World Premier International Research Center Initiative (WPI)
Executive Summary (For Interim Evaluation)

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

Instruction:
Summarize the Self-Evaluation Report for Interim Evaluation (**within 4 pages** including this page).

I. Summary

The Institute for the Advanced Study of Human Biology (ASHBi) has been established as a highly coherent, international institute investigating the core concepts of what makes us human, with 18 PIs, 42 researchers, 99 associated graduate students, and 32 supporting staff (as of April 2022). ASHBi has developed a world-class research environment that enhances scientific interactions and collaborations. This includes three core facilities with forefront technologies (**S**ingle-cell **G**enome I**n**formation **A**nalysis **C**ore: **SignAC**; **Prim**ate Genome **E**ngineering core: **PRiME**; **N**on-human **P**rimate **A**nalysis **F**acility: **NPAF**) as well as an excellent administrative support system. ASHBi has made salient research achievements (209 WPI papers and 281 WPI-related papers), including the elucidation of key principles for mammalian early development, establishment of a foundation for human *in vitro* gametogenesis, identification of age-associated remodeling and clonal expansion in human tissues and diseases, mathematical foundation for novel single-cell RNA sequence analysis methods, and bioethics research for advancing human stem-cell research and human biology, which are congruent with ASHBi's five key goals (see **II. Items 1. Overall Image of Your Center**). Thus, ASHBi has contributed profoundly to the promotion of human biology in development, physiology, and diseases as well as to the fusion of human biology with the fields of mathematics and bioethics. Accordingly, ASHBi PIs have been invited to numerous internationally renowned meetings for lectures and awarded prestigious prizes. ASHBi has established a tight bond with McGill University through Kyoto University (KU)-McGill University Graduate Program, with International Society for Stem Cell Research (ISSCR) as an invited member of "International Circle of Stem Cell Research Institutes and Centers", and with European Molecular Biology Organization (EMBO) as two PIs being elected as EMBO Member/Associate Member, and the establishments of further partnerships with international institutes are in progress/under discussion. ASHBi has so far organized three large-scale international symposia, one international summer school, two SignAC workshops, a number of workshops for mathematics and bioeithcs, and numerous ASHBi seminars, creating ample opportunities for active discussion with world-class researchers. Furthermore, several ASHBi PIs have been actively pursuing industry-academia collaborations and involved in outreach activities targeting younger generations, such as middle and high school students. ASHBi will continue to strive for realizing its goals, in part through rigorously performing the flagship projects, which will further strengthen the interactions among PIs and the identity of ASHBi (see **7. Future Prospects**). After the WPI funding ends, KU will provide support essential for the maintenance of the key activities of ASHBi, including tenure PI posts and support for the core facilities, administrative organization, and the operation of the ASHBi main building. ASHBi and KU will make all the efforts to realize the autonomy of ASHBi and further reformation of the KU research activities.

II. Items

1. Overall Image of Your Center

ASHBi is an institute that investigates the core concepts of human biology, consisting of 18 PIs, 42 researchers, 99 associated graduate students, and 32 supporting staff (as of April 2022). 7 PIs have their labs in the ASHBi main building, 9 PIs have their labs in and around the Faculty of Medicine Campus where the main building is located, and 2 PIs bear their labs in the Shiga University of Medical Science (SUMS).

The research in ASHBi covers four areas of human biology (developmental biology, genome informatics, primate models/macaque genome engineering, and basic/clinical medicine) as well as the fusion of human biology research with mathematics and

bioethics/philosophy. The five major research goals are: 1) To promote the study of human biology, with a focus on genome regulation; 2) To clarify the principles defining the species differences and human traits; 3) To generate primate models for intractable human diseases; 4) To reconstitute key human cell lineages or tissues *in vitro*; and 5) To contribute to formalizing an international ethics standard for human biology research.

ASHBi has also three core facilities with cutting-edge technologies, SignAC, PRiME, and NPAF. SignAC, having joined the Innovative Support Alliance for Life Science (iSAL) at KU, functions as a core facility for life science research across the KU campus.

2. Center's Research Activities

Since the launch in October 2018, ASHBi has published 209 WPI papers and 281 WPI-related papers. 10 representative research results are: 1) Elucidation of key principles for mammalian early development; 2) *In vitro* reconstitution of human segmentation clock and somitogenesis; 3) Establishing a foundation for human *in vitro* gametogenesis; 4) Identification of *cis* regulatory elements in human physiology and disease; 5) Unraveling the mechanism for the plasticity of critical neural circuits in primates; 6) Age-associated remodeling and clonal expansion in human tissues and diseases; 7) Elucidating the role of tertiary lymphoid tissues for kidney pathogenesis; 8) Human immunology in physiology, aging, and diseases; 9) Mathematical foundation for novel single-cell RNA sequence analysis methods; 10) Bioethics for promoting human stem-cell research and human biology (see **Appendix 1-1** for details). Reflecting the top-level research performance of ASHBi PIs, they have been invited to numerous internationally renowned meetings (e.g., International Society for Stem Cell Research (ISSCR) meetings, Cold Spring Harbor Laboratory (CSHL) meetings, etc) to give talks and have also been awarded prestigious prizes for their achievements (the Imperial Prize, the Japan Academy Prize from the Japan Academy, ISSCR Momentum Award, EMBO membership, the Baelz Prize from Boehringer Ingelheim, etc.).

3. Feeding Research Outcomes Back into Society

To return the research outcomes obtained at the Institute back to society, ASHBi PIs are actively pursuing industry-academia collaborations. For example, one PI co-founded a venture company to develop and validate germline production methods, and another PI served as a science advisor at a venture company to provide advice in developing innovative drug discovery and diagnostic methods. In addition, ASHBi's PIs are also active in acquiring intellectual property. As notable examples, some patents were filed by the math-biology fusion study of a new methodology for analyzing single-cell RNA sequencing data, the studies of primate models, and studies of germline production methods.

To publicize the Institute's research activities to society, we make effective use of international news releases, websites, and social networking services. To share important academic discoveries with the world, ASHBi has effectively utilized the international news releases platform (EurekAlert!). In FY2021 alone, we distributed 17 English press releases via EurekAlert! The Institute's website was launched in FY2018. Since the site was launched, it has been viewed more than 600,000 times, with approximately 20% of those views coming from overseas. A Twitter account was also opened in December 2020. Publicity via Twitter has been effective, with more than 20% of visitors to our website coming via Twitter. To attract widespread interest from society (especially young researchers from overseas), we disseminate seasonal photos (e.g. cherry blossoms) and event information (e.g. awards for young researchers at the ASHBi Retreat) on our website and Twitter, allowing outside researchers and the general public to learn about ASHBi's research life.

To stimulate interest in academic research, ASHBi PIs are also actively involved in outreach activities targeting middle and high school students. Two PIs were invited to speak at high schools in Kyoto and Kagawa in FY2021, respectively, and another PI was invited to an online seminar organized by middle school students in FY2021.

4. Generating Fused Disciplines

ASHBi has been conducting research fusion of human biology with mathematics and bioethics/philosophy. The key activities of the mathematics-biology fusion research include ASHBi Math-Biology seminars (~every two weeks), expansion of the mathematics groups, and active collaborations outside ASHBi. This has led to the development of novel analysis algorithms, including RECODE (noise reduction for scRNA-seq data), GMM-OT (elucidating dynamics of single-cell populations), GRN-LiNGAM (identifying gene regulatory network from causality), v-Mapper (clarifying complex topological structure and dynamics in single-cell data), and topological node2vec (reconstructing 3D chromatin conformation from Hi-C data).

The key themes of the ethics-biology fusion have been evolving from those focused on advancing stem-cell biology to those with more general implications. Currently, the three major projects include the establishment of the regulatory frameworks for the research use of 1) human fetal tissues and 2) early postmortem tissues, and 3) the ethics of early developmental biology research. Additionally, ASHBi PIs have been involved in work to revise the guidelines of the ISSCR, published white papers on these guidelines, and responded to hearings at the Cabinet Office's Expert Committee on Bioethics, gradually achieving a track record of activities leading to the establishment of research rules in Japan and abroad. Furthermore, the bottom-up fusion research has been promoted with the "ASHBi Fusion Research Grant Program" and ~10 projects led by young researchers are currently under active progress.

5. Realizing an International Research Environment

Since the Institute's establishment, we have been working to internationalize our research members. To promote the internationalization of the ASHBi PIs, a foreign female researcher was hired as a PI in FY2021. Currently, 4 out of 18 PIs are foreign PIs, and the ratio of foreign PIs is 22% (= 4/18), exceeding the WPI standard of 20%.

To recruit foreign researchers under the COVID-19 epidemic situation, we had focused on hiring foreign researchers who had been already working at Japanese universities and research institutes. In addition, we also utilized the "ASHBi Foreign Researcher Employment Support Program" established in FY2020. Through these efforts, the ratio of foreign researchers had increased to 32% in April 2022, satisfying the WPI standard. In parallel with the recruitment of foreign researchers, we have also made efforts to recruit female researchers, and the percentage of female researchers had increased to 23% in April 2022.

To promote the recruitment of international graduate students, we utilized the McGill-Kyoto International Collaborative Program and the "ASHBi Financial Support Program for International Graduate Students". Through these programs, as of April 2022, ASHBi PIs receive 99 graduate students, of which 22 are international students and 34 are female students.

To create opportunities to interact with overseas researchers even under the COVID-19 pandemic, we have actively held virtual/online meetings. In FY2021 alone, we held 12 ASHBi seminars with overseas researchers. We have also actively organized large-scale international symposiums and international summer schools. The 1st international symposium was held in November 2021, the 2nd symposium was held in March 2022, jointly with the JSPS Grant-in-Aid for Scientific Research on Innovative Areas, and the 3rd Workshop was held in April 2022, jointly with EMBO. An international summer school was also held in September 2021 in collaboration with Norwegian government agencies.

ASHBi has also organized a number of research meetings dedicated to specific objectives. For example, SignAC hosts an annual workshop to present and discuss recent innovations and applications of single-cell approaches to fundamental biological problems. In addition, our Mathematics Group and Bioethics Group have actively organized research meetings to make discussions with world-class researchers regarding the fusion studies of mathematics and biology, and bioethics and biology, respectively.

We provide a variety of support services for foreign researchers when they are accepted. When entering Japan, we provide support for visa applications, house hunting, etc. When setting up a laboratory, we provide appropriate laboratory space and start-up funding. Furthermore, if a foreign researcher faces a problem, the Institute's URA will discuss it with the foreign researcher and find a solution.

6. Making Organizational Reforms

The Director's leadership of the ASHBi's operations is secured under the Kyoto University Institute for Advanced Study (KUIAS) umbrella. KUIAS is designated with special privileges and therefore has a high degree of autonomy, making it easier for ASHBi to implement system reforms.

ASHBi administrative office consists of the "Administrative Management Unit" and the "Research Acceleration Unit". While the former unit is responsible for regular administrative operations, the latter unit is responsible for providing flexible and problem-solving type support. Thus, the Research Acceleration Unit is the centerpiece of the ASHBi administrative office and an indispensable part of the administrative department that creates the research environment required at WPI sites.

As a successful model of a core facility, SignAC is expected to play a central role in the university-wide core facility concept envisioned in KU's future plan. The unique feature of SignAC is that this core facility is constantly updating its analytical technology by having its own research staff. This gives SignAC a strong competitive edge compared with other core facilities. KU highly appreciates this competitive edge and plant to use SignAC as a good practice for university-wide core facility development in its future plan.

KU has provided personnel and financial support which are crucial for developing our institute. KU provided two tenure posts, and ASHBi has been able to hire two new PIs as tenured professors. KU allows us to take the headquarters' dividend, which is half of the total of the indirect funds from competitive grants acquired by ASHBi researchers. KU also provided a special budget (approx. 100 million yen) in FY2021 to purchase a 3rd-generation long-read sequencer. Finally, KU allowed us to introduce a multi-year budget for indirect funds, increasing the flexibility of our budget planning.

7. Future Prospects

ASHBi has been established as a highly coherent, international institute with splendid research environments, ample interactions, and an excellent administrative support system, and has made salient achievements congruent with the five key goals, contributing eminently to the promotion of human biology in development, physiology, and diseases as well as the fusion of human biology with mathematics and bioethics. In the second half, we will continue and expand on what we have done during the first half. Furthermore, to further strengthen the interactions among PIs and the identity of ASHBi, we will embark on the five flagship projects, which are: 1) Mechanism and *in vitro* reconstitution of primate development; 2) Interdisciplinary analysis for disease-associated gene functions in primates; 3) Age-associated genomic alterations and their interplay with immune system; 4) Establishment of "data representation theory"; and 5) Bioethics at the periphery of birth and death. After the WPI funding ends, KU will provide support essential for the maintenance of the key activities of ASHBi, including tenure PI and support for core facilities, the administrative organization, and the running of the ASHBi main building. This will in part depends on the acquisition by KU of the MEXT's "International University of Excellence" program, and ASHBi and KU will make all the efforts to realize the autonomy of ASHBi and the reformation of the KU research activities.

8. Host Institution's Concrete Plan toward Achieving the Center's Independence over the Next 5 Years (from its sixth year)

Minimum functions required to sustain ASHBi will be to maintain (1) employment of PI/Co-PIs and at least one postdoc for each PI group in KU, (2) function of the SignAC Core Facility, (3) research support and administrative functions developed by the ASHBi administrative office, and (4) the ASHBi Main Building serving as the base/hub of ASHBi researchers. KU understands these requirements and will provide the necessary support for the Institute's autonomy (*providing tenure posts, University-wide core facility development, and indirect fund support*). With this support, the institute will be able to maintain its core functions. Furthermore, if KU succeeds in obtaining the MEXT's "International University of Excellence (国際卓越研究大学)" program, KU will provide additional personnel and funding support for the further development of ASHBi/KUIAS as a university-wide research platform that transcends departmental boundaries.

9. Others

Other than the ASHBi, KU hosts another WPI center, the iCeMS (the Institute for Integrated Cell-Material Sciences). To improve the relationships between the two WPI centers, we have actively cooperated in organizing important institutional events, such as retreats and research meetings.

10. Center's Response to Results of FY2021 Follow-up (including Site Visit Results)

ASHBi has responded to all the recommendations on administration and science of ASHBi made by the WPI Program Committee in FY2021. The responses include a concrete plan of KU to support the autonomy of ASHBi in the future, ASHBi's action to increase the number of young female investigators, a polish-up of the Flagship Projects, the publication of a noise reduction method for scRNA-seq data (RECODE), an international leadership in bioethics discussions, a polish-up of the research using primate models, and ASHBi's projects for the identification of the genomic sequences (or regions) that make us human.

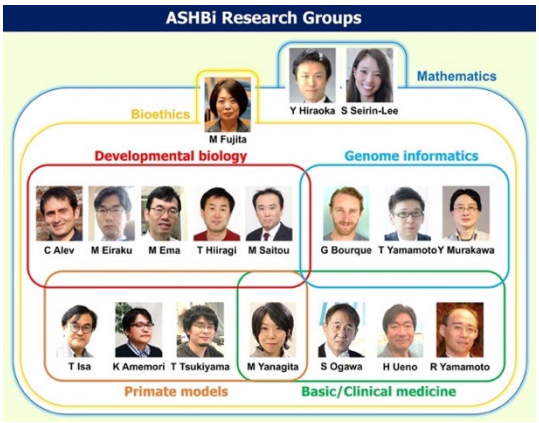
World Premier International Research Center Initiative (WPI)
Self-Evaluation Report for Interim Evaluation

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

Common Instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2022) situation of your WPI center.
* As a rule, keep the length of your report within the specified number of pages. (The attached forms are not included to this page count.)
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

1. Overall Image of Your Center (write within 2 pages including this page)

Describe the Center's current identity and overall image.
・ List the Principal Investigators in Appendix 2, and enter the number of center personnel in Appendix 3-1, 3-2, diagram the center's management system in Appendix 3-3, draw a campus map in Appendix 3-4, and enter project funding in Appendix 3-5, 3-6.



The Institute for the Advanced Study of Human Biology (ASHBi) was launched in October 2018 as an institute to investigate the core concepts of human biology. In the three and a half years since, ASHBi has grown progressively and currently consists of 18 principal investigator (PIs), 42 researchers, 99 associated graduate students, and 32 supporting staff. Specifically, ASHBi consists of four life-science research platforms (Developmental Biology: **Alev**, **Eiraku**, **Ema**, **Hiiragi**, **Saitou**; Genome Informatics: **Bourque**, **Murakawa**, **T. Yamamoto**; Primate Models/Macaque Genome Engineering: **Amemori**, **Isa**, **Tsukiyama**; Basic/Clinical Medicine: **S. Ogawa**, **Ueno**, **R. Yamamoto**, **Yanagita**), two interdisciplinary research platforms (Mathematics: **Hiraoka**, **Seirin-Lee**; Bioethics/Philosophy: **Fujita**), three core facilities (**Si**ngle-cell **G**enome I**n**formation **A**nalysis **C**ore (SignAC): **T. Yamamoto**; **Prim**ate Genome **E**ngineering Core (PRiME): **Tsukiyama**; **N**on-human **P**rimate **A**nalysis **F**acility (NPAF): **Isa**), and the ASHBi administrative office (**T. Ogawa**).

The ASHBi main building (Building B in the Graduate School of Medicine campus) is located in the center of the Graduate School of Medicine campus, and contains the laboratory space for overseas PIs (**Bourque**, **Hiiragi**), early-career PIs (**Alev**, **Amemori**, **R. Yamamoto**), the Kyoto University Institute for Advanced Study (KUIAS) PI (**Murakawa**), Mathematics and Bioethics/Philosophy groups (**Hiraoka**, **Seirin-Lee**, **Fujita**), SignAC, and the administrative office. The laboratories of KU PIs (**Eiraku**, **Isa**, **S. Ogawa**, **Saitou**, **Ueno**, **T. Yamamoto**) and NPAF are located within a 5-minute walking distance from the ASHBi main building, and the laboratory of **Ema** and PRiME are located in the Shiga University of Medical Science (SUMS). Accordingly, ASHBi performs investigations in a highly interactive environment in line with five major areas of focus:

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

Reflecting the expertise of the PIs, focus area **1** covers areas as broad as reproduction, development, growth and aging as well as heredity and evolution. Since October 2018, we have published 209 WPI papers and 281 WPI-related papers (see **2-1. Research results to date** for 10 representative research results). In addition to these results, the impact of the research by the ASHBi PIs is evidenced by their

influential review articles in the relevant fields, including "Symmetry breaking in the mammalian embryo" (*Annu. Rev. Cell Dev. Biol.* **34**, 405-426, 2018) (**Hiiragi G**), "The tectum/superior colliculus as the vertebrate solution for spatial sensory integration and action" (*Curr. Biol.* **31**, R741-R762, 2021) (**Isa G**), "Clonal expansion in non-cancer tissues" (*Nat. Rev. Cancer* **21**, 239-256, 2021) (**Ogawa G**), and "Mammalian *in vitro* gametogenesis" (*Science* **374**, eaaz6830, 2021) (**Saitou G**).

