grant-in-Aid for Young Scientists (B)

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

Monkeys mutant for *PKD1* recapitulate human autosomal dominant polycystic kidney disease., 2019, ***Nature Communications***, 0 citations
Generation of transgenic cynomolgus monkeys that express green fluorescent protein throughout the whole body., 2016, ***Scientific Reports***, 15 citations
A Modified EpiSC Culture Condition Containing a GSK3 Inhibitor Can Support Germline-Competent Pluripotency in Mice., 2014, ***PLoS ONE***, 23 citations
A Comprehensive System for Generation and Evaluation of Induced Pluripotent Stem Cells Using piggyBac Transposition., 2014, ***PLoS ONE***, 14 citations
Identification and Characterization of Two Novel Classes of Small RNAs in the Mouse Germline: Retrotransposon-Derived siRNAs in Oocytes and Germline Small RNAs in Testes, 2006, ***Genes & Development***, 398 citations

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

N/A

Appendix 3-1 FY 2019 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.

For the recruitment of new PIs, 3 PIs and a Co-PI of an overseas PI are scheduled to join ASHBi in FY2020. The names are as follows.

Name	Position at ASHBi	Appointment	Previous Position
Ryo Yamamoto	PI Associate Professor	1st Apr 2020	Research Associate Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine
Fumitaka Inoue	Co-PI Associate Professor	1st Jul 2020 (scheduled)	Assistant Researcher Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco
Kenichi Amemori	PI Associate Professor	1st Sep 2020 (scheduled)	Associate Professor Hakubi Center for Advanced Research and Primate Research Institute, Kyoto University
Yasuhiro Murakawa	PI Professor	1st Aug 2020 or 1st Sep 2020 (scheduled)	Team Leader RIKEN Center for Integrative Medical Sciences RIKEN-IFOM Joint Laboratory for Cancer Genomics

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
Research Center for Animal Life Science, Shiga University of Medical Science	Masatsugu EMA Tomoyuki TSUKIYAMA	

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes

2. Holding international research meetings

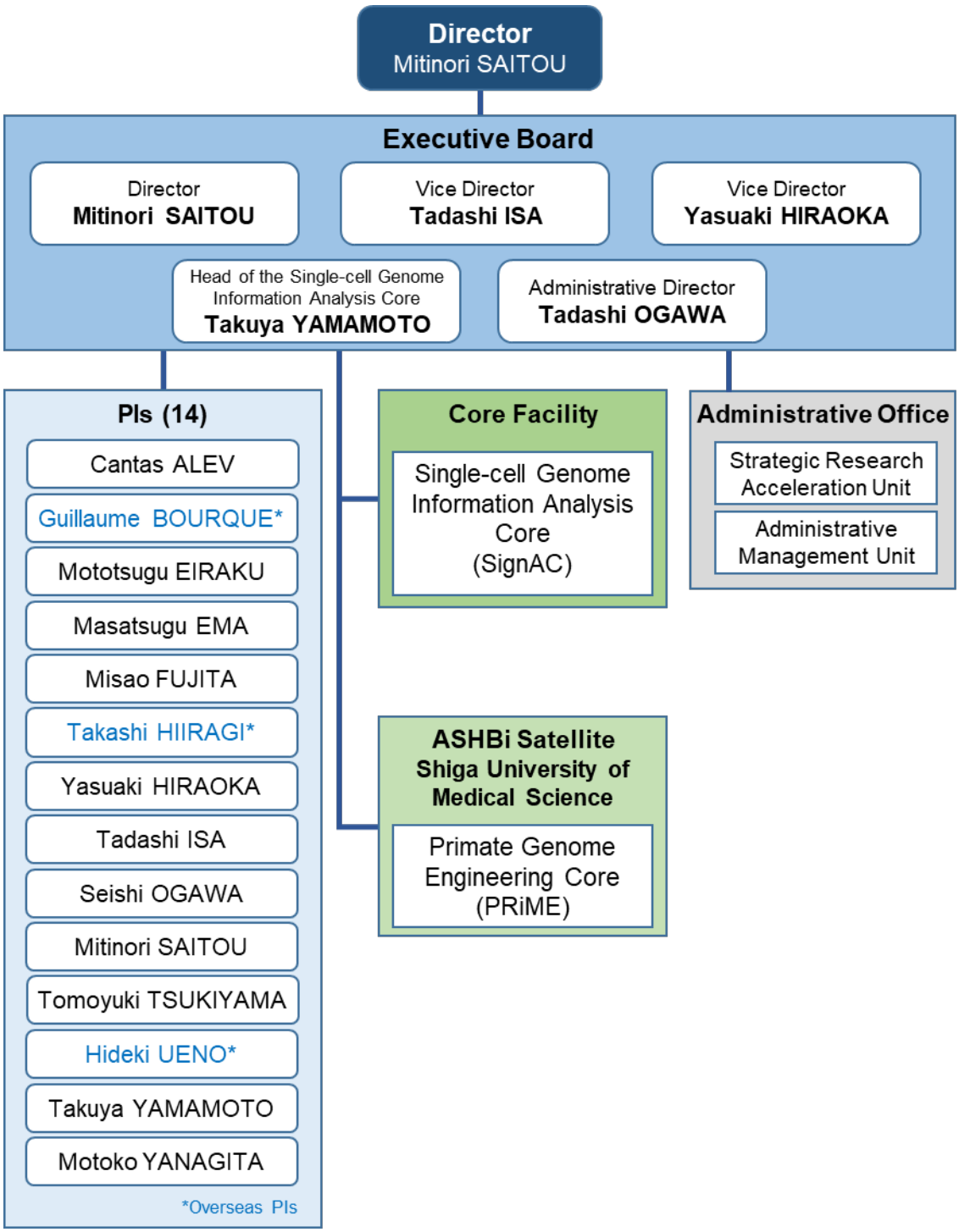
- Indicate the number of international research conferences or symposiums held in FY2019 and give up to three examples of the most representative ones using the table below.