The interdisciplinary research in two areas (**mathematics–biology fusion** and **ethics–biology fusion**) has been performed in both a "top-down" and a "bottom-up" manner. The "top-down" **mathematics–biology fusion** includes organization of an ASHBi Math-Biology seminar (~every two weeks), expansion of the mathematics groups (**Hiraoka G** and **Seirin-Lee G**), and active collaborations outside ASHBi (e.g., **Prof. Iwami** at Nagoya U (math biology), **Prof. Shimizu** at Shiga U (machine learning)), and this has led to the development of analysis algorithms, including RECODE (noise reduction for scRNA-seq data), GMM-OT (elucidating dynamics of single-cell populations), GRN-LiNGAM (identifying gene regulatory network from causality), v-Mapper (clarifying complex topological structure and dynamics in single-cell data), and topological node2vec (reconstructing 3D chromatin conformation from Hi-C data) (see **4-3. Results of research in fused research fields**). We have published a description of the development of RECODE in *bioRxiv* (https://doi.org/10.1101/2022.05.02.490246). The key themes of the **ethics–biology fusion** have been evolving from those focused on advanced stem-cell biology to those with more general implications, along with the publication of several key papers; currently the three major projects consist of establishing the regulatory frameworks for the research use of 1) human fetal tissues and 2) early postmortem tissues, and 3) investigation into the ethics of early developmental biology research, including organoid or synthetic human embryology research. Additionally, **Saitou** and **Fujita** have been involved in revising the guidelines of the ISSCR, have published white papers on these guidelines (*Stem Cell Rep.* **16**, 1398-1408, 2021), and have responded to hearings at the Cabinet Office's Expert Committee on Bioethics, steadily achieving a track record of activities leading to the establishment of standardized research rules in Japan and abroad. The "bottom-up" **mathematics/ethics–biology fusion** has been promoted by the "**ASHBi Fusion Research Grant Program**", with ~10 projects proposed and led by young researchers in ASHBi currently in progress (see **4-2. State of "bottom-up" undertakings**). Notably, some of the achievements from such undertakings have been published in a paper recently involving extensive international collaborations (*Nagano* et al., *EMBO J*, in press).

ASHBi has been making use of primate models as a key resource for promoting human biology and delineating human evolution. With regards to intractable human diseases, we have generated models for autosomal dominant polycystic kidney disease (ADPKD: *PKD1* knockout) (*Nat. Commun.* **10**, 5517, 2019) (**Ema G** and **Tsukiyama G**), nephronophthisis (*NPHP1* knockout) **(Yanagita G**), and psychosis (*DISC1* knockout) (**Isa G**). Unlike the mouse models, both *PKD1* and *NPHP1* knockout (KO) monkeys have shown precise recapitulations of human disease phenotypes, while *DISC1* KO monkeys initiate to develop characteristic neuronal abnormalities. Thus, these models are useful for analyzing early pathological changes as well as the pathogenesis of these diseases, creating a potential target for novel therapeutics. Furthermore, notable progress has been made in areas such as the identification of large-scale plastic change of axonal trajectories of the corticospinal neurons through intensive rehabilitative training after spinal cord injury (**Isa G**) and a program of X-chromosome dosage compensation during the development of cynomolgus monkeys (*Science* **374**, 954 (eabd8887), 2021) (**Saitou G**).

More recently, to further strengthen the interactions among PIs and the identity of the institute, we have set up five flagship projects in accord with the five focus areas described above (for details see **10. The Center's Response to Results of the FY2021 Follow-up, Response 1**):

1. **Mechanism and *in vitro* reconstitution of primate development**
2. **Interdisciplinary analysis for disease-associated gene functions in primates**
3. **Age-associated genomic alterations and their interplay with the immune system**
4. **Establishment of "data representation theory"**
5. **Bioethics at the periphery of birth and death**

With strong support by the ASHBi administrative office (**T. Ogawa**) and through domestic and international active collaborations, we continue to strive to realize our goals for understanding the key biological traits that make us human and for developing innovative therapies.

2. Center's Research Activities (within 8 pages)

2-1. Research results to date

Give an overall picture of the Center's research activities. Select 10 representative research results achieved during the period from 2018 through March 2022. Number them [1] to [10] and provide a description of each.

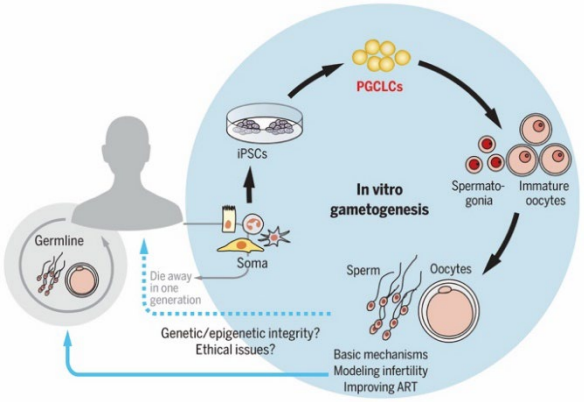
- In Appendix 1-1, list the papers underscoring each research achievement (up to 20 papers) and provide a description of each of their significance. And in Appendix 1-4 list the center's research papers published in 2021.

ASHBi launched in October 2018 as an institute tasked with investigating the key aspects of human biology. ASHBi consists of four life-science research platforms (Developmental Biology, Genome Informatics, Macaque Genome Engineering, and Basic/Clinical Medicine: 15 PIs), two interdisciplinary research platforms (Mathematics and Bioethics/Philosophy: 3 PIs), and three core facilities (SignAC, PRiME, and NPAF). and performs investigations In this highly interactive environment, research is conducted under five major areas of focus (for more details see **1. Overall Image of Your Center**). Since October 2018, we have published 209 WPI manuscripts (original: 175; review: 29; others: 5) and 281 WPI-related manuscripts (original: 254; review: 24; others: 3) (as of early April, 2022). Ten representative research results are as follows:

[1] Elucidation of key principles for mammalian early development
Hiiragi G has revealed a mechanism for hydraulic control of mammalian embryo size and cell fate, which has a general impact on how forces feedback on morphogenesis and tissue function. **Hiiragi G** has also established an *ex vivo* system to study cellular dynamics underlying mouse peri-implantation development, creating a basis for understanding human peri-implantation development (Appendix 1-1: Manuscript number 1, 2) (Developmental Biology; relevant to **Focus Areas 2**, **4**).

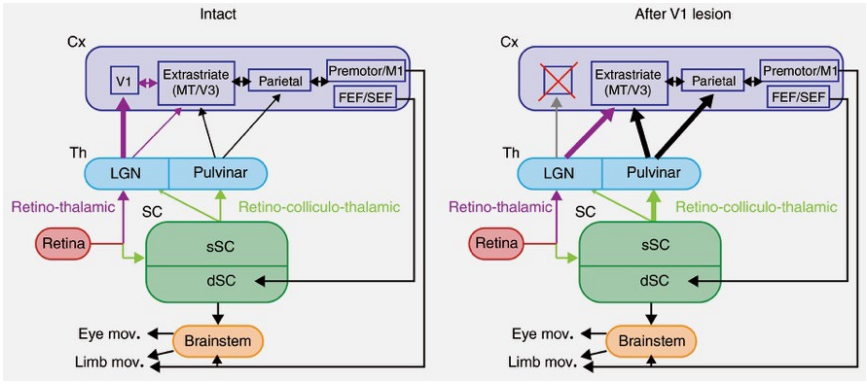
[2] *In vitro* reconstitution of the human segmentation clock and somitogenesis
Alev G, in collaboration with **Yamamoto G**, has succeeded in recapitulating the human segmentation clock with pluripotent stem cells (PSCs), providing critical insights into the human segmentation clock as well as diseases affecting axial skeletogenesis. Based on their *in vitro* system, they have revealed that species-specific oscillation periods of human and mouse segmentation clocks are due to cell autonomous differences in biochemical reaction parameters, and have thus created a basis for understanding an evolutionary mechanism underlying species-specific developmental patterning (Appendix 1-1: Manuscript number 3, 4) (Developmental Biology; relevant to **Focus Areas 1**, **2**, **4**).

[3] Establishing a foundation for human *in vitro* gametogenesis
Human *in vitro* gametogenesis may transform reproductive medicine. **Saitou G** has demonstrated the induction of human oogonia and early oocytes from induced pluripotent stem cells (iPSCs). **Saitou G**, in collaboration with **Yamamoto G**, has identified ZGLP1 as a determinant for the oogenic fate in mice, and, in collaboration with **Ema G** and **Yamamoto G**, elucidated the X-chromosome dosage compensation program during the development of cynomolgus monkeys, creating a critical foundation for further promoting human *in vitro* oogenesis research (**Figure**: *In vitro* gametogenesis: *Science* **374**, eaaz6830, 2021) (Appendix 1-1: Manuscript number 5, 6, 7) (Developmental Biology; relevant to **Focus Areas 1**, **2**, **4**).

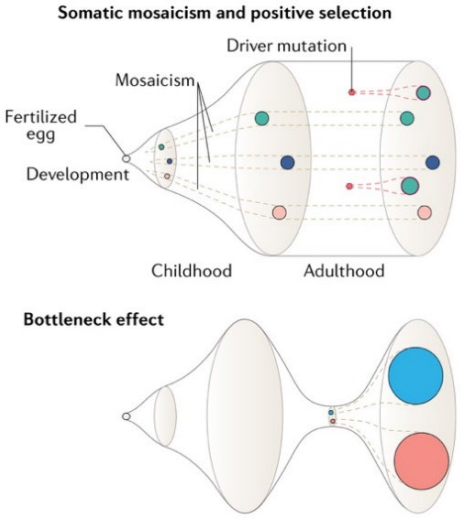


[4] Identification of *cis* regulatory elements in human physiology and disease
Murakawa G has developed a simple and robust method, called native elongating transcript–cap analysis of gene expression (NET-CAGE), to elucidate the architecture and function of enhancers. This led to the identification of tens of thousands of novel active enhancers in the human genome at a single-nucleotide resolution. Building on this work, **Murakawa G** has now developed single-cell NET-CAGE, which will allow the functional interpretation of human genetics data, including genome-wide association studies (Appendix 1-1: Manuscript number 8) (Genome Informatics; relevant to **Focus Areas 1**, **2**).

[5] Unraveling the mechanism for the plasticity of critical neural circuits in primates
Blindsight is a phenomenon in which patients with damage to the primary visual cortex (V1), despite the loss of visual awareness, perform visually guided goal-directed behaviors. Using primate models, **Isa G** has demonstrated that, in animals with the V1 lesion, both the lateral geniculate–extrastriate cortex pathway and the superior colliculus–pulvinar–extrastriate cortex pathway mediate blindsight, thereby clarifying the mechanism underlying the plasticity of neural circuits for visual perception. Furthermore, **Isa G** has shown the similarity of the saccade mechanism among humans, monkeys, and marmosets, demonstrating that marmosets are an appropriate model to study neural mechanisms for active vision and attention (**Figure**: Visual pathway before and after V1 damage: *Curr. Biol*. **31**, R741-R762, 2021) (Appendix 1-1: Manuscript number 9, 10) (Primate Models/Macaque Genome Engineering; relevant to **Focus Area 3**).



[6] Age-associated remodeling and clonal expansion in human tissues and diseases
Ogawa G has demonstrated the age-related remodeling of esophageal epithelia by mutated cancer drivers, creating a basis for delineating a comprehensive picture of clonal selection and evolution as a nascent step of tumorigenesis. **Ogawa G** has also identified frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis, a common inflammatory bowel disease, highlighting the common and discrete mechanisms of clonal selection in inflammatory tissues. In addition, this group delineated a combined landscape of single-nucleotide variants (SNVs) and copy number alterations (CNAs) in clonal hematopoiesis, underscoring the importance of detecting both SNVs/indels and CNAs in the evaluation of clonal hematopoiesis (**Figure**: Somatic mosaicism and positive selection: *Nat. Rev. Cancer* **21**, 239-256, 2021) (Appendix 1-1: Manuscript number 11, 12, 13) (Basic/Clinical Medicine; relevant to **Focus Area 1**).

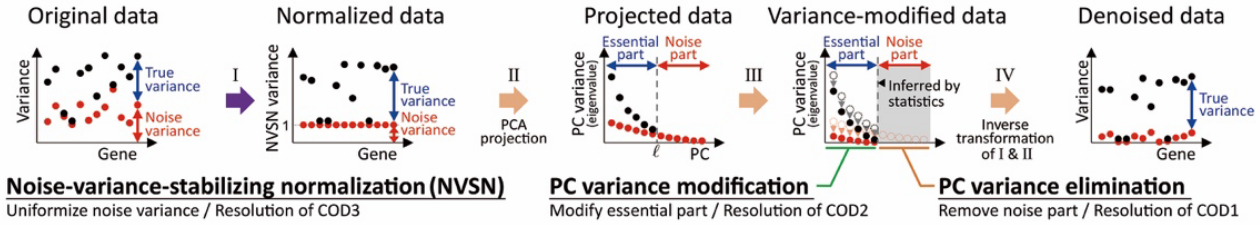


[7] Elucidating the role of tertiary lymphoid tissues for kidney pathogenesis
Tertiary lymphoid tissues (TLTs) facilitate local T and B cell interactions in chronically inflamed organs. **Yanagita G** has analyzed surgically resected kidneys from patients, classified TLTs into three distinct stages, and showed that TLT stages reflect local injury/inflammation in human kidneys. In collaboration with **T. Yamamoto G** and **Murakawa G**, **Yanagita G** has also identified a signaling pathway promoting age-dependent TLT expansion and kidney injury, which could serve as a therapeutic target for slowing down kidney disease progression (Appendix 1-1: Manuscript number 14, 15) (Basic/Clinical Medicine; relevant to **Focus Area 1**).

[8] Human immunology in physiology, aging, and diseases
T follicular helper (Tfh) cells represent the major CD4+ T cell subset associated with antibody responses *in vivo*. Whereas Tfh cells can become memory cells and survive for a long time, the mechanism by which Tfh cells become memory Tfh cells remains largely unclear. **Ueno G** has identified the transcription factor Tox2 as a vital factor for the maintenance of T follicular helper (Tfh) cells in germinal centers (GC) and the generation of memory Tfh cells. Tox2 is highly integrated into the durable GC Tfh cell response and the development of memory Tfh cells in mice and humans

(Appendix 1-1: Manuscript number 16) (Basic/Clinical Medicine; relevant to **Focus Areas 1** and **2**).

[9] Mathematical foundation for novel single-cell RNA sequence analysis methods
Single-cell RNA-seq data are high-dimensional data with substantial technical noise, which engender a statistical problem known as the curse of dimensionality (COD). **Hiraoka G** and **Saitou G**



formulated an algorithm for the resolution of the curse of dimensionality (RECODE) in single-cell RNA sequencing (scRNA-seq) data analysis. RECODE eliminates COD in relevant scRNA-seq data with unique molecular identifiers. RECODE recovers expression values for all genes, including lowly expressed genes, realizing precise delineation of cell-fate transitions/identification of rare cells with all gene information. RECODE represents a general strategy for preprocessing noisy high-dimensional data (**Figure**: Sketch of four procedures in RECODE) (Appendix 1-1: Manuscript number 17) (Mathematics; relevant to **Focus Area 2**).

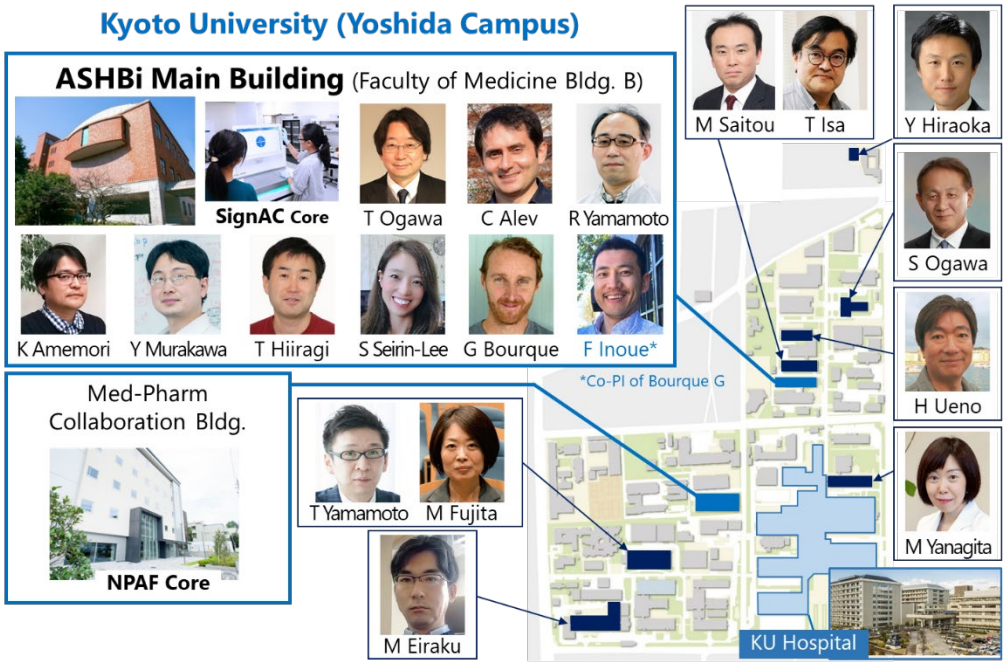
[10] Bioethics for promoting human stem-cell research and human biology
Fujita G has discussed the ethics of cerebral organoid research, with a focus on answering the question, "What type of consciousness in cerebral organoids would make them ethically problematic?" They also discussed the moral status of human embryo-like structures, providing a rationale for the application of the 14-day rule to embryoid structures *in vitro*. Furthermore, through an intensive international discussion over nearly two years, **Fujita** and **Saitou** have contributed to the preparation of a white paper summarizing the major updates of the ISSCR Guidelines for Stem Cell Research and Clinical Translation (Appendix 1-1: Manuscript number 18, 19, 20) (Bioethics/Philosophy; relevant to **Focus Area 5**).

2-2. Research environment including facilities and equipment

Describe the degree to which the Center has prepared a research environment appropriate for a world premier international research center, including facilities, equipment, and support systems, and describe the functionality of that environment.

Research environment with close interactions

Of the 18 PIs, 16 PI group laboratories are concentrated within a 5-minute walking distance from the **ASHBi Main Building** (Medical Campus Building B), enabling ASHBi researchers for close interaction. The main building houses two overseas PIs and one co-PI, five newly hired early-career PIs, and the Administrative Director.
Furthermore, the Building is located in the heart of the KU Graduate School of Medicine and KU



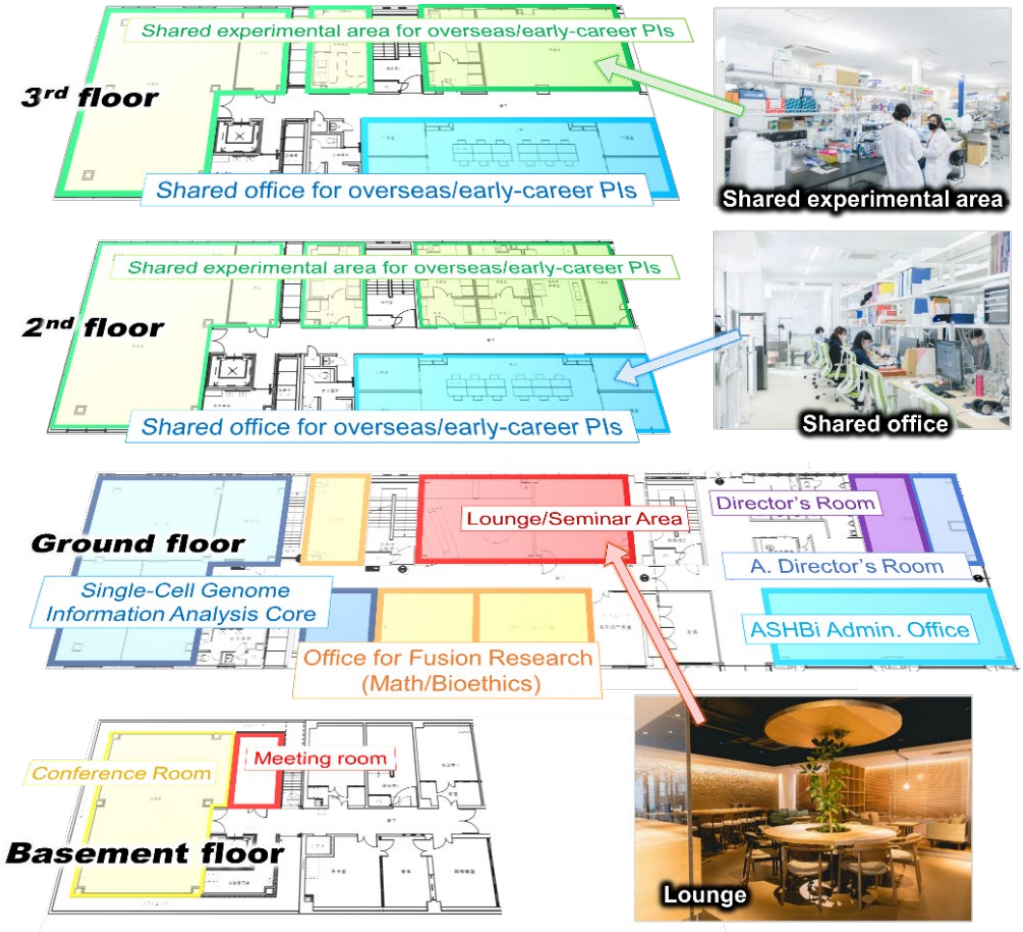
Hospital area, serving as an interaction hub with those researchers.