FY 2019: 2 meetings

Major examples (meeting titles and places held)	Number of participants
23 Aug 2019 1st ASHBi Mathematical Biology Workshop Seminar room, 2F, KUIAS main building, Kyoto University	From domestic institutions: 57 From overseas institutions: 2
7,8 Feb 2020 ASHBi Retreat 2020 Awaji Yumebutai International Conference Center	From domestic institutions: 76 From overseas institutions: 2
19-20 March 2020 [cancelled] ASHBi Symposium 2020 Shirankaikan, Kyoto University	[Speakers/Posters] From domestic institutions: 43 From overseas institutions: 22

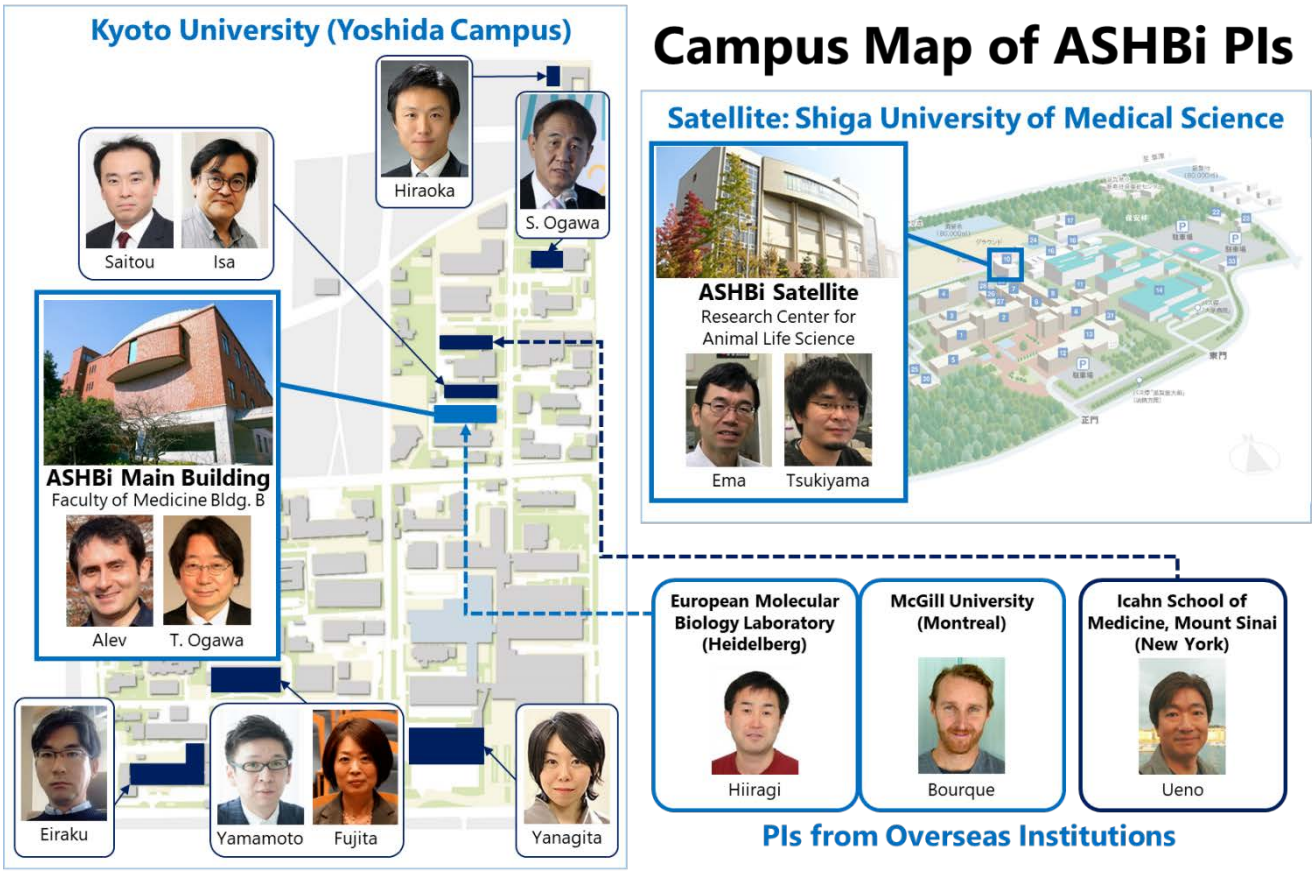
3. Diagram of management system

- 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 FY2019

Total: **806,940,931 yen**

**Amount(yen) shown in this section stands for the amount which are proportionally distributed according to effort ratio of each PI from the original secured amount unless otherwise specified.*

- 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.)

[Breakdown according to type of funding]

Type of Funding	Funding Amount (Proportionally distributed)
Grants-in-Aid for Scientific Research (KAKENHI)	190,166,506 yen
Commissioned Research Projects	426,974,837 yen
Joint Research Projects	158,641,010 yen
Others (Donation funds, etc)	31,158,578 yen
Total* (total for above mentioned)	**806,940,931 yen**

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

Organization	Fund name	PI	Funding amount (Secured amount)
Collaboration Research	TMK Project	Motoko Yanagita	88,864,901 yen
AMED	Project for Cancer Research and Therapeutic Evolution (P-CREATE)	Seishi Ogawa	81,539,500 yen
JSPS	KAKENHI Specially Promoted Research	Mitinori Saitou	77,700,000 yen
AMED	Practical Research Project for Rare/Intractable Diseases	Seishi Ogawa	57,734,615 yen
AMED	Project of Translational and Clinical Research Core Centers(CREST)	Seishi Ogawa	49,999,900 yen
AMED	Practical Research for Innovative Cancer Control	Seishi Ogawa	35,000,000 yen
Collaboration Research	Chordia Therapeutics Inc.	Seishi Ogawa	34,177,341 yen
JSPS	KAKENHI-Grant-in-Aid for Scientific Research (S)	Seishi Ogawa	33,000,000 yen
JSPS	KAKENHI-Grant-in-Aid for Scientjfjc Research on Innovative Areas(Research in a Proposed Research Area)	Seishi Ogawa	30,500,000 yen

Appendix 3-1a FY 2019 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)