The remaining 2 PI group laboratories are located in the Research Center for Animal Life Science (RCALS) at the Shiga University of Medical Science, only an hour's drive away from Kyoto City.

We have established three core facilities in ASHBi to serve as the foundation for cutting-edge research. First is the **S**ingle-cell **G**enome I**n**formation **A**nalysis **C**ore (**SignAC**), located in the main building, and second is the **N**on-human **P**rimate Phenotype **A**nalysis Facility (**NPAF**), located just a 3-minute walk from the main building, thereby providing easy access to both for ASHBi researchers. The other core is the **Prim**ate Genome **E**ngineering Core (**PRiME**) located in RCALS.

ASHBi Main Building

After the launch of ASHBi in October 2018, we have continuously renovated our 2,010 m^2 main building to improve its function as the interaction hub. The first floor houses facilities and organizations that play a central role in the interaction of researchers within/outside ASHBi: the SignAC core facility, offices of mathematics and bioethics for interdisciplinary studies, a lounge, seminar room, the Director's room, the Administrative Director's room, and the administrative office. The lounge functions as a place with its relaxing atmosphere, has become an ideal spot to gather and discuss for ASHBi members across research disciplines, not only to serve as a resting place. The second and third floors consist of labs and office space for overseas PIs and early-career PIs. These areas have been designed to have a shared style in order to maximize the efficient use of resources and maximize interactions among the PI groups.



Core-facilities at ASHBi

The three core facilities play a central role as basic infrastructure to promote human biology research.

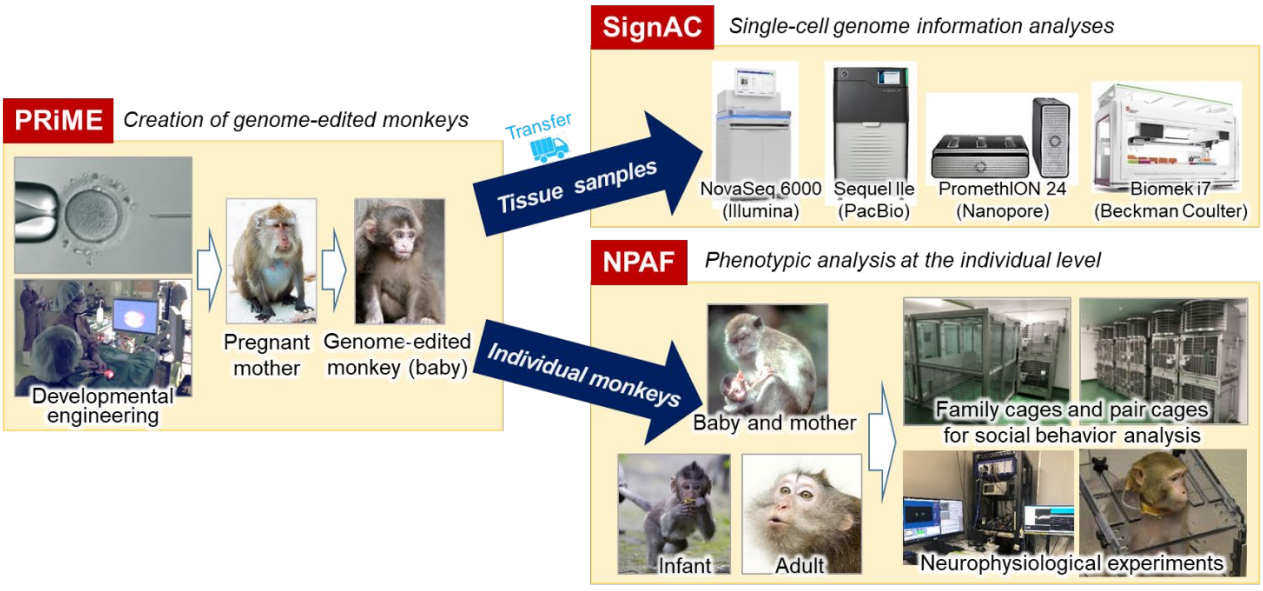
SignAC provides support for large-scale genomic analyses, including at single-cell resolution using

high-end facilities for sample processing, high–throughput DNA/RNA sequencing, and computational analysis. SignAC not only manages such shared equipment but also provides analysis services so that researchers without such expertise can also have access and use these facilities. **T Yamamoto** supervises the operation of SignAC as the Core Head. **Taro Tsujimura** has been appointed as the Core Manager of SignAC, and is actively involved in the development of new analytical methods while overseeing on-site facility operations. Additionally, we have also hired four staff (one postdoc, two technical staff, and one office assistant) to develop new genome analysis methodologies and to assist the facility operations.

In December 2020, SignAC joined the **"Innovative Support Alliance for Life Science (iSAL)"** at KU, a unified platform of core facilities from various departments related to life science studies. Using the online management system of iSAL for equipment reservation and payment, SignAC now provides smooth access to its facilities even for researchers outside of ASHBi. Starting in May 2022, five instruments and DNA/RNA sequencing analysis services will be made available to researchers inside and outside the University through iSAL. Thus, an increasing number of researchers will be able to utilize the SignAC facility.

PRiME is a domestic satellite of ASHBi and is located in RCALS of the Shiga University of Medical Science. RCALS maintains a large primate colony (~700 cages) and has some of the most advanced technologies for animal reproduction. In order to specifically generate genome-edited monkeys and retrieve oocytes/embryos for the research of ASHBi, we have been expanding the space of PRiME to maintain cynomolgus monkeys (162 m^2, 140 cages). We have appointed **Tsukiyama** as the Core Head, and have hired two trained staff with advanced skills and knowledge of animal reproduction and breeding management.

NPAF is located in the Med-Pharm Building at the Faculty of Medicine Campus. In this facility, we aim to analyze the phenotypic aspects of genome-edited macaque monkeys, including social interaction behavior, cognitive function, and emotional expressions. We have installed 4 family cages (9.0 m^3), 4 pair-cages (each 3.7 m^3) and 1 connected cage (8.22 m^3, composed of 6 compartments) for observing social interactions. We also have 2 isolation cages for animals after viral vector injection, which allows the total capacity of up to 38 monkeys in the entire facility. Additionally, we have also established a laboratory space for conducting physiological experiments (56.4 m^2). **Isa** supervises the operation of this facility, and **Hirotaka Onoe** is responsible for studies using genome-edited monkeys. Two staff members have been employed for the purposes of animal health care, animal feeding, cage cleaning, etc. In FY2021, NPAF cleared the UK standard of animal welfare for primate research and established a collaborative project with the MRC Laboratory of Molecular Biology in Cambridge University.



These three core facilities function closely together. As an example, tissues of a genome-edited monkey created at the PRiME are transferred to the SignAC to analyze the effects of genome editing on gene expression at the single neuron level. Furthermore, genome-edited monkeys are also transferred to the NPAF to examine their phenotypic effects on social behavior and cognitive abilities at the individual animal level. Thus, collaborations between the three facilities at ASHBi make it possible to examine the effects of a given genome alteration on brain function, both at the individual animal as well as the single-cell gene expression level.

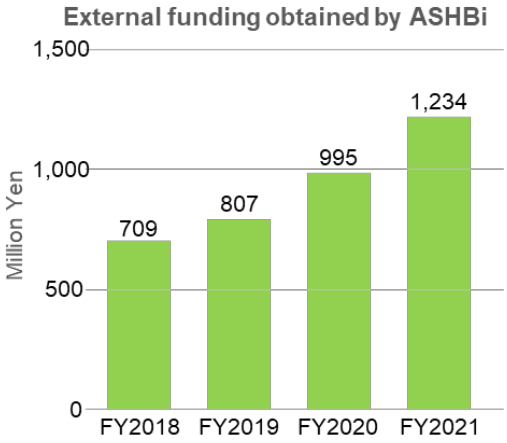
2-3. Competitive and other funding

Describe the results of the Center's researchers to date in securing competitive and other research funding.
・ In Appendix 3-6, describe the transition in acquiring research project funding.

Increase in external funding at the Institute

Since its establishment, ASHBi has steadily received increasing amounts of external funding. In FY 2018, the amount of external funds obtained was 709 million yen, which increased to 807 million yen in FY 2019, 995 million yen in FY 2020, and 1.23 billion yen in FY 2021. In parallel with the increase in external funding, indirect funding granted to ASHBi reached 148 million in FY2021.

The breakdown of acquired external funding in FY 2021 is as follows. 214 million yen from Grants-in-Aid for Scientific Research, 786 million yen from Commissioned Research Projects, 111 million yen from Joint Research Projects, and 123 million yen from donations and etc. Securing such a large amount of external funding will allow us to sustain the further development of the ASHBi as a world-class research center.



2-4. State of joint research

Describe the results of joint research conducted with other research organizations both in and outside Japan.

Diverse collaborations through ASHBi PIs

ASHBi PIs are actively pursuing a variety of collaborative research projects internationally, and the following research papers and grants are representative examples. **Isa** is working closely with Prof. Wim Vanduffel in Katholic University (Leuven, Belgium) on the study of structure and function of dopaminergic pathways in primates (e.g. Vancraeyenest et al. *Neuron*, 2020). **Ueno** is collaborating with Prof. Virginial Pascual in Cornell University (NewYork, USA) on the study of CD4+ T cells present in the blood and the inflamed tissues of systemic lupus erythematosus (e.g. Caielli et al. *Nature Medicine*, 2019). **Yanagita** is working closely with Profs. Jurgen Floege and Peter Boor of RWTH University of Aachen (Aachen, Germany) on the analysis of TLTs in human samples (e.g. Sato et al. *J. Clin. Invest.*, 2022). **Fumitaka Inoue**, the Co-PI of Bourque Group, is working closely with Dr. David Gokhman in the Weizmann Institute of Science (Rehovot, Israel) on the study of gene regulations that shape human evolution and diseases (e.g. Weiss et al. *eLife*, 2021). **Saitou** is working closely with Dr. Jan-Michael Peters in the Research Institute of Molecular Pathology (Vienna, Austria) and Prof. Leonid Mirny of MIT (Cambridge, USA) on the study of mammalian germline development (e.g. Nagano et al. *EMBO J.* accepted). **Alev** is collaborating with Prof. Alfonso Martinez-Arias at University of Cambridge (Cambridge, UK) and Dr. Naomi Moris at the Francis Crick Institute (London, UK) to establish a 3D model of human somitogenesis and somite formation, and they successfully obtained a joint MRC-AMED grant in FY2021.

Collaborations with research organizations outside Japan

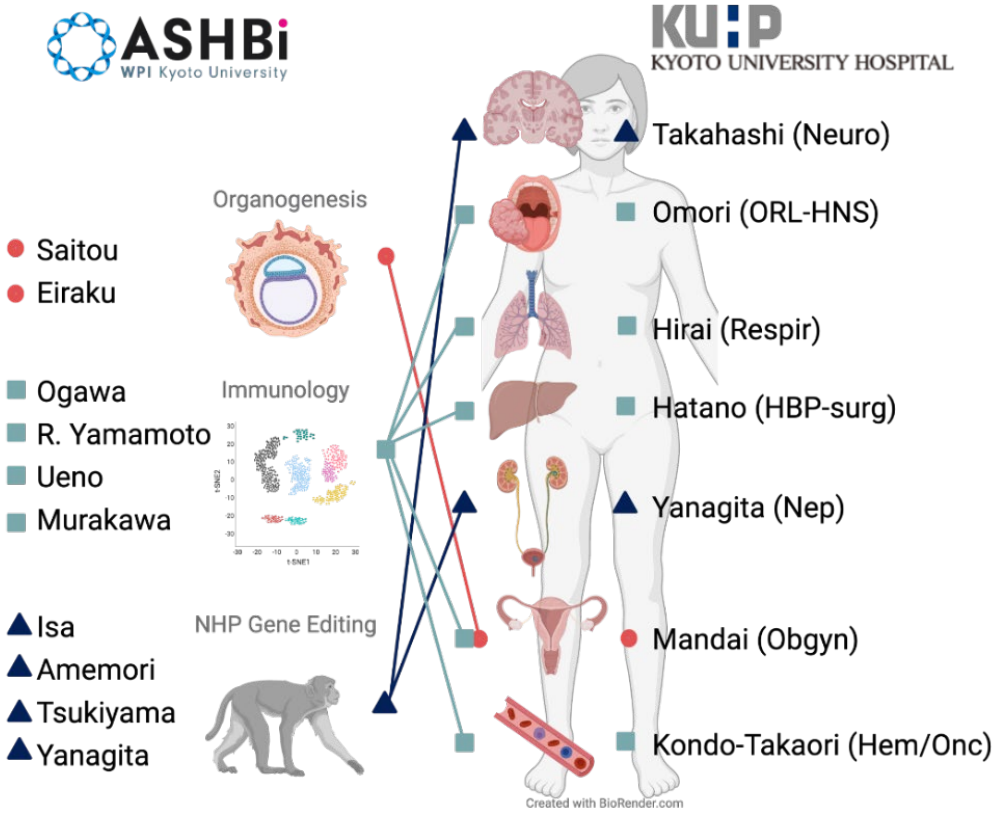
Prof. Bernard de Massy is the group leader of meiosis and recombination at the **Institute of Human Genetics, CNRS Montpellier University**, and is also an ASHBi researcher. He is a leading researcher on meiotic recombination mechanisms in mammals and typically stays in the **Saitou** lab for an extended period of time each year (e.g., 7 months in FY2021) for collaborative research between the two groups. In addition, the Institute of Human Genetics and ASHBi will co-host "Summer School in Life Science" in Montpellier in FY2022.

The **Murakawa Group** has been actively collaborating with **the FIRC Institute of Molecular Oncology (IFOM)** in Milan via the RIKEN for Cancer Genomics. IFOM is a cancer research institute focused on the study of cancer formation and development at molecular level, with a view to a rapid transfer of results from bench to bedside. This institute has strategically established a network of partnerships with cutting-edge scientific organizations around the world, and his group has been selected as a suitable partner for the institute's vision.

ASHBi has been selected as a member of **"International Circle of Stem Cell Research Institutes and Centers"** by ISSCR, and has also been selected as the Japanese counterpart of **"EMBO-Japan Virtual Lectures"** by EMBO (see Section 2-5 for details). Thus, as an organization, ASHBi plays an important role in the world-leading research community.

Collaborations with clinical scientists

ASHBi PIs have been actively collaborating with clinical doctors to obtain human tissue samples and to investigate the etiology of critical diseases/promote human biology. Major collaborations with clinicians include: the **Ogawa Group** with Prof. Kondo-Takaori of the Department of Hematology and Oncology (KU Hospital) to investigate the mechanism of hematological malignancies; the **Ueno Group** with Prof. Hatano of the Department of Hepato-Biliary-Pancreatic Surgery (KU Hospital), Prof. Hirai of the Department of Respiratory Medicine (KU Hospital), Prof. Mandai of the Department of Gynecology and Obstetrics (KU Hospital), and Prof. Omori of the Department of Otolaryngology, Head and Neck Surgery (KU Hospital), to promote human immunology research; the **Murakawa Group** with Prof. Yanagita of the Department of Nephrology (KU Hospital: ASHBi PI) and Prof. Kondo-Takaori of the Department of Hematology and Oncology (KU Hospital), to investigate disease-associated human enhancers; the **Isa Group** with Prof. Takahashi of the Department of Neurology (KU Hospital) to investigate the Parkinson's disease and Assoc. Prof. Koganemaru of Human Brain Research Center (KU Hospital), to develop the therapeutic strategies of the stroke patients; the **Eiraku Group** with Prof. Takahashi (Kobe Eye Center) to promote translational research on hiPSC-derived neural retina; the **Saitou Group** with Prof. Mandai of the Department of Gynecology and Obstetrics (KU Hospital) to promote human *in vitro* oogenesis research; the **R. Yamamoto Group** with Prof. Mandai of the Department of Gynecology and Obstetrics (KU Hospital) to investigate the gene expression of human cord blood.



In addition, the **Fujita Group** has been actively involved in establishing the ethical guidelines for "the Act on the Safety of Regenerative Medicine". The group participated in MHLW (Ministry of Health, Labour and Welfare)'s consignment project "Study to Improve the Quality of Screening at the Certified Regenerative Medical Committee (PI: Morikuni Tobita, Juntendo University)," in which they surveyed how CCRMs evaluate regenerative medicine "treatment" and have contributed to the legal revisions of these applications.

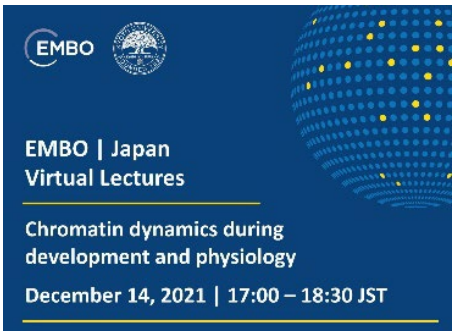
2-5. Appraisal by society and scientific organizations

Describe how society and/or scientific organizations in and outside Japan have recognized the Center's research achievements.
· To substantiate the above evaluation, list the main awards received and invitational/Keynote lectures given by the Center's researchers in Appendix 1-3.

ASHBi as a globally visible research institute

As a result of our continued efforts to gain international recognition, ASHBi has been invited by some of the world's leading research communities to represent Japan. One example is our relationship with the International Society for Stem Cell Research (ISSCR), which is the largest stem cell society in the world dedicated to the advancement of stem cell research. In Aug 2020, ASHBi joined the "**International Circle of Stem Cell Research Institutes and Centers**", consisting of 19 leading institutes/centers, that includes the Gladstone Institutes, Boston Children's Hospital, and Penn IRM.

ASHBi was also invited by EMBO (the European Molecular Biology Organization), an organization of more than 1800 researchers that promotes excellence in the life sciences in Europe and beyond, to co-organize "**EMBO-Japan Virtual Lectures**". The first lecture entitled "Chromatin dynamics during development and physiology" was held on December 14 2021 and the second is scheduled in November 2022.