	At the beginning of project	At the end of FY 2019	Final goal (Date: March, 2021)
Researchers from within the host institution	8	9	13
Researchers invited from overseas	4	3	3
Researchers invited from other Japanese institutions	1	2	2
Total principal investigators	13	14	18

b) Total members

	At the beginning of project		At the end of FY2019		Final goal (Date: March, 2021)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	13		56		71	
Overseas researchers	4	31%	11	20%	22	31%
Female researchers	3	23%	10	18%	21	30%
Principal investigators	13		14		18	
Overseas PIs	4	31%	3	21%	3	17%
Female PIs	3	23%	2	14%	2	11%
Other researchers	0		23		19	
Overseas researchers	0	-	2	9%	7	37%
Female researchers	0	-	2	9%	7	37%
Postdocs	0		19		34	
Overseas postdocs	0	-	6	32%	12	35%
Female postdocs	0	-	6	32%	12	35%
Research support staffs	2		18		20	
Administrative staffs	3		14		14	
Total number of people who form the "core" of the research center	**18**		**88**		**105**	

Appendix 3-2 Project Expenditures

1) Overall project funding

(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	30	4
	Principal investigators (no. of persons):11	98	24
	Other researchers (no. of persons):20	63	57
	Research support staff (no. of persons):15	33	33
	Administrative staff (no. of persons):26	69	31
	Subtotal	293	149
Project activities	Research startup cost	41	39
	Fusion Research startup cost	3	2
	Cost of satellite organizations (no. of satellite organizations):1	72	72
	Cost of international symposiums (no. of symposiums):1	2	1
	Rental fees for facilities	21	20
	Cost of utilities	2	0
	Cost of outreach activities	4	5
	Cost of Young Researcher Foster programs	5	4
	Cost of consumables	64	31
	Cost of maintenance of Core Facility	14	12
	Cost of maintenace cotracts	29	17
	Other costs	7	0
	Subtotal	264	203
Travel	Domestic travel costs	1	1
	Overseas travel costs	4	3
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):3	1	1
	Travel cost for scientists on transfer (no. of domestic scientists):1 (no. of overseas scientists):3	1	
	Subtotal	7	5
Equipment	Depreciation of buildings	413	334
	Depreciation of equipment	27	9
	Subtotal	440	343
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1	3	
	KAKENHI	190	
	Commissioned research projects, etc.	427	
	Joint research projects	159	
	Ohers (donations, etc.)	31	
	Subtotal	810	0
Total		1814	700

Costs (Million yens)

WPI grant in FY 2019	700
Costs of establishing and maintaining facilities	187
Establishing new facilities	0
Repairing facilities	179
(no of facilities: 1 , about 1,800 m²)	
Others	8
Costs of equipment procured	156
Zeiss Microscope (1)	83
Lab Benches (16)	20
Freezers	10
Others	43

*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):0		
	Administrative staff (no. of persons):0		
	Subtotal	27	18
Project activities	Subtotal	28	28
Travel	Subtotal	0	0
Equipment	Subtotal	26	26
Research projects	Subtotal	10	–
Total		91	72

Appendix 4 FY 2019 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2019 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. 2020 and not described in Appendix 1.

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

1)
2)
3)
4)

Overseas Satellite 2 **Name** (Total: OO 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
FY2019					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2019					

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
FY2019					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2019					

Appendix 5 FY 2019 Visit Records of Researchers from Abroad

* If researchers have visited/ stayed at the Center, provide information on them in the below table.

Total: 47

	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
			Position title, department, organization	Country				
1	Bernard de Massy	61	Research Director Genome Dynamics 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	01 Apr-30 Apr 2019	short-term stay for joint research
2	Greg Bognar		Senior Lecturer Practical Philosophy at Stockholm University	Sweden	PhD Normative Ethics, Bioethics	He has currently worked on three projects: on the ethics of demographic change; on a book draft on moral relativism; and on the philosophy of disability. 2019 Laurance S. Rockefeller Visiting Faculty Fellow, Princeton Univ	19 Apr 2019	He gave a lecture, "If it looks like a sheep, then it's a sheep: Sources of confusion in bioethical arguments."
3	Douglas Munoz		Professor Queens University	Canada	PhD	Specialist of eye movement control system His research provide new information about how the brain controls voluntary behaviour, also leading new treatments to improve congnitive function.	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
4	Neeraj Gandhi		Associate Professor, Otolaryngology University of Pittsburgh Swanson School of Engineering	USA	PhD	Specialist of eye movement control systems His major research is neural basis of sensorimotor integration and cognition.	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
5	Kathleen Cullen		Professor Johns Hopkins University	USA	PhD	Specialist of eye movement control systems Program Chair and Vice President of the Society for the Neural Control of Movement Halpike-Nylen medal of the Barany Society Sarrazin Award Lectureship from the Canadian Physiological Society (CPS)	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
6	John van Opstal		Professor Biophysics Radboud University	Netherlands	PhD	Specialist of eye movement control systems 2001-2010 Faculty's coordinator of the recent International Visitation of the Physics Curriculum 1999-2003 Chairman of the Physics Curriculum Committee of the Physics Faculty	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
7	Paul J. May		Professor Ophthalmology University of Mississipi, Jackson	USA	PhD	Specialist of eye movement control systems His research is gaze control utilizing anatomical and, in some cases, physiological methods. He is also interested in Trigeminal pathways,Circuitry of eyelid, pupil and lens reflexes.	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University

	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
			Position title, department, organization	Country				
8	Pierre-Paul Vidal		Professor Head of the CESeM Paris Descares University	France	PhD	Specialist of eye movement control systems Current position:Directeur d'Unité (UMR MD) His research is vestibular compensation for the statics and dynamic sysorders.	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
9	Ziad Hafed		Professor Tuebungen University	Germany	PhD	Specialist of eye movement control systems He has received many prestigious awards in recognition for his academic achievements, including the British Association Medal for Great Distinction and NSERC (Canada) and Sloan-Swartz (USA) Fellowships for Neuroscience.	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
10	Stefan Everling		Professor Western University	Canada	PhD	Specialist of eye movement control systems 2007 Dean's Team Award 2006 Dean's Junior Excellence Award 2004, 2006 USC Teaching Honour Roll Award of Excellence 2002 EJLB Foundation Scholar Research Award 2001 Premier's Research Excellence Award	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
11	Marc Sommer		Professor Duke University	USA	PhD	Specialist of eye movement control systems He researches Neuronal circuits of the brain. 2017 Bass Society of Fellows. Duke University 2017 Capers and Mario McDonald Award for Excellence in Mentoring and Advising 2005 Sloan Research Fellowship-Neuroscience	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
12	Kevin Johnston		Research Scientist Western University	Canada	PhD	Specialist of eye movement control systems He research visual working memory.	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
13	Danping Wang		Professor Paris Descares University	France	PhD	Specialist of eye movement control systems Her research is motor style rest during locomotion in human	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
14	Tim Darlington		Research Scientist Duke University	USA	PhD	Specialist of eye movement control systems His project is investigating this in the context of target-direction estimation for smooth pursuit eye movements in nonhuman primates.	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
15	Brian Corneil		Professor Western University	Canada	PhD	Specialist of eye movement control systems He is the head of Brian and Mind Institute.his interests are sensory and motor processing.	21 Apr-22 Apr 2019	Participating a symposium which I organized in Kyoto University
16	Uta Erdbrügger	49	Associate Professor Division of Nephrology University of Virginia	USA	MD	2018 The Treasurer of the International Society of Extracellular Vesicles 2017 Department of Medicine Employee of the Year for Excellence in ResearchEditorial Board Member: American Journal of Physiology Renal Physiology	23 Apr 2019	Short-term stay for the seminar and discussion