Awards

Saitou received the Imperial Prize, the Japan Academy Prize from the Japan Academy and the ISSCR 2020 Momentum Award in 2020. He was also an Invited Member of the International Circle of Stem Cell Institute and Center Directors and became an EMBO Associate Member in 2020. **Hiiragi** was also invited to become an EMBO member in 2021. **Bourque** received the Canada Research Chair (Tier 1) in Computational Genomics and Medicine and Research Scholars Emeritus of the Fonds de Recherche en Santé du Québec in 2020. **Ogawa** received the Baelz Prize from Boehringer Ingelheim (1st Prize) in 2019, and Yanagita received the same prize (2nd Prize) in 2021.

Invitational/Keynote lectures

ASHBi PIs were invited to numerous internationally renowned meetings and conferences to give lectures. **Saitou** and **Fujita** were invited to present at ISSCR annual meetings in 2018 (Melbourne, Australia) 2020 and 2021 (online), respectively. **Bourque** and **Ueno** were invited to the Royal Society in 2019 (London, UK) and 2021 (online). **Isa** was invited to NIH Neuroscience Seminar Series in 2020 (Bethesda, USA). Some PIs were invited to present at conferences apart from their original research field to promote interdisciplinary interactions: **Hiiragi** was invited to have a lecture at Kavli Institute for Theoretical Physics in 2020 (online, Santa Barbara, USA), **Seirin-Lee** in GA2LEN UCARE Urticaria Conferences in 2021 (Hiroshima, Japan), and **Murakawa** in Immuno-UK in 2021 (London, UK).

3. Feeding Research Outcomes Back into Society (within 2 pages)

3-1. Applications of research results

Describe the applications created from research results, their effect in spawning innovation, intellectual properties (IPs) obtained, and joint research activities conducted with corporations, etc.

Collaborations with industry

To return the research outcomes obtained at the Institute to society, ASHBi researchers are actively pursuing industry-academia collaborations. Just as a few examples, **Saitou** co-founded and is the executive director of a venture company (Houjou Inc.), that develops and validates methodologies for generating germ cells, especially oocytes, using human, primate, and mammalian PSCs. Such a collaboration has the potential to create a foundation for realizing the significant potential of *in vitro* gametogenesis in future societies. **Murakawa** collaborates with Revorf Co., Ltd as its science advisor, which is making innovative drug discoveries and developing diagnostic methods by combining the knowledge of medical and pharmaceutical sciences, bio-informatics, and advanced computational processing such as machine learning.

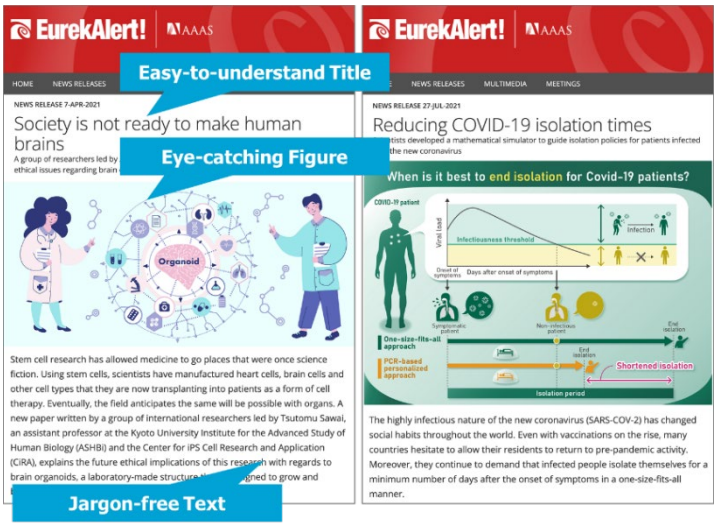
In addition, ASHBi's PIs are also active in acquiring intellectual property. As notable examples, some patents were filed by the math-biology fusion study of a new methodology for analyzing single-cell RNA sequencing data (**Hiraoka and Saitou Groups**, PCT/JP2021/22318), the studies of primate models (**Ema and Tsukuyama Groups,** JP2021-135524; **Isa Group**, JP2021-5325A), and studies of germline production methods (**Saitou Group**, PCT/JP2018/045011, PCT/JP2022/ 16658).

3-2. Achievements of Center's outreach activities

* Describe what was accomplished in the center's outreach activities during the period from 2018 through March 2022 and how the activities have contributed to enhancing the center's "globally visibility." In Appendix 5, describe the concrete contents of these outreach activities and media reports or coverage of the activities.

Outreach to the global media

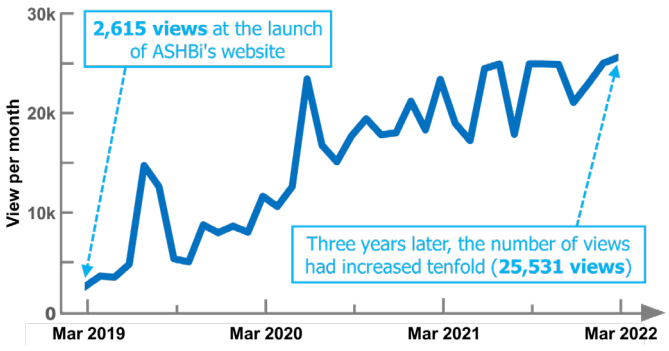
In order to increase the international visibility of ASHBi's research activities, we have been actively disseminating news releases through EurekAlert!, one of the largest international scientific news distribution platform operated by AAAS. We strive to deliver English press releases with easy-to-understand titles, illustrations and images that capture people's interest, together with clear, jargon-free, research stories. This has enhanced recognition of the work conducted at the ASHBi globally and the overall uptake by foreign media. In FY2021 alone, we posted English press releases for 17 research papers to EurekAlert! and to the ASHBi website.



Strategic use of the Institute's website and SNS to attract interest from society

To publicize the Institute's research activities to society, we make effective use of websites and social networking services. The Institute's website was launched in FY2018. The number of monthly page views has steadily increased from an initial 2,615 in February 2019 to 25,531 in March 2022, a nearly tenfold increase. Since the site was launched, it has been viewed more than 600,000 times, with approximately 20% of those views coming from overseas.

We also opened a Twitter account in December



2020. We currently have 728 followers, 71% of whom are international. Publicity via Twitter has been effective, with more than 20% of visitors to our website coming via Twitter.

In order to attract widespread interest from society (including overseas researchers), we disseminate not only research outcomes but also Japanese cultural and seasonal photos (e.g. cherry blossoms) and event information (e.g. awards for young researchers at the ASHBi Retreat) on our website and Twitter. This allows outside researchers and the general public to learn about ASHBi's research life.

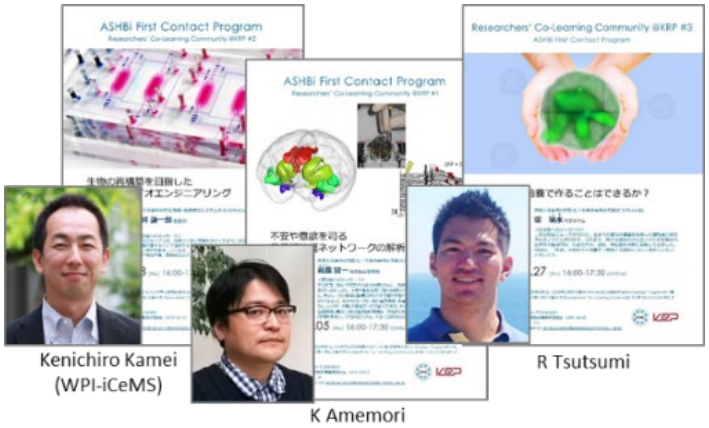
Outreach to middle and high school students

To stimulate interest in academic research, ASHBi PIs are actively involved in outreach activities targeting middle and high school students. At the request of junior high school students, the ASHBi PI **Fujita** was invited to speak at an online seminar organized by junior high school students in November 2021. As a new initiative, two junior high school students took on the roles of organizer and moderator, and 267 participants, mostly students from Japanese schools in Japan and abroad, learned about and discussed ethical issues in iPS cell research.

The ASHBi PI, **Isa,** was invited to a lecture at Higashiyama High School in Kyoto city in July 2021. He gave a lecture on the cognitive function of human brains and on the regenerative function of the injured spinal cord. Another ASHBi PI, **Seirin-Lee,** was also invited to give a lecture at Takamatsu Dai-ichi High School in Kagawa prefecture in Nov 2021. She inspired the female students to the joys of mathematics and to the career option of becoming academic researchers.

Outreach to industry researchers

ASHBi is also active in outreach activities to industry. In FY2020, ASHBi launched the ASHBi First Contact Program, which is designed to promote bi-directional knowledge exchange between researchers in academia and industry. This program allows participants (researchers from industry) to ask questions, even in the middle of a presentation, to deepen their understanding of the content of the presentation and encourage more active participation. It also provides an opportunity for more interactive discussions, where one question triggers another, which leads to further insights and deeper understanding. Three WPI researchers have presented in FY2021 and three more will present in FY2022.



4. Generating Fused Disciplines (within 3 pages)

4-1. State of strategic (or "top-down") undertakings toward creating new interdisciplinary domains

Describe the content of "top-down" measures taken by the Center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields.

Mathematics-Biology Fusion

1) ASHBi Math-Biology seminar: We organized a series of seminars about mathematical biology in about every two weeks during the first half term. The purpose of this seminar is to share advanced mathematical methods and state-of-the-art biological research for all ASHBi members, and to strongly promote fusion research. About 30-40 members participated in every seminar, and the topics covered are scRNA-seq data analysis, gene regulatory network, 3D epigenetics, and AI in biology. Most of the fusion researches listed in 4-3 were initiated by this seminar.

2) Strengthening the mathematics group: In the first half term, we strategically focused on mathematical data analysis for math-biology fusions, and succeeded in creating new interdisciplinary research, as explained in 4-3. In order to further accelerate the fusion towards the latter half, we strengthened the organization of mathematics group by adding one more (female) PI, Professor **Seirin-Lee**, from October 2021. Her research subject is mathematical modeling in biology, including chromatin reorganization, asymmetric cell division, and skin disease by applying phase field modelings and reaction diffusion equations. With the addition of her group that is complementary to math data analysis, further fusion research will be achieved in the latter half.

3) Collaborations outside Kyoto University: To execute math-biology fusions efficiently and effectively with limited financial resources, we promoted collaborations with researchers outside Kyoto university, and especially, appointed Prof. **Iwami** (Nagoya U, math biology) and Prof. **Shimizu** (Shiga U, machine learning) as associate investigators. The collaborative researches and discussions with them are mathematical modeling of the differentiation dynamics of Tfh2 and Tfr cells, inference of gene regulatory networks by causality, and some mathematical analyzes related to COVID-19 (with **Ueno**, **Saitou**, and **Hiraoka** Groups).

Ethics-Biology Fusion

One of the situations in which the fusion of advanced biology and bioethics works most effectively is in the process of developing rules that promote scientific research ethically (e.g. the national councils, ethics review committees). Research in ASHBi is sometime too new that there are still no clear rules domestically and/or internationally. Therefore, we promoted the following three fusion projects, which aim to clarify ethical issues and formulate rules closely related ASHBi's research.

1) Fetal Tissue Research: A research team led by **Fujita** in charge of its management consists of scientists, including **Saitou**, philosophers/ethicists and jurists to create guidelines for conducting fetal tissue research and compile a report that will serve as the theoretical basis for such research. It also serves as an opportunity for the postdocs in **Fujita** Group who participate in the project to learn how to proceed with fusion research projects.

2) Research use of early postmortem tissue: This project aims to develop guidelines and establish a platform for research use of early postmortem tissue. This is a Junior Flagship Project, in which a part of the ASHBi's Flagship Project, "Mechanism and regulation of aging-associated disorders," is entrusted to a research team consisting of young researchers from each PI group. The core of the project will be managed by **Go Okui** of **Fujita** Group.

3) Organoid research: This is a project led by **Tsutomu Sawai** (Assistant Professor, **Fujita** Group) to build an interdisciplinary network with ASHBi Associate Professor **Alev** and other researchers in Japan and abroad to clarify ethical issues associated with human embryo models and brain organoid research. By encouraging independent efforts by young researchers with early careers, the project also provided an opportunity for them to learn the management skills they will need when they become PIs in the future.

In each of the above projects, lectures and symposia were held to share the obtained knowledge and human network with all ASHBi researchers. These lectures and symposia were jointly organized by researchers in biology and bioethics to promote mutual understanding and dialogue among researchers in different research fields.

4-2. State of "bottom-up" undertakings from the center's researchers toward creating new interdisciplinary domains

Describe the content of "bottom-up" measures taken by the Center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields.

Promoting bottom-up research by young researchers

To promote bottom-up interdisciplinary research based on unrestrained ideas of young researchers, we established the "**ASHBi Fusion Research Grant Program**" in 2020. The feature of this program is that young researchers must form a team consisting of different research fields (math-biology, ethics-biology, or biology-biology) to propose a project, which must be of collaborative nature within the Institute. The team will receive funding of up to 3 million yen per year for a maximum research period of three years. There are currently 12 research projects underway, with 6 teams each having started in 2020 and in 2021. Progress report meetings are held twice a year, and reviewed by the evaluation committee (3 ASHBi PIs: **Hiraoka**, **Fujita**, and **Eiraku**) to determine the budget for the following year. The most recent progress report meeting was held in February 2022 in conjunction with the ASHBi retreat. Three experts outside the Institute also joined the evaluation committee to provide comments from a broader perspective.

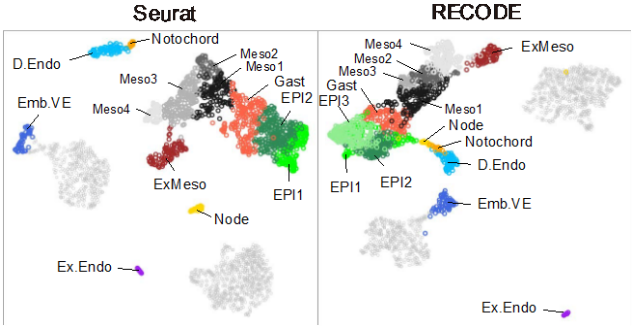
Starting year	Category	Applicant representative	Project title
2020	Math-Bio	Y Imoto	Identification of multi-resolution cell differentiation dynamics from scRNA-seq data via mathematical data analysis and interactive visualization system
	Math-Bio	T Yachimura	Characterization of gene regulatory networks in human and non-human in vitro segmentation clocks
	Math-Bio	T Tsujimura	Topological approaches for integrative 3D epigenomics
	Math-Bio	Y Yabuta	Inference of genome-wide DNA demethylation kinetics by dynamic model fitting research
	Ethics-Bio	T Sawai	Examining ethics and governance in developmental biology
	Bio-Bio	X Chen	Deciphering evolutionary differences of germline transposable element dynamics
2021	Math-Bio	R Yamaguchi	Statistical inference of the causality with polarity among brain regions associated with recovery from spinal cord injury
	Ethics-Bio	G Okui	The research use of fresh postmortem tissues: From a regulatory and ethical perspective
	Bio-Bio	H Saito	Functional dissection of primate striatal structure using viral vectors guided by genome informatics
	Bio-Bio	Y Yamanaka	Spatial transcriptome analysis of human axial development in vitro
	Bio-Bio	S Hamidi	Reconstruction and analysis of peri & post-implantation non-human primate development
	Bio-Bio	S Bhagat	Deciphering regulatory heterogeneity of human hematopoietic stem and progenitor cells

4-3. Results of research in fused research fields

Describe the Center's record and results by interdisciplinary research activities yielded by the measures described in 4-1 and 4-2.
- In Appendix 1-2, list up to 10 of the Center's main papers on interdisciplinary research that substantiate the above record of results, and describe their content.

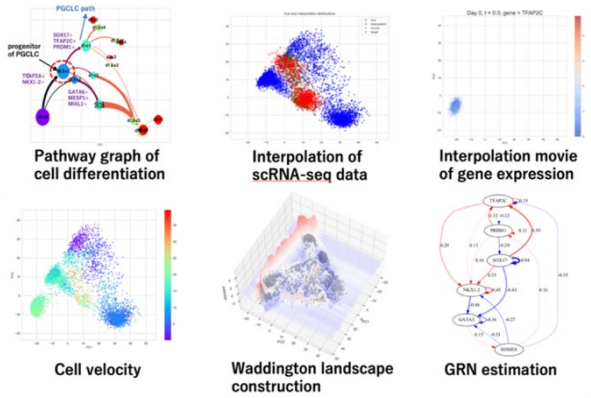
Mathematics-Biology Fusion

In the first half term, we focused on creating new interdisciplinary researches on scRNA-seq data analysis and epigenetic data analysis under close collaborations with biologists in ASHBi. We have developed RECODE (noise reduction for scRNA-seq data), GMM-OT (elucidating dynamics of single-cell populations), GRN-LiNGAM (identifying gene regulatory network from causality), v-Mapper (clarifying complex topological structure and dynamics in single-cell data), and topological node2vec (reconstructing 3D chromatin conformation from Hi-C data; the related paper (Nagano et al, 2022) is accepted in The EMBO Journal). Although it took four years to build solid foundations, all of them realized innovative analytical methods incorporating new mathematical ideas at the level required for advanced biological researches. In fact, by applying these methods within ASHBi, we have succeeded in obtaining new biological results that could not be clarified by conventional methods, and those results are now being summarized as original papers. Furthermore, motivated by these interdisciplinary researches, we are now challenging ourselves to formulate a new mathematical theory, which we will call "data representation theory", and this challenge is now set as a new Flagship Project. Here, due to the limitation of the space, we only explain RECODE and GMM-OT in detail.



RECODE identified a new pathway through notechord even in rare populations during mouse gastrulation

- RECODE: ScRNA-seq can simultaneously determine gene expression in numerous individual cells, however, those data are high-dimensional with substantial technical noise, including dropouts. Upon the analysis of scRNA-seq data, such noise engenders statistically serious problems known as the curse of dimensionality. Based on mathematical high-dimensional statistics, we formulated a noise reduction method called RECODE to resolve those problems. RECODE eliminates noise in scRNA-seq data with unique molecular identifiers, enabling good classification of cells during development and identification of rare cells. RECODE employs different mathematical principles from and outperforms conventional imputation methods, solidifying a true single-cell resolution analysis. These results are submitted to a journal and available from bioRxiv (https://biorxiv.org/cgi/content/short/2022.05.02.490246v1). The software of RECODE is now open to the public (https://yusuke-imoto-lab.github.io/RECODE/index.html), and it is currently being applied to many projects in ASHBi (**Saitou**, **Ueno**, **Alev**, **Eiraku**, **T. Yamamoto**, and **R. Yamamoto** Groups). We highly expect these fusion researches will produce many biological results in the latter half.
- GMM-OT: This project aims to infer the trajectory during cell differentiations from scRNA-seq time-series data. We have developed a novel method combining the Gaussian mixture model (GMM) with optimal transport (OT) theory, called GMM-OT. Here, GMM is used for clustering and estimating probability distributions of scRNA-seq data, while OT enables time tracking of these probability distributions to study dynamics. Because GMM-OT has versatility and strength, it can provide various functions at once for comprehensive analysis of scRNA-seq data, each of which proposes a new method or exceeds conventional methods. Applying GMM-OT to the time-series scRNA-seq data of human PGCLCs (hPGCLCs), we identified a progenitor cell population for hPGCLCs and some significant genes controlling the induction process (e.g., TFAP2A, NKX1-2, GATA6). These results are now being summarized as an original paper and will be submitted soon. The software will also be available from our website.