	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
			Position title, department, organization	Country				
17	Fei LAN		Professor Co-Director of the Epigenetics Key Laboratory of Shanghai Ministry of Education	China	PhD Molecular Biology	2017 VCAN BIOMED Discovery Award 2016 Tan Jiazhen Discovery Award (Innovation) 2016 Outstanding Field Leader of Shanghai 2014 Thousand Talents (Shanghai City) 2012 Thousand Youth Talents 2012 Program of Oriental Scholars (Shanghai) 2007 Profiled in Harvard Medical School Dean's Report 2002-2008 Fu Graduate Fellowship, Harvard University 2001 Guanghua Graduate Scholarship, Fudan Medical School 1999 Magna cum Laude, Fudan University	31 May 2019	seminar
18	Jonathan Kimmelman		James McGill Professor / Director of the Biomedical Ethics Unit of McGill University	Canada	PhD Bioethics, Meta-science	He chaired the ethics committee of the International Society of Stem Cell Research. 2014 Friedrich Bessel-Humboldt Award 2008 CIHR New Investigator Award	10 Jun 2019	He gave a lecture, "Risk, benefit, and ethics in early phase trials of novel therapies."
19	Yuqin Xiong		Undergratuate student, Columbia University	USA		Medical student	14 Jun-12 Aug 2019	Summer student on the exchange program
20	Laurent Magnin	50	Big Data Consultant, agile DSS Instrutor Concordia University	Canada	PhD Computer Science/Artificial Intelligence	2018- Current Position over 20 years of IT experience, played many roles, including project management, development team leader, architect, business rules expert, developer, research team leader, as well as researcher	26 Jun-27 Jun 2019	short-term stay for joint research Discussion about collavolation research: Cancer Genome and AI
21	Mahmoud Salami		Professor Director of Physiology, Kashan University	Iran	PhD	Specialist in neuroscience He is interested in memory and aninmal model of alzheimer's disease	29 Jun-23Dec 2019	Search collaboration
22	Agata Zielinska	28	MD-PhD student, Cambridge	UK	Medical Doctor	2019 Otto Hahn Medal, Max Planck Society 2018 Young Scientist of 2018 award, German Society of Cell Biology and Nikon	01 Jul-15Aug 2019	short-term stay for joint research
23	Aaron Zorn		Professor Cincinnati Childrens Hospital, Center for Stem Cell & Organoid Medicine (CuSTOM)	USA	Ph.D., Developmental Biology	He is a world-leading scientist and the head of CuSTOM, CCHMC; working in the field of human endodermal organoid research and in vivo/in vitro endoderm development	11 Jul-12 Jul 2019	Scientific Discussions
24	Jacqueline Severino	29	PhD student, Center for Genomic Regulation	Italy	PhD Molecular Biology	Currently in Gene Regulation, Stem Cells and Cancer Group 2014-2016 Master student at Huber Lab, EMBL	Aug.01- Aug.31, 2019	short-term stay for joint research
25	Akira Sawa		Professor Johns Hopkins University	USA	MD, PhD	Specialist in psychiatry Director of Johns Hopkins Schizophrenia Center	2 Aug 2019	Discussion on the genome-edited macaque monkey project
26	Hazam Zohny		Research Fellow University of Oxford	UK	Ph.D., Practical Ethics	He has conducted collaborative research in philosophy and applied ethics, and proactively engaged with policymakers, medical and criminal justice professionals, and the general public.	5 Sep 2019	He gave a lecture, "A welfarist account of medicalization."

	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				
27	Doug McConnel		Research Fellow, University of Oxford	UK	Ph.D., Practical Ethics	He has published and presented work related to the Wellcome Trust project 'Responsibility and Healthcare', the Centre for Neuroethics, and the forum for Mind, Value, and Mental Health.	5 Sep 2019	He gave a lecture, "Conscientious objection in healthcare: How much discretionary space best supports good medicine? "
28	Jacek Majewski		Associate Professor, Department of Human Genetics, McGill University and Genome Quebec Innovation Centre	Canada	PhD Biological Sciences	2011-2015 Canada Research Chair in Statistical Genomics (salary award)2005-2010 Canada Research Chair in Statistical Genomics (salary award) 2008 Department of Human Genetics, McGill University Teaching Award 2005 Finalist, CIHR Maud Menten Award 2004 Locust Valley High School Mentor Award	10 Sep 2019	seminar
29	Kei Igarashi		Assistant Professor Anatomy & Neurobiology, School of Medicine, UC Irvine	USA	PhD	specialist in the function of hippocampus and relatd structures 2020 CNLM Award Recipients 2019 New Vision Award, Donors Cure Foundation 2018 Ando Momofuku Award, Ando Foundation 2017 Mishima Kaiun Prize, Mishima Kaiun Memorial Foundation 2016 PRESTO Career Development Award, Japan Science and Technology Agency	11 Sep 2019	Seminar and lab tour
30	Peter Janssen		Professor KU Leuven	Belgium	MD, PhD	Specialist in visual and motor functions 2005 Career Development Award of the Human Frontiers Science Program 2001 Honorary Fellowship of the Belgian American Educational Foundation 2001 Award of the Research Council of the KU Leuven Biomedical Sciences	17 Sep 2019	Seminar and lab tour
31	Muhammad Zubair		PhD student KU Leuven	Belgium	PhD	PhD student in neuroscience	21 Sep-10 Oct 2019	collaborative project
32	Wim Vanduffel		Professor KU Leuven	Belgium	PhD	Specialist in visual and cognitive functions Head of the Research Group Neurophysiology Head of the Laboratory for Neuro- and Psychophysiology member of LBI - KU Leuven Brain Institute	26 Sep-30 Sep 2019	Discussion for collaborative project and seminar
33	Takamichi Tohyama		Research fellow University of Newcastle	UK	MD, PhD	Specialist in motor functions	4 Oct 2019	Seminar and lab tour

	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
			Position title, department, organization	Country				
34	Aris N.Economides	51	Vice President Research Skeletal Diseases TFA &Genome Engineering Technologies Co-founder & Head of Functional Modeling; Regeneron Genetics Center Regeneron Pharmaceuticals,Inc	USA	Ph.D	Analyzed the mechanism of a rare disease FOP, invented heteromeric receptor-based antagonists for cytokines ("Cytokine Traps"), and developed proprietary technology for rapid generation of 'knock-out' and transgenic animals	15 Oct 2019	Short-term stay for the seminar and discussion
35	Sara Karimi		Research fellow, Shahid Beheshti University of Medical Sciences	Iran	PhD	Postdoctoral fellow in neuroscinece	27 Oct 2019 -28 Feb 2020	Research experience based on IBRO fellowship
36	Muhhamad Zubair		PhD student, KU Leuven	Belgium	PhD	PhD student in neuroscience	28 Oct-13 Dec 2019	collaborative project
37	Konstantin Mischaikow		Professor Math Department, Rutgers University	USA	PhD	Specialist of Topological Methods for the Analysis of Dynamical Systems (Conley Index Theory) 2010 AMS Invited Address, AMS Sectional Meeting 2003 Best Paper Award, Trans, Japanese SIAM 1999 AMS Invited Address	28 Oct-1 Nov 2019	Speaker of ASHBi distinguished seminar. Collaboration with math G about dynamical system models of gene regulatory networks
38	Tomas Gedeon		Professor Department of Mathematidal Science Montana State University	USA	PhD	Specialist of Applied dynamical systems, mathematical biologyhe interested applied dynamical systems with applications in biological models, especially models of cell dynamics and gene regulation. 2015 Provost's Distinguished Lecture Serires 2012 Kopriva Lecture 2010 Dean's Award for Meritorious Research and Creativity	28 Oct-1 Nov 2019	Collaboration with math G about dynamical system models of gene regulatory networks
39	Marcio Gameiro		Assistant Professor Department of Applied Mathematics and Statistics, University of São Paulo at São Carlos	Brazil	PhD	Specialist of Applied dynamical systems, mathematical biology	28 Oct-1 Nov 2019	Collaboration with math G about dynamical system models of gene regulatory networks
40	Xiaoqin Wang		Professor Biomedical Engineering Johns Hopkins University	USA	PhD	Specialist in the auditory systems	22 Nov 2019	Seminar and lab tour
41	Yang Zhou		Assistant professor Faculty of Medicine, McGill University	Canada	PhD	He has generated SHANK3 KO monkey and published a Nature paper in 2019	4 Dec-6 Dec 2019	seminar, discussion about a collaborati
42	Thongchai Sooksawate		Associate Professor Faculty of Pharmaceutical Sciences, Chulalongkorn University	Thailand	PhD	Specialists in electrophysiology and behavioral anakysis	15 Dec-24 Dec 2019	Collaborative works on the function of superior colliculus in control of innate behavior