Available functions in GMM-OT

Ethics-Biology Fusion

The achievements and results of three research projects promoting the integration of advanced biology and bioethics are as follows:
1) Fetal tissue research: Dr. **Takashima** (Associate Professor, CiRA), who participates in this project, won the AMED-CREST project "Creating innovative human embryology using stem cells," which **T. Yamamoto** and **Fujita** of ASHBi joined as co-chairs to initiate this new fusion research project. **Fujita** participated in the task force on Informed Consent for Human Fetal Tissue Donation for Research organized by the International Society for Stem Cell Research (ISSCR). The task force members were invited to a two-day seminar attended by a cumulative total of 143 participants, not limited to scientists and bioethicists from ASHBi and other research institutions but also Japanese government officials.
2) Research use of early postmortem tissue: Although this project has been in operation for less than a year, the research team of young researchers has been meeting regularly and successfully. So far, the team has organized domestic regulations, surveyed previous cases, reviewed ethics discussions, and collaborated with Kyoto University Hospital and Autopsy Center for the research use of early postmortem tissues. In addition, a website for this project is under development with the aim of opening discussions to society.
3) Organoid research: **Sawai** established an interdisciplinary network of domestic and international researchers and organized several workshops, including "Ethics of Early Developmental Research." Ethical issues in organoid research, which were clarified through discussions in the project, were summarized in a review article and a book (Sawai T, et al. ***AJOB Neuroscience***. 2021, etc.). These achievements were highly evaluated, and **Sawai** obtained a tenure post as an Associate Professor at Hiroshima University from April 2022.
In addition to the above, **Saitou** and **Fujita** have been involved in the work to revise the guidelines of the ISSCR, published white papers on the guidelines, and responded to hearings at the Cabinet Office's Expert Committee on Bioethics, steadily achieving a track record of activities leading to the establishment of research rules in Japan and abroad.

5. Realizing an International Research Environment (within 4 pages)

5-1. International Circulation of Best Brains

5-1-1. Center's record of attracting and retaining top-world researchers from abroad

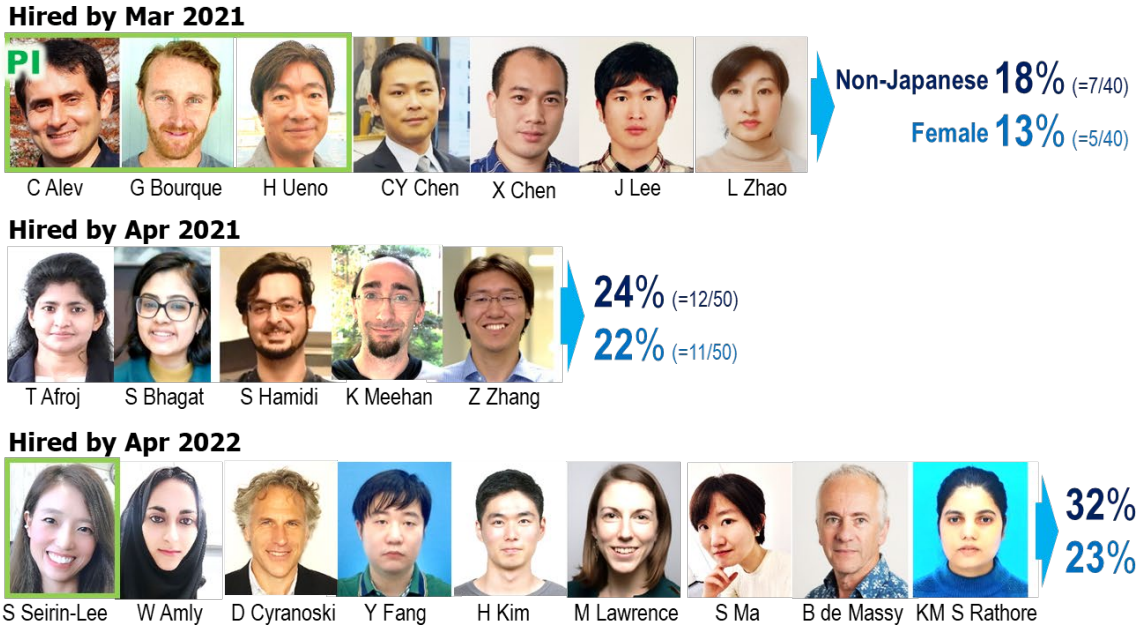
Describe the participation of top-world researchers as PIs and their stays as joint researchers at the Center.
In Appendix 3-2, give the number of overseas researchers among all the Center's researchers, and the yearly transition in their numbers. In Appendix 4-2 give the achievements of overseas researchers staying at the center to substantiate this fact.

Internationalization of PIs

To promote the internationalization of ASHBi PIs, a foreign female researcher (**Seirin-Lee**) was hired as a PI in FY2021. Currently, 4 out of 18 PIs are foreign PIs (**Bourque**, **Ueno**, **Alev**, and **Seirin-Lee**), and the ratio of foreign PIs is 22% (= 4/18), exceeding the WPI standard of 20%.
Bourque (Canadian national) has visited Japan twice from Canada in FY 2019, staying for 3 weeks and 1 month, respectively. Due to the COVID-19 pandemic, he has not been able to enter Japan since February 2020, but continues to meet online twice a week with lab members at ASHBi. The remaining three foreign PIs, **Ueno**, **Alev,** and **Serin-Lee** (US, German, Korean nationals) are employed by KU and conduct research at ASHBi.

Internationalization of researchers and students

To recruit foreign researchers under the COVID-19 epidemic situation, we focused on recruiting foreign researchers already present in Japan that are enrolled in Japanese universities and research institutions. In addition, we also established the **"ASHBi Foreign Researcher Employment Support Program"** in FY2020, which covers the personnel costs associated with hiring foreign researchers. Through these efforts, the ratio of foreign researchers increased significantly from 18% in March 2021 to 32% in April 2022, satisfying the WPI standard. In parallel with the recruitment of foreign researchers, we have also made efforts to recruit female researchers. The percentage of female researchers was only 13% in March 2021, but it had increased significantly to 23% in April 2022. Moreover, to promote the female researcher recruitment, we also established **"ASHBi Foreign/Female Researcher Employment Support Program"** in FY2021, replacing the existing support program for hiring foreign researchers. Through this program, we have already hired 3 female researchers in April 2022, and one more female researcher is planned to be hired within FY2022.



To promote the recruitment of international graduate students, we have effectively utilized two programs. First, using the **"McGill-Kyoto International Collaborative Program in Genomic Medicine (Joint Ph.D.)"** established between KU and McGill University, the ASHBi has so far accepted three foreign students (May 2019 – July 2020, November 2020 – October 2021, and November 2021 – present). Second, we established the **"ASHBi Financial Support Program for International Graduate Students"** in 2020 to support the living expenses of international students studying at ASHBI. Through this program, we successfully recruited 8 international students during FY2021. As of April 2022, there are 99 graduate students in the ASHBi PI groups, including

22 international students and 34 female students, representing 22% and 34% of the total, respectively.

5-1-2. Employment of young researchers at the Center and their job placement after leaving the Center

Describe the Center's employment of young researchers, including postdoctoral researchers, and the positions they acquire after leaving the Center.

- Enter the following to substantiate the facts provided above:
  - In Appendix 4-3, describe the Center's state of international recruitment of postdoctoral researchers, the applications received, and selections made.
  - In Appendix 3-2, give the percentage of postdoctoral researchers employed from abroad
- - In Appendix 4-4, describe the positions that postdoctoral researchers acquire upon leaving the Center.

To accommodate for a quick start of research activity at ASHBi upon its initial launch, we were not able to allocate sufficient time to properly conduct an open call for FY 2018 recruitment. Therefore, we selected 19 young researchers that were already employed by PIs from the ASHBi who were able to start their research from the launch. The international open call for young researchers (post-doctoral fellows and assistant professors) began in April 2019. From FY 2019 to FY 2021, we received 135 applications in total, 104 (77%) of which were from foreign researchers. From these applicants, 36 young researchers were hired at ASHBi, 15 (42%) of whom were foreign researchers. As of April 2022, 32 young researchers hired by the Institute have moved on, with 13 having transferred within KU, 10 to other universities/institutes, and 9 have advanced to career paths outside academia (e.g., doctors, pharmaceutical companies).

5-1-3. Overseas satellites and other cooperative organizations

- In Appendix 4-1, describe the state of cooperation with overseas satellites and other cooperative organizations. In Appendix 4-5, describe the state of the Center's agreements concluded with these organizations.

Joint PhD program between KU and McGill University

The joint PhD program, "**Kyoto-McGill International Collaborative Program in Genomic Medicine"** was established in October 2018 between the KU Graduate School of Medicine and McGill University. The ASHBi PI **Bourque** is one of the main organizers at McGill University.

Academic exchange between KU and the Max Delbrück Center for Molecular Medicine

Preparations are underway to establish an academic exchange agreement between KU Graduate School of Medicine/KUIAS and the Max Delbrück Center for Molecular Medicine (Berlin, Germany), Germany, with the ASHBi PI **Murakawa,** serving as the contact person on the KU side. Once the agreement is signed, joint research and student exchange between the two institutions will occur.

5-2. Center's record of holding international symposia, workshops, research meetings, training meetings and others

In Appendix 4-6, describe the main international research meetings held by the Center.

ASHBi Seminar as a forum for exchange with overseas researchers

Before the COVID-19 epidemic, we actively invited overseas researchers and held seminars in-person called ASHBi Seminars. In FY2019, we invited 10 foreign researchers to our seminars. However, after the COVID-19 pandemic, we only invited 4 overseas researchers. To overcome this situation, in FY2021 we switched to online seminars and invited 12 foreign researchers to our seminars, allowing them to interact closely with outstanding foreign researchers.

International symposium and international summer school

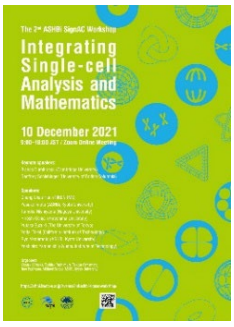
We have actively organized large-scale international symposiums and international summer schools. The 1st international symposium entitled **"Human Development, Genetics, and Evolution"** was held in November 2021 (postponed from March 2019), the 2nd symposium entitled **"Development**

and Plasticity of neural Systems" was held in March 2022 (postponed from March 2020), jointly with the JSPS Grant-in-Aid for Scientific Research on Innovative Areas, and the 3rd international workshop entitled **"Molecular mechanisms of Developmental and Regenerative Biology"** was held in April 2022 (postponed from November 2020), jointly with EMBO. An international summer school entitled **"JANUBET Primate Neurobiology School"** was also held in September 2021 in collaboration with Norwegian government agencies. Due to COVID-19 pandemic, these meeting were held in an online or hybrid format.

Date	Name of International Conference/School	Organizers	# of Presenters all (overseas)	# of Participants all (overseas)
Sep 10-16 2021	***JANUBET Primate Neurobiology School*** (hybrid)	**T Isa**, M Takada, K Tsutusi	Oral 17 (7)	60 (17)
Nov 8-10 2021	***International Symposium "Human Development, Genetics, and Evolution"*** (online)	**M Saitou**, **T Hiiragi**, J Briscoe, B Treutlein	Oral: 22 (16) Poster: 12 (3	279 (78)
Mar 2-4 2022	***Fetal Tissue Research: Science and Ethics at the Frontier in the United States and Europe*** (online)	**M Fujita**, Y Takashima, **M Saitou**	Oral: 5 (5)	152 (10)
Mar 14-17 2022	***International Symposium "Development and Plasticity of Neural System"*** (online)	R Kageyama, **T Isa, M Eiraku**	Oral: 39 (17) Poster: 15 (1)	479 (173)
Apr 26-29 2022	***EMBO Workshop "Molecular mechanisms of Developmental and Regenerative Biology"*** (online)	I Chambers, **T Ogawa**, **M Saitou**	Oral 32 (24) Poster 43 (39)	480 (274)

SignAC workshop

Since 2021, the **"ASHBi SignAC Workshop"** has been held annually. The main organizers are **T Yamamoto** (SignAC Core Director), **Tsujimura** (SignAC Core Manager), and **Saitou**. The purpose of this workshop is to provide an overview of the current advances in single-cell biology from various angles and to introduce recent innovations and applications of single-cell approaches to basic biological problems. In particular, we hope that the workshop will lead participants to formulate new ideas for future research.



Bioethics-Biology Fusion Seminars

The Bioethics Group actively organizes interdisciplinary bioethics-biology seminars. ASHBi PIs **Fujita** and **Saitou** organized an international seminar entitled **"Fetal Tissue Research; Science and Ethics at the Frontiers in the United States and Europe"** in March 2022. During the seminar, world leaders in the science and ethics of fetal tissue research presented the latest scientific findings, international trends and regulations, and practices for obtaining consent. In addition, ASHBi's bioethics and biology researchers (**Alev**, **Tsuyoshi Okui**, and **Tsutomu Sawai**) collaborated to organize five bioethics and biology integration seminars, inviting international researchers as speakers.

Math-Biology Interdisciplinary Workshop

Starting in 2019, the Mathematics Group has hosted an annual Mathematical Biology Workshop. The workshop is organized by PIs **Hiraoka** and **Seirin-Lee** of the Mathematics Group and aims to explore and develop new frameworks for mathematical research in human biology. In addition, the Mathematics

Group regularly holds math-biology seminars. The purpose of these seminars is to share advanced mathematical methods and cutting-edge biological research with the Institute's researchers and to promote fusion research.

5-3. System for supporting the research activities of overseas researchers

Describe the Center's preparations to provide an environment conducive for overseas researchers to concentrate on their work, including for example living support in various languages or living support for their families.

Support for foreign researchers when they enter Japan

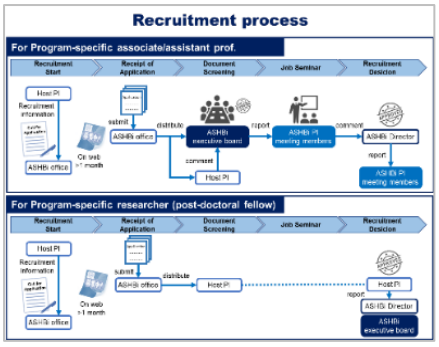
We provide support for foreign researchers and their families in obtaining visas and entering Japan, in close cooperation with the overseas research support staff at KUIAS. We assist them in obtaining and applying for the necessary documents at the Japanese Embassy. ASHBi's English-speaking secretary in charge of foreign PIs and foreign researchers also provides assistance in finding housing, opening bank accounts, applying for tax credits, and so on.

Support for foreign researchers to set up a laboratory

When a foreign researcher is hired as an overseas PI at the ASHBi, we provide 30 million yen to cover the start-up costs for two years and 22.5 million yen per year for personnel costs to hire his/her team members. We also provide 270 m^2 of office space and 530 m^2 of lab space, shared by two overseas PIs and 5 early-career PIs.

Support for foreign researchers when problems arise in their research activities

When setting up a new laboratory, it is necessary to purchase supplies and hire laboratory members. However, the complicated administrative procedures of Japanese universities can be a obstacle for foreign researchers. Therefore, ASHBi has prepared an illustrated manual in English that explains basic administrative procedures such as hiring and purchasing equipment in an easy-to-understand manner. ASHBi has also established a consultation platform operated by ASHBI's URA and English-speaking secretary. When a foreign PI/researcher faces a problem, the URA discusses it with the foreign PI/researcher and consults with the relevant department to find a solution. The URA shares the solution with the secretary so that the next time the same problem arises, the secretary can handle it himself/herself.



5-4. Others

Describe the Center's policy for sending Japanese researchers overseas to gain international experience, and give examples of how the Center is working to create career paths for its researchers within a global environment of researcher mobility.

As mentioned above, the Institute actively provides opportunities for students and young researchers to interact with overseas researchers by introducing the Kyoto-McGill International Collaborative Program, organizing international summer schools, and holding ASHBi Seminars regularly with inviting overseas researchers. Due to the COVID-19 pandemic, we have been unable to send young Japanese researchers abroad for the past two years, but once the situation improves (as of April 2022, KU Graduate School policy prohibits overseas travel except for unavoidable official business), we will support travel and lodging expenses for young researchers to gain experience at overseas research institutions.

6. Making Organizational Reforms (within 3 pages)

6-1. Decision–making system in the Center

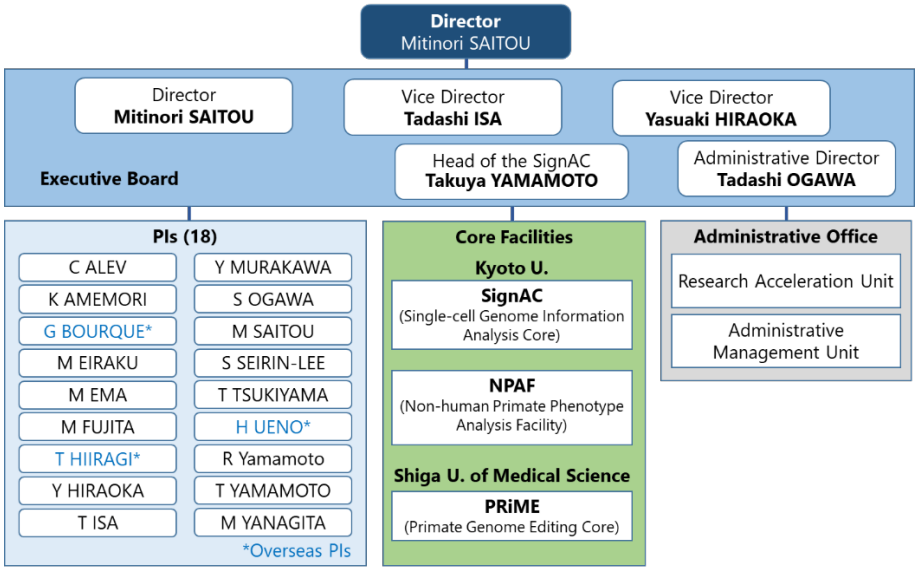
Describe the strong leadership that the director is giving on the Center's operation and its effect, and the division of roles and authority between the Center and its host institution.
- In Appendix 3-3, draw a concrete diagram of the Center's management system.

The Institute's independence and the Director's leadership

In April 2016, KU created a new organizational structure called the Kyoto University Institute for Advanced Study (KUIAS), which has been organized as an international research hub hosting the WPI centers as its core components. KUIAS is designated with special privileges and therefore has a high degree of autonomy. Under the KUIAS's umbrella, the directors of the respective WPIs can exercise strong leadership and implement better top-down management.

The Institute director has the authority to make the final decision on important matters concerning the operations at the Institute. The Executive Board consists of director **Saitou**, vice directors **Isa** and **Hiraoka**, SignAC core head **Yamamoto**, and administrative director **T Ogawa**. Executive board meetings are regularly held twice a month (it was once a week until March 2019). The Executive Board meetings discuss and make decisions with regards to the research direction of the Institute, personnel affairs, budgetary concerns, as well as proposals and requests made by the ASHBi PIs and its members.

The PI board, consisting of all 18 PIs of the Institute, one co-PI (**Inoue**), and the administrative director, meets monthly to deliberate the matters proposed by the Executive Board and make concrete decisions and action plans and share various information concerning the Institute.



6-2. Arrangement of administrative support staff and effectiveness of support system

Describe the assignment of the Center's administrative support staff who have English language and other specialized skills, effort made in establishing the support system, and the system's effectiveness.