	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
			Position title, department, organization	Country				
43	Takafumi Ichikawa	33	postdoctoral fellow DB unit, EMBL	Germany	PhD, Agriculture	Postdoc at EMBL from 2017 His research is in Genetics, Cell Biology and Molecular Biology	23 Dec-25 Dec 2019	short-term stay for the lab set-up
44	Matilda Kjellander	27	PhD-student Karolinska University Hospital	Sweden	Master's degree Medical Study Program	2019 Parva Scintilla Medicorum 2019 medal Research of Comprehensive profiling of chronic (CMML) and juvenile (JMML) myelomonocytic leukemia aiming to identify novel targets for treatment	6 Jan-28 Feb 2020	short-term stay for joint research
45	Jon F. Merz		Associate Professor Department of Medical Ethics & Health Policy University of Pennsylvania	USA	Ph.D., Research Ethics	He is a prolific writer of journal articles and is the author of Current Controversies in the Biological Sciences: Case Studies of Policy Challenges from New Technologies, with Karen F. Greif.	23 Jan 2020	He gave a lecture, “Waivers of informed consent for research: A legal and historical review and consideration of emerging practice.”
46	Shigeki Nakagome		Ussher Assistant Professor School of Medicine, Faculty of Health Sciences Trinity College Dublin, University of Dublin	Ireland	Ph.D.	Specialist in population and functional genomics to develop statistical approaches for understanding selective pressures on immunity genes and to connect genetic polymorphisms to their functional consequences in the immune system 2013-2016 JSPS Overseas Resaearch Fellow 2011-2014 competitive Research Fellowship, JSPS	12 Feb 2020	Giving us a presentation about his study and having discussion about collaboration works
47	Andrew S. Levey	69	Chief Emeritus, Division of Nephrology, Professor Tufts University School of Medicine Dr. Gerald J. and Dorothy R. Friedman Professor Emeritus Tufts University School of Medicine	USA	MD	Established the measurement and estimation of kidney function. 2015-2020, "Top Doctor," Boston Magazine 2019, Web of Science Highly Cited Researcher 2014-18, "Highly Cited Researcher," Thomson Reuters/Clarivate Analytics 2016, Member, Association of American Physicians 2013, Belding H. Scribner Award from the American Society of Nephrology 2013, Distinguished Alumnus Award, Boston University School of Medicine 2012, David M. Hume Award from the National Kidney Foundation 2011, NKF Spring on the Park Gala honoree 2007, Faculty Recognition Award (25 years of service) from Tufts University School of Medicine 2004, Distinguished Faculty Award from Tufts University School of Medicine	20 Feb 2020	Short-term stay for the seminar and discussion

Appendix 6 FY2019 State of Outreach Activities

* Fill in the numbers of activities and times held during FY2019 by each activity.
* Describe the outreach activities in the "6. Others" of Progress Report, including those stated below that warrant special mention.

Activities	FY2019 (number of activities, times held)
Website	ASHBi website renewal
PR brochure, pamphlet	[Brochures] ASHBi brochure, WPI brochure vol 15, KUIAS 2019 brochure Kyoto U Research News 2020 Spring [Booklet] "Working with Professional Illustrators to Visualize Your Science" "Make Your Research Results into International News" [Flyers] 7 ASHBi Colloquium flyers, 20 ASHBi Seminar flyers,
Lectures, seminars for general public	25 Sep 2019 Lecture Series "東京で学ぶ京大の知 32 再生医療-現状と展望-" 17 Sep 2019 "WPIサロン" at Knowledge Capital, Osaka (joint with iCeMS, iFReC)
Participating, exhibiting in events	12 Jan 2020 8th WPI Science Symposium (Tokyo) 6-8 Aug 2019 SSH Festival (Kobe)
Press releases	14 Feb 2020 Research Result of Saitou on Science (Kyoto U) 19 Jan 2020 Saitou earns ISSCR Momentum Award (Kyoto U) 09 Jan 2020 Saitou wins Uehara Prize (Kyoto U) 06 Jan 2020 Saitou wins Asahi Prize (Kyoto U) 20 Dec 2019 Research Result of Ogawa on Nature (Kyoto U) 13 Dec 2019 Research Result of Ema&Tsukiyama on Nature Communications (Kyoto U, Shiga U of Medicine) 19 Sep 2019 Research Result of Isa on Journal of Neuroscience (Kyoto U) 21 May 2019 Research Result of Yamamoto on Stem Cell Reports
Others (Major Visits to ASHBi)	06 Feb 2020 Springer Nature Editorial leaders visit to ASHBi 16 Dec 2019 NCKU-iCeMS-ASHBi Joint Meeting 30 Oct 2019 British Embassy visit to 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 the Center's outreach activities carried out in FY 2019 that have contributed to enhancing the brand or recognition of your Center and/or the brand of the overall WPI program, if any, 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.