ASHBi administrative office

The administrative office, also known as the "ASHBi Office", provides the administrative support of the ASHBi. The Office consists of the "**Administrative Management Unit**" and the "**Research Acceleration Unit**", and is managed by the administrative director **T Ogawa**. While the former unit is responsible for regular operation (e.g. general affairs, personnel, and accounting services), the latter unit is responsible for flexible and problem-solving type support. For example, the Research Acceleration Unit provides support for planning the Institute's events (e.g. international symposium and retreat), creating a support program to address an institute-wide issue (e.g. internationalization of the Institute's researchers), and promoting the foreign researcher activities. In addition, this unit organizes seminars to foster young researchers.

To fulfill the above roles, the Unit has hired four experts. **Spyros Goulas** is a former scientific editor at Cell Press (Journal Name: *Developmental Cell*) and is expected to support the Institute's members (especially young researchers) to develop and improve their abilities in writing their research papers. **Tomoki Shimizu** is appointed as the public relations manager and is responsible for increasing the Institute's visibility through international news releases. **Makoto Shida** is hired as an industry-academia collaboration manager and is also responsible for strengthening the ability to obtain grants. **Hiromi Inoue** has five years of experience as a lab manager specializing in life sciences at UCSF. She utilizes this experience to support the Institute's management. She is also responsible for strengthening the visualization of research results.

6-3. System reforms advanced by WPI program and their ripple effects

Concisely itemize the system reforms made to the Center's research operation and administrative organization, and describe their background and results. Describe the ripple effects that these reforms have on the host institution. (If any describe the ripple effects on other institutions.)

SignAC as a good practice model for a university-wide core facility

As a successful model of a core facility, SignAC is expected to play a central role in the university-wide core facility concept envisioned in KU's future plan. The unique feature of SignAC is that this core facility is constantly updating its analytical technology by having its own research staff (**Tsujimura** and one postdoc). This gives SignAC a strong competitive edge compared with other core facilities. KU appreciates this competitive edge and plans to use SignAC as a good practice to develop university-wide core facilities (see Section 8 for details).

Multiple-Year Budgeting for Indirect Funds

KU allowed us to introduce a multi-year budget for indirect funds. As a benefit, we have been able to carry over indirect costs to the next fiscal year (maximum carryover amount is 40 million yen). This greatly increases the flexibility of our budget planning.

6-4. Support by Host Institution

The following two items concern the support that the host institution provides the Center. Describe the measures that the host institution has taken to sustain and advance the Center's project. That include the item of support that it committed to at the time of the initial project proposal submittal.

6-4-1. Record of host institution support and its effects

・ In Appendix 6-1, describe the concrete measures being taken by the host institution.

KU has provided two tenured faculty positions to ASHBi, and we have hired **Yasuhiro Murakawa** in October 2020 and **Sungrim Seirin-Lee** in November 2021 as tenured professors. KU allows ASHBi to take the headquarters' dividend, which is half of the total of the indirect funds from competitive grants acquired by ASHBi researchers. With this financial support, ASHBi was able to acquire approximately 148 million yen as indirect funds in FY2021. In addition, KU provided a special budget (approx. 100 million yen) to purchase a new 3rd-generation long-read sequencer (PacBio IIe) in FY2021.

6-4-2. Position of the Center within the host institution's mid-term plan

・ To Appendix 6-2, excerpt the places, in the host institution's "Mid-term objectives" and/or "Mid-term plan" that clearly show the positioning of the WPI center within its organization.

In its mid-term goal regarding research, KU has declared the establishment of the **K**yoto **U**niversity **I**nstitute for **A**dvanced **S**tudy (KUIAS), which has been established as an international research center with the WPI Center at its core. In addition, the mid-term goal on internationalization declares that KUIAS will develop flexible central management and research support functions for our internationalization goals and to strengthen KUIAS as a world-class research center.

6-5. Others

6-5-1. System for fostering young researcher (e.g. start-up funding)

Collaboration with the KU graduate school of medicine

Starting from FY2020, ASHBi is co-hosting the "**Developmental Biology/Cell Biology/Systems Biology Course**" with the KU Graduate School of Medicine. The course offers cross-disciplinary discussions and is held as a monthly seminar that includes two lectures: one by a young researcher (30 min) and the other by an invited researcher (1 hour). In FY2020, 3 ASHBi PIs: **Alev**, **Hiraoka**, and **R Yamamoto** hosted the seminar; in FY2021, **Amemori**, **Murakawa**, and **Seirin-Lee** hosted

the seminar. This collaboration with the Graduate School of Medicine gives the Institute the opportunity to approach and recruit more graduate students from KU.

Participation of undergraduate medical students in math-biology research
As a ripple effect of the math-biology fusion studies actively conducted in ASHBi, undergraduate students in the KU School of Medicine have become interested in this type of research. As of April 2022, at least five undergraduates are currently participating in research activities at the **Saitou**, **Murakawa**, **Seirin-Lee**, and **SignAC Groups**. Thus, fusion research at ASHBi is helping to guide medical students' interest in new research fields.

Start-up funding support for young researchers and early-career PIs
ASHBi encourages fusion research based on the ideas of young researchers and those selected for the "**ASHBi Fusion Research Grant Program**" (see above) will receive an annual research grant of up to 3 million yen for three years. This program encourages the start of new research, greatly motivates young researchers, and contributes to the active exchange of young researchers at ASHBi. Researchers hired as early-career PIs at ASHBi are allocated 10 million yen as start-up funding for two years and 10 million yen or more for personnel expenses every year. Shared secretaries are assigned to support administrative procedures such as recruitment of laboratory members and purchase of experimental equipment. In addition, to providing help for early-career PIs to obtain external funding, ASHBi's dedicated URA provides information on grants and guidance in preparing an appropriate application.

Research Acceleration Programs for fostering foreign/early-career researchers
The Research Acceleration Unit actively organizes seminars in English for foreign/early-career researchers to help them acquire the necessary knowledge and skills for their research activities. For example, in FY2022, **Goulas** will hold a series of seminars on scientific paper writing and how to publish papers. Early-career researchers tend to have difficulties in developing their research stories in their papers. The seminar will be designed to develop their ability for allowing editors and reviewers to better understand their research story and their significance. In addition, **Shida** has held seminars on how to write effective grant proposals. Some application guidelines for Japanese research grants (such as KAKENHI) and doctoral fellowships (such as JSPS DC1 and DC2 fellowships) are not available in English. Therefore, he has translated the useful information into English and convey it to the participants in his seminars.

Our seminars are open to universities and research institutions throughout Japan. The four seminars held over the past year have been attracted 502-878 registrants from 40-51 institutions.

6-5-2. Participation of female researchers

- On the transition in the number of female researchers, enter the figures in Appendices 3-1 and 3-2.

Promoting the employment of female researchers
As mentioned earlier, we are actively recruiting female researchers and have established a program to promote the employment of female researchers (see Section 5-1-1 for details).

Creating an environment that balances work and family life
ASHBi is also making efforts to create an environment that balances work and family life to promote better employment conditions for female researchers. In consideration of researchers raising children, starting in FY2022, the regular board meetings, PI meetings, and ASHBi Colloquium will be held earlier, so that all meetings will end by 5:00 pm. We will continue our efforts to create a comfortable working environment for young as well as female researchers.

7. Future Prospects (within 2 pages)

7-1. Policy and plan for achieving the Center's research objectives in the future

ASHBi continues to strive to investigate a key concept of human biology with a particular focus on genome regulation and disease modeling, thereby creating a foundation of knowledge for understanding the key biological traits that make us human and for developing innovative therapies. Towards this goal, we have been performing research in line with five key areas of focus:

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

As outlined in sections **1. Overall Image of Your Center**, **2-1. Research results to date** and **4-3. Results in fused research fields**, over the previous three and a half years, ASHBi has been established as an institute with a highly coherent research direction and splendid research environments, ample interactions among research groups, and an excellent administrative support system, and has made a number of salient achievements congruent with its five key goals, contributing eminently to the promotion of human biology in development, physiology, and diseases as well as the fusion of human biology with mathematics and bioethics. In the second half of the 10-year WPI funding period, we will therefore essentially continue and expand on what we have done during the first half. On top of that, in response to advice from the WPI Working Group, we will embark on the five flagship projects mentioned above. This will not only further strengthen the interactions among PIs and the identity of ASHBi, but it will also facilitate the realization of the ASHBi's research objectives. The themes and brief contents of the five flagship projects are as follows (for details see **10. The Center's Response to Results of the FY2021 Follow-up, Response 1**):

1. Mechanism and *in vitro* reconstitution of primate development
This project will focus on understanding the mechanism of pre-/post-implantation primate development and reconstituting it *ex vivo* and *in vitro*, in order to provide critical insights into the mechanism of human development and stem cell-based regenerative medicine (**Alev**, **Eiraku**, **Ema**, **Hiiragi**, **Hiraoka**, and **Saitou G**) (relevant to **Focus Areas 1**, **2** and **4**).

2. Interdisciplinary analysis for disease-associated gene functions in primates
This project will consist of **a)** a systematic study of anxiety disorders by an integrative approach that combines functional genomics and neuroscience, and **b)** a systematic study of the gene regulatory network in the corticospinal motor neurons that accounts for the massive plasticity in the adult primate brain, creating a basis for the development of innovative medical interventions (**Amemori**, **Bourque**, **Isa**, **Murakawa**, and **Yamamoto G**) (relevant to **Focus Areas 1**, **2** and **3**). This project is highly relevant to the project creating disease models using gene-knockout monkeys (*PKD1*, *NPHP1*, *DISC1*) (**Ema**, **Isa**, **Tsukiyama**, and **Yanagita G**).

3. Age-associated genomic alterations and their interplay with the immune system
This project will explore age-associated genomic alterations and their interplay with the local immune system, with a particular focus on the pathogenesis of primary sclerosing cholangitis (PSC), a rare, chronic cholestatic liver disease associated with a high incidence of inflammatory bowel disease and an increased malignancy risk of cholangiocytes, thereby unraveling age-associated systems impairments and their consequences in humans (**Ogawa** and **Ueno G**). In addition, the Basic/Clinical Medicine platform will explore age-associated systemic alterations in diverse organs, creating a solid basis for developing the flagship project (**Ogawa**, **Ueno**, **R. Yamamoto**, and **Yanagita G**) (relevant to **Focus Area 1**).

4. Establishment of "data representation theory"
This project will establish a new mathematical paradigm called "data representation theory". By combining optimal transport, topological data analysis, and pattern formation theory, data representation theory aims to understand the mathematical structures underlying large and complex datasets in a comprehensive manner and to develop precise and informative descriptors for such

datasets, contributing to the innovation of both biology and mathematics (**Hiraoka**, **Seirin-Lee**, and **ASHBi G**) (relevant to **Focus Area 2**).

5. Bioethics at the periphery of birth and death
This project will aim **a)** to create a guideline for conducting human fetal tissue research and compile a report that will serve as a theoretical basis for performing such research, and **b)** to create a guideline and a feasible platform for the research use of early postmortem human tissues, thereby contributing to the development of an ethical framework that is essential for promoting key projects not only in ASHBi, but also more generally in human biology (**Fujita** and **ASHBi G**) (relevant to **Focus Area 5**).

We believe that these endeavors will lead to the realization of ASHBi's research objectives.

7-2. Center's plan to maintain its posture as a globally visible institute after WPI funding ends

ASHBi consists of 11 KU PIs (4 KUIAS PIs, 7 non-KUIAS KU PIs), 2 overseas PIs, 1 SUMS PI, 4 early-career PIs (1 in SUMS), three core facilities (SignAC, PRiME, NPAF), and the ASHBi administrative office.

The KUIAS PIs (**Hiraoka**, **Murakawa**, **Saitou**, **Seirin-Lee**) will continue to be the core of ASHBi and maintain/extend their research activities through their own funding. KU will provide at least 3 tenure PI posts for ASHBi by FY2027, and 3 early-career PIs will be evaluated for these positions. SUMS has also provided 1 tenure PI post for the WPI program, together with essential support for the operation of PRiME, so that the research activities of 1 SUMS PI in PRiME can be maintained/extended. The 7 non-KUIAS, KU PIs and 1 SUMS PI have now been highly integrated into the activities of ASHBi with the shared vision of promoting human biology, and will continue to be an essential part of ASHBi.

To create a research environment competitive with other internationally top-level universities/institutes, KU considers it imperative to implement and develop university-wide core facilities (e.g., those for genomics, epigenomics, metabolomics, microscopes, etc.) with constant updates of the most advanced equipment and capacities to support the in-house development of cutting-edge technologies, thereby serving as a hub for strongly driving the university-wide research activities forward. Toward this end, KU is planning to significantly broaden the organization and function of KUIAS, so that it truly serves as a core and broad organization for the reformation of the KU research activities, including the expansion and management of advanced core facilities. SignAC (led by **T. Yamamoto** and **T. Tsujimura**), as part of iSAL (Innovative Support Alliance for Life Science) in KU, has grown to be a critical core facility for genomics and epigenomics research, including single-cell genome information analysis, in ASHBi as well as KU. The uniqueness and strength of SignAC includes its close collaborative relationship with the mathematics groups in ASHBi (**Hiraoka** and **Seirin-Lee G**), which has allowed it to contribute to the development of innovative analysis algorithms such as RECODE and GMM-OT. Accordingly, KU is committed to providing support for maintaining/expanding on SignAC as a university-wide core facility for advanced genomics/epigenomics studies.

Based on the considerations/situations described above and the indirect funding support by KU, we have calculated the minimum costs for maintaining the core functions of ASHBi, including the maintenance of the ASHBi administrative office and the provision of appropriate support to each PI (e.g., 1 ASHBi postdoc position/PI), leading to the conclusion that we should be able to maintain these functions in a feasible manner after the WPI period (see Table 1 and 2 in **8. Host Institution's Concrete Action Plan toward Making its Center an Autonomous Research Institute in the Second Half of the Grant Period (from the 6th Year of the Center's Operation)**).

The KU plan for the reformation of the KU research activities, including prioritized support for ASHBi, depends in part on their designation as an "International University of Excellence (国際卓越研究大学)" by MEXT, and we will make all efforts to realize the autonomy of ASHBi and support the reformation of the KU research activities

8. Host Institution's Concrete Action Plan toward Making its center an autonomous research institute in the second half of the grant period (from the 6th year of the center's operation)

Describe the Host Institution's plan for realizing a research system including the allocation of resources (e.g. personnel, infrastructure) that will sustain the Center as a "top world-level research institute" after its WPI funding period ends. To enable this, describe the assets that the Host Institution will provide the Center (e.g. expected acquisition of external funding, allocation of personnel, provision of budgets). Describe actions that the Host Institution has taken toward achieving the Center's independence up to the point of this midterm evaluation.

KU will provide necessary support to ASHBi for sustaining the Institute's research capabilities after the end of WPI funding period.

Necessary functions for ASHBi's autonomy
Minimum functions required to sustain ASHBi after the WPI funding period will be to maintain (1) employment of PI/Co-PIs and at least one postdoc for each PI group in KU, (2) function of the SignAC Core Facility, (3) research support and administrative functions developed by the ASHBi Office, and (4) the ASHBi Main Building serving as the base/hub of ASHBi researchers.

To further develop ASHBi's role and functions, KU will actively seek possibilities for additional personnel and funding supports to ASHBi.

KU's support for ASHBi autonomy

A. **Providing tenure posts**: KU will provide at least three tenure posts as PI positions by FY2027. Currently, there are three non-tenure PIs.

B. **University-wide core facility development**: As SignAC serves as a fundamental facility for ASHBi and KU researchers, maintaining and expanding the facility function must be highly prioritized. KU plans to apply for MEXT's new "International University of Excellence (国際卓越研究大学)" program, and if selected, KU will further expand SignAC's functions and utilize SignAC as the best practice model to develop a university-wide core facility for life sciences under the KUIAS umbrella.

C. **Indirect fund support**: Of the indirect funds acquired from the external funding, KU allocates half to the department and the other half to the university headquarters. For indirect funds acquired by PIs/researchers affiliated with ASHBi, university headquarters' portion is allocated to ASHBi as university support.

D. **Further development:** KU will consider to form a cross-departmental platform in KUIAS when KU succeeds in obtaining the MEXT's "International University of Excellence (国際卓越研究大学)" program. This platform, with ASHBi as one of its core, will be the hub to accelerate research among the whole university. In the relevant process, KU will provide not only the necessary funding to maintain ASHBi's functions, but also provide additional personnel and funding to further support the core function for the development of KUIAS's new platform.

Concrete action plan for ASHBi's autonomy
We have calculated the budget required for ASHBi's autonomy and summarized in Table 1. The minimum budget to maintain Institute's core functions is estimated to be approximately 360 million yen per year, based on the accumulation of actual budgets for FY2021.

On the other hand, financial support by KU is summarized in Table 2. Of the minimum budget requirement, 114 million yen will be covered by KU Support A (Providing tenure posts) and B (University-wide core facility development). In addition, through KU's Support C (Indirect fund support), ASHBi is expected to secure approximately 199 million yen in indirect funding (based on FY2022 forecast).

Thus, the total support from KU (KU's Support A, B and C) is expected to amount to approximately 313 million yen, which is equivalent to 87% of the minimum required budget of 360 million yen.

Table 1. The minimum costs for maintaining the core functions of ASHBi. The cost accumulations required for ASHBi's autonomy is estimated based on the executed amount in FY2021.

Personnel costs per year		Unit: thousand yen
PIs/Researchers SignAC	Personnel costs for 3 PIs Personnel costs for 2 researchers, 2 technical staff, and 1 admin. Staff	59,590
PIs/Researchers ASHBi Office	Personnel costs for 1 Co-PI and 16 postdocs, Allowance to the PIs Personnel costs for the Admin. Director, 4 specialists, and 5 admin. Staff	214,830
Operational costs per year		
SignAC	Maintenance contract costs for the equipment, Electric utility expenses	51,600
Non SignAC	Utility expenses, Room cleaning costs, Consumable expenses, etc.	12,700
Infrastructure costs per year		
SignAC	Rental costs of the ASHBi Main Building (space used by SignAC)	3,200
	Rental costs of the ASHBi Main Building (other spaces)	17,900
Total		**359,820**

Table 2. KU's support for ASHBi's autonomy. The amount of indirect funds associated with the external funding is estimated on the basis of the FY2022 forecast.

Amount to be funded by KU's support	Unit: thousand yen
KU's Support A (Providing tenure posts) KU's Support B (University-wide core facility development)	114,390
KU's Support C (Indirect fund support)	198,960
KU's Support D (Further development)	46,470
Total	**359,820**

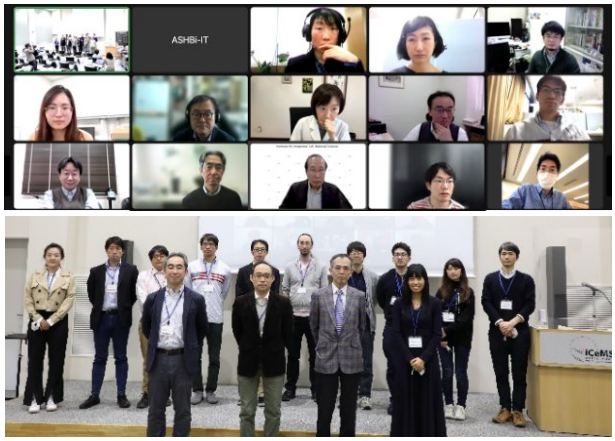
9. Others (within 1 page)

Cooperation with WPI-iCeMS

Other than the ASHBi, KU hosts another WPI center, the iCeMS (the Institute for Integrated Cell-Material Sciences), which was established in December 2007. The two WPI centers are located in a 5-minute walking distance. In order to improve the relationships between the two institutions, we have actively cooperated in organizing important institutional events.

iCeMS Deputy Directors Invited to ASHBi Retreat: At the first ASHBi retreat held at Awaji Island, Japan, on February 7-8, 2020, we invited two iCeMS Deputy Directors (Prof. Jun Suzuki and Prof. Mineko Kengaku). They introduced iCeMS' research activities and core facilities to ASHBi members. The two-day retreat featured 22 oral presentations including invited talks and 33 poster presentations, where 77 participants were able to bond and enjoy the interactive gathering.

iCeMS-ASHBi Exchange Gathering: With the aim of strengthening collaboration and active exchange of young researchers between the two WPI institutions of Kyoto University, we held an exchange meeting on March 24, 2022. This event was originally planned to be held in a face-to-face setting in order to promote interaction between the two institutions, but due to the COVID-19 pandemic, the meeting was held in a hybrid format. With six long talks and 26 short talks, lively discussions were held among the 122 participants.