Appendix 7 FY 2019 List of Project's Media Coverage

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

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
1	04 Apr 2019	news website 1	[The Scientist] Bioethicists Concerned over Japan's Chimera Embryo Regulations - Introduction of the recent research result published in *Cell Stem Cell* by Fujita Group
2	11 Apr 2019	news website 1	[Diabetes Resource Guide Japan] 1型糖尿病の根治療法「バイオ人工膵島移植」も視野に　日本で「動物性集合胚」研究の規制が大幅に緩和　京都大学iPS細胞研究所など - Introduction of the recent research result published in *Cell Stem Cell* by Fujita Group
3	26 Jun 2019	jounal 1	[Science] Embryo experiments take 'baby steps' toward growing human organs in livestock - Introduction of her comment by Prof. Fujita
4	28 Jun 2019	jounal 1	[Science] Taking 'baby steps' to human organs in livestock - Introduction of her comment by Prof. Fujita
5	03 Jul 2019	news website 1	[Sputnik Mundo] Científicos quieren hacer crecer órganos humanos en... animales de granja - Introduction of her comment by Prof. Fujita
6	16 Sep 2019	newspaper 1	[Nikkan Kogyo Shimbun] - Introduction of the research result published in *Journal of Neuroscience* by Isa Group
7	28 Oct 2019	newspaper 1	[NIKKEI] - Introduction of the research result published in *Cell Reports* by Yamamoto Group
8	19 Dec 2019	news website 1	[科学网 小柯机器人] 研究揭示溃疡性结肠炎NFKBIZ通路存在频繁突变 - Introduction of the recent research result published in *Nature* by Ogawa Group

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
9	20 Dec 2019	newspaper 1	[The Kyoto Shimbun] - Introduction of the research result published in *Nature* by Ogawa Group
10	22 Dec 2019	news website 1	[医療NEWS] 潰瘍性大腸炎に罹患の大腸上皮、IL-17経路に発がん抑制の変異を持つと発見－京大ほか - Introduction of the research result published in *Nature* by Ogawa Group
11	23 Dec 2019	news website 1	[Asahi Shimbun Digital] 通常の3倍の速さで遺伝子が変異　腸の難病と発がん関係 - Introduction of the research result published in *Nature* by Ogawa Group
12	01 Jan 2020	newspaper 1	[Asahi Shimbun] - Introduction of the Asahi Prize for Prof. Saitou
13	01 Jan 2020	news website 4	[YAHOO news Jan. 1, The Sankei News Jan. 1, msn news Jan. 1, Mainichi Shimbun Jan. 1, excite news Jan. 4] - Introduction of The Asahi Prize for Prof. Saitou
14	08 Jan 2020	jounal 1	[Natureハイライト] 遺伝学：正常組織と炎症が関わる腫瘍組織におけるクローン選択パターン - Introduction of the research result published in *Nature* by Ogawa Group
15	14 Jan 2020	news website 1	[News Break] - Introduction of ISSCR Momentum Award for Prof. Saitou
16	21 Jan 2020	jounal 1	[Nature Research Highlight] Shining a spotlight on somatic mutations in ulcerative colitis - Introduction of the research result published in *Nature* by Ogawa Group
17	24 Jan 2020	newspaper 1	[Yomiuri Shimbun Jan. 24] - Introduction of the recent research result published in *Nature* Communications by Ema Group
18	24 Jan 2020	newspaper 1	[Yomiuri Shimbun] - Introduction of the recent research result published in *Nature Communications* by Ema Group

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
19	14 Feb 2020	news website 1	[JIJI.COM] 卵子形成が始まる仕組み解明　マウスの生殖細胞ー京大 - Introduction of the research result published in *Science* by Saitou Group
20	14 Feb 2020	television 1	[NHK Kyoto] - Introduction of the research result published in *Science* by Saitou Group
21	14 Feb 2020	news website 1	[The Kyoto Shimbun] - Introduction of the research result published in *Science* by Saitou Group
22	16 Feb 2020	news website 1	[NIKKEI] 卵母細胞への成長、詳細な仕組み解明 - Introduction of the research result published in *Science* by Saitou Group
23	16 Feb 2020	news website 1	[医療NEWS] 世界初、生殖細胞が卵母細胞に分化する仕組みを解明ー京大 - Introduction of the research result published in *Science* by Saitou Group
24	17 Feb 2020	news website 1	[科学网 小柯机器人] ZGLP1是小鼠卵源命运的决定因素 - Introduction of the recent research result published in *Science* by Ogawa Group
25	18 Feb 2020	newspaper 2	[Asahi Shimbun Feb. 20, Yomiuri Shimbun Feb. 18] - Introduction of the recent research result published in *Science* by Saitou Group
26	02 Apr 2020	newspaper 2	[Nikkan Kogyo Shimbun Apr.2, NIKKEI Apr. 6] - Introduction of the research result published in *Nature* by Alev Group
27	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