10. Center's Response to Results of FY 2021 Follow-up (including Site Visit Results)

* Describe the Center's response to results of FY 2021 follow-up. Note: If you have already provided this information, please indicate where in the report

Administration

1) Next year (2022) when the center will undergo its interim evaluation, ASHBi should summarize the achievements it has made so far and devise a plan for its goals and strategies in the second half of the 10-year WPI funding period.

Response 1. Please see Sections 2-7 for details. The achieved results to date since the Institute's establishment are described in Sections 2-6 of this report. The Institute's goals and strategies in the second half of the 10-year of WPI grant period are described in Section 7 (plans for the ASHBi Flagship Project are described later in this section).

2) Looking beyond the 10-year funding period, further support from Kyoto University will be necessary to sustain the center's operation in and beyond its 11th year, although the university has already helped to build up ASHBi over the previous few years.

Response 2. Please see Section 8 for details. Minimum functions required to sustain ASHBi after the WPI funding period will be to maintain (1) employment of PI/Co-PIs and at least one postdoc for each PI group in KU, (2) function of the SignAC Core Facility, (3) research support and administrative functions developed by the ASHBi administrative office, and (4) the ASHBi Main Building serving as the base/hub of ASHBi researchers.

As described in Section 8, KU will provide the necessary support for the Institute's autonomy: Providing tenure posts, University-wide core facility development, and Indirect fund support. Thus, with these supports, we will be able to maintain the minimum core functions of the Institute after the WPI program ends. Furthermore, if KU succeeds in obtaining the MEXT's new "International University of Excellence (国際卓越研究大学)" program, KU will provide additional personnel and funding support for the further development of ASHBi/KUIAS as a university-wide research platform that transcends departmental boundaries.

3) ASHBi's still relatively small number of young female investigators appears to be at odds with the trend in other world top-level research institutes, such as Stanford, Broad Institute, UCSF, etc. Continuous efforts to address the under-representation of female scientists at ASHBi is especially important at this stage.

Response 3. As described in Section 5-1-1, we are actively recruiting female researchers. At the end of FY2020, the percentage of female researchers was only 13%. However, by April 2022, the percentage has significantly increased to 23%. To further increase the number of female researchers, in FY2021, we introduced the "ASHBi Foreign/Female Researchers Employment Support Program" replacing the existing support program for hiring foreign researchers ("ASHBi Foreign Researchers Employment Support Program). By introducing this program, we have already hired 3 female researchers in April 2022, and one more female researcher is planned to be hired within FY2022. We expect that further employment of female researchers will be achieved through this program.

As described in Section 6-5-2, the Institute is also making efforts to create an environment that balances work and family life to promote the employment of female researchers. In consideration of researchers raising small children, starting in FY2022, starting time of regular board meetings, PI meetings, and ASHBi Colloquium has been moved earlier, so that all meetings will end by 5:00 pm. We will continue our efforts to create a comfortable working environment for young researchers and female researchers.

Science

1) Toward establishing ASHBi's scientific brand, it will be important to polish up its Flagship Projects and vigorously execute them in ways that will serve as a beacon or light house to be seen by the international science community in recognizing ASHBi's unique scientific identity.

Response 1. To address this comment of the WPI Working Group, we have discussed the flagship projects in a more rigorous manner and set up the following five projects:

1. Mechanism and *in vitro* reconstitution of primate development

Recent studies, including those from ASHBi PIs, have shown that the mechanisms underlying early developmental processes, including cell-fate specifications in blastocysts, early post-implantation development, and germ-cell specification, are very different between mice and primates/humans. Moreover, the mechanisms for post-implantation development in primates/humans are largely unknown due to technological and ethical difficulties in accessing/manipulating the relevant samples. These notions point to the importance of studying the mechanism of embryonic development in primates, which will provide critical insights into the mechanism of human development and stem cell-based regenerative medicine. Accordingly, as a flagship project of the Developmental Biology subdivision (**Alev**, **Eiraku**, **Ema**, **Hiiragi**, and **Saitou G**), we will focus on the "**Mechanism and *in vitro* reconstitution of primate development**" (relevant to **Focus Areas 1**, **2** and **4**).

This project will consist of three interrelated initiatives:

a) To explore the mechanism of post-implantation primate development at a single-cell resolution using methodologies including scRNA-seq combined with novel analysis methods such as RECODE and GMM-OT.

b) To develop *ex vivo* culture systems for analyzing the pre-/post-implantation development of mouse and monkey embryos using technologies including advanced light-sheet imaging coupled with scRNA-seq analysis.

c) To perform *in vitro* reconstitution and analysis of pre-/post-implantation development of human and non-human primates using PSC-based synthetic embryo model systems and high-end 3D/4D imaging and scRNA-seq analysis.

2. Interdisciplinary analysis for disease-associated gene functions in primates

Understanding the mechanisms of human diseases using non-human primate models is a key goal of ASHBi. ASHBi PIs bear relevant expertise, including skill with technologies for manipulating neural circuits in primates and for identifying critical regulatory elements, i.e., enhancers, at a single-cell resolution. Accordingly, as a joint flagship project of the Primate Models/Macaque Genome Engineering subdivision and the Genome Informatics subdivision (**Amemori**, **Bourque**, **Isa**, **Murakawa**, and **Yamamoto G**), we will perform an "**Interdisciplinary analysis for disease-associated gene functions in primates.**" The phenotypes of knockout monkeys for *PKD1* (**Ema G**), *NPHP1* (**Yanagita G**) and *DISC1* (**Isa G**) will be analyzed through this collaborative platform (relevant to **Focus Areas 1**, **2**, and **3**).

The core of this project will consist of two interrelated studies:

a) A study of anxiety disorders (**Amemori** and **Murakawa G**):

To produce a primate model for anxiety disorders, the groups will systematically sample brain tissues from disease-relevant areas, including the striatum, and analyze gene expression and enhancer activation using the original 5' scRNA-seq method. They will perform integrative analysis of the single-cell brain enhancer atlas with the large-scale human genetics data to fine-map causal genetic variants as well as to identify disease-relevant target genes and cell types. They will then perform cell type-specific manipulations of the disease-relevant cells to validate the functionality *in vivo*, creating a general framework to elucidate the molecular basis of human psychiatric disorders and to pave the way for innovative medicines.

b) A study of the plasticity of corticospinal motor neurons (**Isa** and **Murakawa G**):

Isa G has revealed that after spinal cord injury, the corticospinal neurons originating from the primary motor cortex of adult macaque monkeys show large-scale plastic change in their axonal trajectories through intensive rehabilitative training and electrical stimulation of the motor cortices, to a much greater extent than previously known, leading to a recovery in hand movements. To explore the underlying mechanism, the groups will sample corticospinal motor neurons in control and operated monkeys, and compare their gene regulatory networks using the original 5' scRNA-seq method to

identify key genes for the plasticity of axonal trajectories. The groups will then perturb the candidate genes in monkeys to delineate the function of such genes in the massive plasticity and functional recovery, creating a platform for the treatment of spinal cord injury.

3. Age-associated genomic alterations and their interplay with the immune system
Aging involves progressive and continuous mutations in the genome, leading to systems malfunctions, and eventually to critical age-associated disorders, including cancers. Mutations in pre-cancerous cells can create neo-antigens and may alert the adaptive immune system to the emergence of "non-self" cells for their effective removal. Whether and how such interplay between pre-cancerous cells and the local immune system operates in humans remains largely unknown. Notably, aging also impairs the immune system itself. Is human cancer mainly caused by the accumulation of mutations in the driver genes? Or is it driven by escape from the local immune system? Alternatively, does human cancer arise due to an aging-related impairment in surveillance by the local immune system? To address these fundamental questions and unravel the age-associated systems impairments and their consequences in humans, we will explore "**Age-associated genomic alterations and their interplay with the immune system**" (relevant to **Focus Area 1**) as a flagship project of the Basic/Clinical Medicine platform (**Ogawa**, **Ueno**, **R. Yamamoto**, and **Yanagita G**).

Specifically, this project will focus on the pathogenesis of primary sclerosing cholangitis (PSC), a rare, chronic cholestatic liver disease associated with a high incidence of inflammatory bowel disease and an increased risk of cholangiocyte malignancy. Normal and PSC liver tissues at both pre- and post-malignancy stages are available at KU Hospital, and three lines of investigations will be performed (**Ogawa and Ueno G**):
a) Investigations to establish the effect of aging on alterations in the gene profiles and functions of the local immune cells in normal and PSC liver.
b) Investigations to establish the effect of aging on the genomic alterations in cholangiocytes and other cells in normal and PSC liver.
c) Investigations to determine the differences in the interplay between cancerous organ cells and the local immune system at the pre-malignancy and post-malignancy stages.

Furthermore, the Basic/Clinical Medicine platform will continue to explore age-associated systems alterations in diverse organs, creating a solid basis for attaining the flagship project.

4. Establishment of "data representation theory"
To create fusion between mathematics and biology, ASHBi has not only explored novel applications of existing mathematical methodologies to biological data, but also developed new mathematical concepts, theorems and descriptors. Key findings include the notion that high-dimensional data with noise—such as scRNA-seq data—possesses intrinsic mathematical structures that can cause improper biological conclusions when analyzed by conventional statistical methods, leading to the formulation of RECODE (for details see **4-3. Results of research in fused research fields**). Accordingly, as a flagship project of the mathematics groups (**Hiraoka** and **Seirin-Lee G**) and **ASHBi G**, we will embark on an "**Establishment of 'data representation theory'**" project, the goal of which will be to comprehensively understand mathematical structures (both static and dynamic) underlying large and complex data and to develop precise and informative descriptors tailored to the respective specific analyses (relevant to **Focus Area 2**).

This project will consist of two interrelated goals:
a) To develop a new theory for characterizing large and complex data by means of the optimal transport and topological data analysis, with possible applications for noise reduction including batch effects, time-series analysis of scRNA-seq data, phase separation and 3D reconstruction of chromatin structure, and inference of gene regulatory networks.
b) To establish an objective index to evaluate the structural similarity between experimental/clinical data and *in silico* patterns by combining topological data analysis and pattern formation theory. This is based on the notion that despite pattern similarity between real and *in silico* data is a key measure for the validation of *in silico* programming, all studies to date have evaluated the pattern similarity by

subjective indices (human perception), but not by objective indices.

5. Bioethics at the periphery of birth and death
The procurement and use of human samples are critical for promoting human biology. For example, tissues from aborted fetuses are an ideal material for promoting human developmental biology, and the procurement of tissues from healthy elderly individuals or from early postmortem individuals will accelerate investigations into human aging. However, it is difficult to access such tissues, and critically, there are no clear rules/regulations for such research in Japan. Accordingly, as a flagship project of the bioethics group (**Fujita G**) and **ASHBi G**, we will embark on to create "**Bioethics at the periphery of birth and death**", and explore philosophical and empirical approaches for making rules/guidelines on the research use of such human tissues (relevant to **Focus Area 5**).

This project consists of two interrelated initiatives:
a) To formule rules for fetal tissue research:
Fujita G and collaborators led by **Fujita**, including scientists, philosophers/ethicists, and jurists, will create guidelines for conducting fetal tissue research and compile a report as a theoretical basis for such research.
b) To construct a platform for early postmortem tissue research:
Young investigators led by **Dr. Okui** in **Fujita G** will develop an institutional guideline and a feasible platform for the research use of early postmortem tissues, while taking the opinions of citizens and the feelings of bereaved families into account.

Both these initiatives involve the use of postmortem human tissues for research, require emotional consideration for donors or their families, and require the cooperation of physicians in clinical settings, and thus they will be impacted by the synergistic effects of all these factors. The first effort is relevant to the flagship project of the Developmental Biology platform, and the second is relevant to that of the Basic/Clinical Medicine platform, contributing to the promotion of key projects not only in ASHBi, but also in human biology in general.

ASHBi will provide appropriate support for all five flagship projects and create a system for evaluating their progress.

2) It is important for ASHBi to quickly make its xRECODE method universally available to see how it competes with many other methods.

Response 2. To address this comment of the WPI Working Group, we have published the manuscript on RECODE in ***bioRxiv*** : https://doi.org/10.1101/2022.05.02.490246 (manuscript under revision for *Molecular Systems Biology*). The revised manuscript demonstrates a superior performance of RECODE over representative imputation methods, including SAVER, MAGIC, ENHANCE, scImpute, DrImpute, and ALRA, as well as a widely used dimension reduction program, Seurat. The RECODE source code is available at https://yusuke-imoto-lab.github.io/RECODE/index.html.

3) ASHBi is encouraged to take a leadership position in bioethics discussions.

Response 3. Please see **2-1. Research results to date**, item [10], **Appendix 1-1**, item [10] manuscript number 18, 19, 20, and **4-3. Results of research in fused research fields**, **Ethics–biology Fusion** for the activities of the Bioethics/Philosophy group (**Fujita G**) in ASHBi.

For example, **Fujita** and **Saitou** have been involved in the work to revise the guidelines of the International Society for Stem Cell Research (ISSCR), published white papers on the guidelines, and responded to hearings at the Cabinet Office's Expert Committee on Bioethics, steadily achieving a track record of activities leading to the establishment of research rules in Japan and abroad.

Fujita has served as a task force member on the Informed Consent for Human Fetal Tissue Donation for Research working group organized by the International Society for Stem Cell Research (ISSCR).

Fujita, **Takashima** at CiRA, and **Saitou** organized a two-day workshop on "Fetal Tissue Research", to which the task force members were invited. The final attendance at this workshop was 143 participants, including scientists and bioethicists from ASHBi and other research institutions, as well as Japanese government officials.

Accordingly, we believe that ASHBi is taking a leadership position in bioethics discussions.

Furthermore, it is of note that **David Cyranoski**, the former Asia Pacific Correspondent at *Nature*, joined ASHBi in November 2021. In his capacity as a Program Specific Senior Lecturer, he has been embarking on a critical analysis of modern science from a historical perspective, focusing on how science impacts society while itself being shaped by social factors. A grasp of these historical processes can help us better understand the trajectory of science and inform our attempts to deal with often controversial implications of cutting-edge science today. **Cyranoski** is currently working in three areas: assisted reproduction in humans, neurological disease redefinition, and the clinical introduction and regulation of stem cells.

4) From the standpoint of ASHBi's translational research into human medical science, it would be useful to try to connect human diseases to non-human primate models and vice versa.

Response 4. Please see **Responses 5 and 7. The Center's Response to the Results of Last Year's Follow-up** of the **FY2020 Progress Report** for the rationale and the process for the selection of the creation of gene KO models in cynomolgus monkeys. The current status of the *PKD1*, *NPHP1*, and *DISC1* KO projects is as follows:

PKD1 KO (**Ema** and **Tsukiyama G**):
Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common hereditary diseases and is a major cause of end stage renal failure. ADPKD patients with heterozygous mutations in *PKD1*, a major causative gene, develop renal cysts during the fetal stage. **Ema** and **Tsukiyama G** have shown that, unlike rodent models, *PKD1* heterozygous monkeys develop renal cysts at the perinatal stage, recapitulating the human phenotype (*Nat. Commun*. **10**, 5517, 2019). **Ema G** has continued to observe these monkeys, and has found that the number and size of their renal cysts has progressively increased, pheno-copying the human disease. These models are useful for analyzing the pathogenesis of ADPKD1 and for exploring therapeutic strategies.

NPHP1 KO (**Yanagita G**):
Nephronophthisis is a genetic disease that causes end-stage renal disease in children. *NPHP1*, encoding Nephrocystin 1, is a major causative gene, but its exact function *in vivo* remains unknown, due to the lack of an appropriate animal model. Pathological analysis of human kidneys is also limited, and early phenotypes are totally unknown. **Yanagita G** has so far generated three *NPHP1* KO monkeys, and euthanized two KO and three control monkeys aged 1 to 1.7 years old. Nephrocystin 1 was expressed in the Loop of Henle and collecting ducts. The kidneys of *NPHP1* KO monkeys showed tubular diverticulum and tubular florets, which are characteristic features in human nephronophthisis, associated with significant fibrosis around tubules in the corticomedullary region. In addition, cellular polarity was disturbed in about half of the collecting ducts in the KO kidneys, and primary cilia in the Loop of Henle and collecting ducts, where NPHP1 was expressed, were shorter in the KO kidneys. Taken together, these results lead **Yanagita G** to conclude that the *NPHP1* KO monkeys recapitulate human nephronophthisis, and would be extremely useful for analyzing early pathological changes as well as the pathogenesis of this disease.

DISC1 KO (**Isa G**):
DISC1 is a hub in the interactome of genes related to neuropsychiatric disorders. **Isa G** hypothesizes that *DISC1* KO affects a number of critical genes and causes psychosis, and have so far generated 5 KO and 3 control monkeys. They were carried to NPAF at 7–8 months of age, and were separated from their mothers after 1 year of age to exert environmental stress. All the monkeys are still younger than 2 years old, and **Isa G** is currently analyzing (1) gene expression in the iPS cells derived from the KO and control monkeys (in collaboration with SignAC), (2) general behavior including the social interaction in the cage, (3) brain morphology by MRI, and (4) sleep state in the night. In the RNA seq analysis of iPS cells, **Isa G** confirmed the *DISC1* deletion and reduction in expression of some related genes. In (3),

compared with the age-matched control, the brains of the KO monkeys appeared to be smaller. In (4), some KO monkeys seemed to have sleep disturbances. On the other hand, it is premature to draw conclusions at this stage. **Isa G** is now establishing a system for recording the resting state fMRI with 7T MRI to analyze the whole brain network properties and conducting additional in-depth behavioral analysis including olfactory functions and eye movements, which are known as prodromal symptoms of neuropsychiatric disorders.

Furthermore, as described in **Response 1** in **Science**, we have initiated a flagship project for the interdisciplinary analysis of disease-associated gene functions in primates, focusing on investigation of the mechanism of anxiety disorders and the plasticity in the corticospinal motor neurons using primate models. We will perform these lines of investigations carefully and in a long-term manner to achieve translational outcomes.

5) Whatever human-specific traits are observed, they are ultimately generated from the human-specific genomic sequence. The kinds of epigenetic modifications introduced, how much certain genes are activated, and the activity of gene products would be in fact determined by genomic sequences. It could, therefore, be said that one of ASHBi's goals is to identify the genomic sequences (or regions) that make us human.

Response 5. We would like to thank the WPI Working Group for this constructive suggestion. We have indeed been performing a number of investigations in line with this recommendation.

For example, genetic variations associated with human diseases are significantly enriched within transcribed enhancers. Based on the expertise in 5' scRNA-seq analysis and Micro-C, **Murakawa G** has been creating an "enhancer atlas" of a diverse population of CD4-positive T cells under various conditions, and has succeeded in comprehensively identifying enhancers showing polymorphisms significantly associated with human immunological disorders and susceptibility to COVID-19. **Murakawa G** has found that many of these enhancers are specific to primates, and is currently analyzing the ontogeny of such primate-specific enhancers and their specific association with human diseases. **Murakawa G** has also been generating a catalog of genes and non-coding RNAs present in humans and non-human primates, but absent in rodents, and in the process identifying genes only present in humans.

Fumitaka Inoue, co-PI of **Bourque G**, has also been working on the evolution of the human regulome. By comparing primate genomes and epigenomes (i.e., human, neanderthal, chimpanzee, gorilla, etc.), **Inoue** and his colleagues have been creating a comprehensive catalog of functional variants that are fixed specifically in the human lineage, and identifying genomic regions that may be responsible for human evolution. **Inoue** is aiming to comprehensively validate and quantify the impact of these evolutionary variants (as many as 5 million fixed nucleotide variants between human and chimpanzee genomes) on transcriptional activities in iPSC-derived neurons to define their function as either "neutral" or "functional". This line of research may provide a blueprint for the discovery of what makes us human.

We will continue our efforts along these lines of research and will discuss within ASHBi the best approach for the further expansion of such investigations.

Appendix 1-1 List of Papers Underscoring Each Research Achievement

* List papers underscoring each research achievement [1] ~ [10] listed in the item 2-1 "Research results to date" of 2. "Advancing Research of the Highest Global Level" (up to 20 papers) and provide a description of the significance of each (within 10 lines).
* 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 the same. If a paper has many authors, underline those affiliated with the Center.
* If a paper has many authors (say, more than 10), all of their names do not need to be listed.
* Place an asterisk (*) in front of those results that could only have been achieved by a WPI center.

* [1] Elucidation of key principles for mammalian early development

1. Chan, C. J., Costanzo, M., Ruiz-Herrero, T., Mönke, G., Petrie, R. J., Bergert, M., Diz-Muñoz, A., Mahadevan, L., and Hiiragi, T. **Hydraulic control of mammalian embryo size and cell fate.** *Nature* 571, 112–116, 2019.

Size control is fundamental in development and homeostasis. Using mouse blastocysts as a model, this work unravels a key role of the fluid-filled lumen in size control and cell fate specification. Luminal pressure acts as a mechanical signal to drive cell stretching and stiffening, which reinforce junctional maturation through 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. Furthermore, luminal pressure and cavity size affect the allocation of cells within the embryo, thereby influencing cell fate specification. Given that many organ systems are built with fluid (e.g., the lungs and kidneys) or for fluid transport (e.g., the vasculature), how forces feed back on their form and function is critical, and the impact of this study goes beyond developmental patterning (relevant to **Focus Areas 2** and **4**).

*2. Ichikawa, T. (1/12), Hiiragi, T. (12/12), et al. **An ex vivo system to study cellular dynamics underlying mouse peri-implantation development.** *Dev. Cell* 57, 373–386.e9, 2022.

This study develops an *ex vivo* 3D culture to recapitulate mouse peri-implantation development. The system recapitulates embryonic growth, anterior-posterior axis initiation, and overall 3D architecture in 49% of the cases, and enables the study of cellular dynamics through automatic cell segmentation with light-sheet microscopy. This work shows that, upon implantation, release of the increasing tension in the polar trophectoderm is necessary for its constriction and invagination. The resulting extra-embryonic ectoderm plays a key role in growth, morphogenesis, and patterning of the neighboring epiblast, which subsequently gives rise to all embryonic tissues. This *ex vivo* system thus offers unprecedented access to peri-implantation development for *in toto* monitoring and measurement, revealing a mechano-chemical interplay between extra-embryonic and embryonic tissues. This study serves as a basis for the understanding of human peri-implantation development (relevant to **Focus Areas 2** and **4**).

*[2] *In vitro* reconstitution of human segmentation clock and somitogenesis

*3. *Matsuda, M. (1/22), *Yamanaka, Y. (2/22), Yamamoto, T. (18/22), Alev, C. (22/22), et al. **Recapitulating the human segmentation clock with pluripotent stem cells.** *Nature* 580, 124-129, 2020.

Using iPSC-based technologies, this work models the human segmentation clock, a biological mechanism underlying the rhythmic and controlled emergence of somites, which give rise to the segmental vertebrate axial skeleton. The work identified oscillatory expression of core segmentation clock genes, determined the period of the human segmentation clock to be around 5 hours, and demonstrated the presence of dynamic travelling-wave-like gene expression *in vitro*. The work compared oscillatory genes in the human and mouse presomitic mesoderm, which revealed species-specific and shared molecular components and pathways. Using CRISPR–Cas9-based genome editing, the authors mutated genes responsible for segmentation defects of the vertebrae, such as spondylocostal dysostosis, and revealed gene-specific alterations in oscillation, synchronization or differentiation properties, providing insights into the human segmentation clock as well as diseases associated with human axial skeletogenesis (relevant to **Focus Areas 1**, **2**, and **4**).

4. Matsuda, M., Hayashi, H., Garcia-Ojalvo, J., Yoshioka-Kobayashi, K., Kageyama, R., Yamanaka, Y., Ikeya, M., Toguchida, J., Alev, C., and Ebisuya, M. **Species-specific oscillation periods of human and mouse segmentation clocks are due to cell autonomous differences in biochemical reaction parameters.** *Science* 369, 1450-1455, 2020.

Based on the system established in (3), this work showed that the species difference in the oscillation periods of segmentation clocks (mice: 2–3 hours; humans: 5–6 hours) is due to differences in multiple biochemical reactions of *HES7*, the core segmentation clock gene, including degradation and expression delays. Accordingly, this study proposes that cell-autonomous differences in biochemical reaction speeds underlie

temporal differences in development between species. The possible origin and molecular explanation for the slower biochemical reaction speeds in humans are still missing and remain a topic of ongoing research. Overall, this study is a good example of how *in vitro* models of a developmental concept such as the segmentation clock can help to address and possibly even answer fundamental questions related to the nature of human biology (relevant to **Focus Areas 1**, **2**, and **4**).

*[3] Establishing a foundation for human *in vitro* gametogenesis
5. Yamashiro, C. (1/13), Yabuta, Y. (3/13), Nakamura, T. (5/13), Yamamoto, T. (12/13), Saitou, M. (13/13), et al. **Generation of human oogonia from induced pluripotent stem cells *in vitro*. *Science*** 362, 356-360, 2018.
Germ cells differentiate into sperm or eggs, which unite to form new individuals and transmit the genetic information. This work demonstrates the induction of human induced pluripotent stem cells (iPSCs) first into primordial germ-cell like cells (PGCLCs), and then into oogonia, the immediate precursors of oocytes, by a xenogeneic reconstituted ovary culture. The hPGCLC-derived oogonia display hallmarks of epigenetic reprogramming—genome-wide DNA demethylation, imprint erasure, and extinguishment of aberrant DNA methylation in hPSCs—and acquire an immediate precursory state for meiotic recombination. This work will serve as a critical basis for understanding the mechanism of human oogonia development and its disease states, including infertility (relevant to **Focus Areas 1**, **2**, and **4**).

*6. Nagaoka, S. I. (1/11), Yabuta, Y. (6/11), Nakamura, T. (9/11), Yamamoto, T. (10/11), Saitou, M. (11/11), et al. **ZGLP1 is a determinant for the oogenic fate in mice.** *Science* 367, 1089 (aaw4115), 2020.
This work shows that ZGLP1, a conserved transcriptional regulator with GATA-like zinc fingers, determines the oogenic fate in mice. ZGLP1 acts downstream of bone morphogenetic protein, but not retinoic acid (RA), and is essential and sufficient for the oogenic program and meiotic entry. These findings elucidate the mechanism for mammalian oogenic fate determination, providing a foundation for promoting *in vitro* gametogenesis and reproductive medicine (relevant to **Focus Areas 2** and **4**).

*7. Okamoto, I., Nakamura, T., Sasaki, K., Yabuta, Y., Iwatani, C., Tsuchiya, H., Nakamura, S., Ema, M., Yamamoto, T., and Saitou, M. **The X-chromosome dosage compensation program during the development of cynomolgus monkeys.** *Science* 374, 954 (eabd8887), 2021.
X chromosome dosage compensation ensures a balanced gene dosage between the X chromosome and autosomes and between the sexes, involving divergent mechanisms among mammals. This work elucidates a distinct mechanism for X chromosome inactivation (XCI) in cynomolgus monkeys, a model for human development. In particular, this work reveals that the epiblast lineage attains XCI by a week after implantation, with extended maintenance of an active intermediate bearing repressive modifications and compacted structure. This work also shows that males achieve X chromosome up-regulation (XCU) progressively, whereas females show XCU coincidentally with XCI, with both sexes establishing the X:autosome dosage compensation by 1 week after implantation. Conversely, primordial germ cells undergo X chromosome reactivation by reversing the XCI pathway early during their development. These findings establish a foundation for clarifying the dosage compensation mechanisms in primates, including humans (relevant to **Focus Area 2**).

[4] Identification of *cis* regulatory elements in human physiology and disease
8. Hirabayashi, S. (1/16), Bhagat, S. (2/16), Murakawa. Y. (16/16), et al. **NET-CAGE Characterizes Dynamics and Topology of Human Transcribed Cis-regulatory Elements.** *Nat. Genet.* 51, 1369-1379, 2019.
This study develops a simple and robust method, native elongating transcript–cap analysis of gene expression (NET-CAGE), to sensitively detect the 5′ ends of nascent RNAs in diverse cells and tissues, including unstable transcripts such as enhancer-derived RNAs, leading to the identification of tens of thousands of new enhancers. The study shows that while promoters are activated ubiquitously, enhancers tend to function in specific cell types, and that enhancer–promoter pairs are generally activated simultaneously upon stimulation. Furthermore, by integrating NET-CAGE data with chromatin interaction maps, this work shows that *cis*-regulatory elements are topologically connected according to their cell type specificity. The NET-CAGE dataset derived from human and mouse cells expands the FANTOM5 atlas of transcribed enhancers, with broad applicability to biomedical research. This work has been serving as a basis for developing single-cell NET-CAGE technology (relevant to **Focus Areas 1** and **2**).

*[5] Unraveling the mechanism for the plasticity of critical neural circuits in primates
9. Kinoshita. M., Kato. R., Isa. K., Kobayashi, K., Kobayashi, K., Onoe, H., and Isa, T. **Dissecting the circuit for blindsight to reveal the critical role of the pulvinar and superior colliculus.** *Nat. Commun.* 10, 135, 2019.
Blindsight is a phenomenon in which patients with primary visual cortex (V1) damage, despite loss of visual awareness, perform visually guided goal-directed behaviors. There has been a long-lasting debate on the neural pathways of blindsight—namely, whether it is a direct pathway from the retina to the lateral geniculate nucleus and then to the extrastriate visual cortex, or a pathway from the retina to the superior colliculus, the pulvinar and finally the extrastriate visual cortex. Using macaque monkey models, this work demonstrates that the pulvinar as well as the pathway from the superior colliculus to the pulvinar are critical for the blindsight. Combined with a more recent work (Takakuwa et al., *J. Neurosci.*, 41, 1755-1768, 2021), it has been demonstrated that with the intact V1, the lateral geniculate mainly regulates the visual behavior, but with the V1 lesion, both pathways (the lateral geniculate to extrastriate cortex and superior colliculus - pulvinar – extrastriate cortex) mediate blindsight (relevant to **Focus Area 3**).

*10. Chen. C-Y., Matrov. D., Veale. R., Onoe, H., Yoshida, M., Miura, K., and Isa, T. **Properties of visually-guided saccadic behavior and bottom-up attention in marmoset, macaque, and human.** *J. Neurophysiol.* 125:437-457, 2021.
Saccadic eye movements are rapid eye movements to precisely capture the images of objects in the visual field, and they are closely coupled with special attention. Saccadic systems are typically developed in primates. This study compared the results of a video free-viewing task and visually guided saccade tasks among three different species: marmoset, macaque, and human. Marmosets are expected to be a promising new primate model animal to study the mechanisms of human cognitive functions and neuropsychiatric disorders, and across-species comparison of saccade systems is a crucial step for further studies in this field. This work shows that all species exhibit qualitatively similar saccadic kinematics and saliency-driven saccadic behavior albeit with different parameters, and suggests that marmosets possess neural mechanisms for saccadic control similar to those of macaques and humans, and thus are an appropriate model to study the neural mechanisms underlying active vision and attention (relevant to **Focus Areas 2** and **3**).

*[6] Age-associated remodeling and clonal expansion in human tissues and diseases
11. Yokoyama, A. (1/40), Ogawa, S. (40/40), et al., **Age-related remodeling of esophageal epithelia by mutated cancer drivers.** *Nature* 565, 312-317, 2019.
With an intensive genome sequence of 682 micro-scale esophageal samples, this work demonstrates that clones carrying mutations in driver genes (predominantly NOTCH1 mutation) progressively expand with age in physiologically normal esophageal epithelia, and such mutations are substantially accelerated by alcohol consumption and smoking. Driver-mutated clones emerge multifocally from early childhood and increase in number and size with aging, and ultimately replace almost the entire esophageal epithelium in the very elderly. Thus, the remodeling of the esophageal epithelium by driver-mutated clones is an inevitable consequence of normal aging, which—depending on lifestyle risks—may affect cancer development. This work serves as a basis for delineating a comprehensive picture of clonal selection and evolution as a nascent step of tumorigenesis (relevant to **Focus Area 1**).

*12. Kakiuchi, N. (1/54), Inoue, Y. (6/54), Hirano, T. (13/54), Takeuchi, Y. (15/54), Ochi, Y. (16/54), Watatani, Y. (19/54), Fujii, Y. (20/54), Kon, A. (22/54), Nakagawa, M. M. (25/54), Yoda, A. (26/54), Nanya, Y. (27/54), Makishima, H. (28/54), Ogawa, S. (54/54), et al. **Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis.** *Nature* 577, 260-265, 2020.
Chronic inflammation is a major cause of morbidity and mortality and confers a substantial cancer risk. This work shows that in patients with ulcerative colitis (UC), a common inflammatory bowel disease (IBD), the inflamed intestine undergoes widespread remodeling by pervasive clones with mutations involving *NFKBIZ*, *TRAF3IP2*, *ZC3H12A*, *PIGR*, and *HNRNPF*, which are implicated in downregulation of IL-17 and other pro-inflammatory signaling pathways. Notably, the *NFKBIZ* mutations were rarely found in either sporadic or colitis-associated cancer, suggesting that negative selection of NFKBIZ-mutated cells occurs during colorectal carcinogenesis. This work highlights the common and discrete mechanisms of clonal selection in inflammatory tissues, which could be utilized for therapeutics of colorectal cancer (relevant to **Focus Area 1**).

*13. Saiki. R. (1/22), Nakagawa, M. M. (4/22), Ogawa. S. (22/22), et al. **Combined landscape of single-nucleotide variants and copy number alterations in clonal hematopoiesis.** *Nat Med.* 2021.

Using a combination of targeted sequencing and array-based copy number alteration (CNA) detection of blood-derived DNA, this work delineated the landscape of clonal hematopoiesis (CH)-related single nucleotide variants (SNVs)/indels and CNAs in 11,234 individuals without hematopoietic malignancies (HM) from the BioBank Japan cohort, including 672 individuals with subsequent HM development, and studied the effects of these somatic alterations on mortality from HM and cardiovascular disease, as well as on hematological and cardiovascular phenotypes. The results showed that CH-related SNVs/indels and CNAs exhibited statistically significant co-occurrence in the same individuals. Co-occurrence of SNVs/indels and CNAs also modulated risks for cardiovascular mortality. These findings highlight the importance of detecting both SNVs/indels and CNAs in the evaluation of CH (relevant to **Focus Area 1**).

*[7] Elucidating the role of tertiary lymphoid tissues for kidney pathogenesis
14. Sato, Y., Boor, P., Fukuma, S., Klinkhammer, B. M., Haga, H., Ogawa, O., Floege, J., and Yanagita, M. (2020). Developmental stages of tertiary lymphoid tissue reflect local injury and inflammation in mouse and human kidneys. *Kidney International* 98, 448-463, 2020.
Tertiary lymphoid tissues (TLTs) are inducible ectopic lymphoid tissues in chronic inflammatory states and function as sites of priming local immune responses. **Yanagita G** has previously demonstrated that aged mice, but not young mice, exhibit multiple TLTs after acute kidney injury, and that TLTs are also detected in human aged and diseased kidneys. This study analyzed surgically resected kidneys from aged patients with or without chronic kidney disease as well as kidneys resected for pyelonephritis, and classified TLTs into three distinct developmental stages based on the presence of follicular dendritic cells and germinal centers. Accordingly, this study suggests that TLT formation may not be a disease-specific phenomenon but rather a common pathological process. This study provides insight into the biological features of TLT in the kidney and implicates the TLT stage as a potential marker reflecting local injury and inflammation (relevant to **Focus Areas 1** and **2**).

*15. Sato. Y. (1/28), Oguchi. A. (2/28), Toriu. N. (5/28), Yamamoto. T. (18/28), Murakawa. Y. (26/28), Yanagita. M. (28/28), et al. **CD153/CD30 signaling promotes age-dependent tertiary lymphoid tissue expansion and kidney injury.** *J. Clin. Invest.* 132, e146071, 2022.
This study identifies the TNF superfamily CD153/CD30 signaling between two unique age-dependent lymphocyte subpopulations, CD153+PD-1+CD4+ senescence-associated T (SAT) cells and CD30+T-bet+ age-associated B cells (ABCs), as a driver for TLT expansion. In kidney injury models, CD153 or CD30 deficiency impairs functional SAT cell induction, resulting in reduced ABC numbers and attenuated TLT formation with improved inflammation, fibrosis, and renal function. Clonal analysis shows that SAT cells and ABCs in the kidneys arise from both local differentiation and recruitment from the spleen. Furthermore, this work shows a possible contribution of this signaling pathway to human TLT formation. Together, these results reveal a previously unappreciated function of CD153/CD30 signaling in TLT formation and suggest that the CD153/CD30 signaling pathway could be a therapeutic target for slowing kidney disease progression (relevant to **Focus Areas 1** and **2**).

[8] Human immunology in physiology, aging, and diseases
16. Horiuchi. S. (1/12), Ueno, H. (12/12), et al. **Tox2 is required for the maintenance of GC TFH cells and the generation of memory TFH cells.** *Sci. Adv.* 7, eabj1249, 2021.
T follicular helper (Tfh) cells represent the major CD4+ T cell subset associated with antibody responses in vivo. Whereas Tfh cells can become memory cells and survive for a long time the mechanism by which Tfh cells become memory Tfh cells remains largely unclear. This work identifies the transcription factor Tox2 as a vital factor for the maintenance of T follicular helper (Tfh) cells in germinal centers (GC) and the generation of memory Tfh cells. High Tox2 expression was almost exclusive to GC Tfh cells among human tonsillar and blood CD4+ T cell subsets. Tox2 overexpression maintained the expression of Tfh-associated genes in TCR-stimulated human GC Tfh cells and inhibited their spontaneous conversion into Th1-like cells. Tox2-deficient mice displayed impaired secondary Tfh cell expansion upon re-immunization with an antigen as well as upon secondary infection with a heterologous influenza virus. Thus, Tox2 is highly integrated into the durable GC Tfh cell response and development of memory Tfh cells in mice and humans (relevant to **Focus Areas 1** and **2**).

*[9] Mathematical foundation for novel single-cell RNA sequence analysis methods
*17. Imoto, Y., Nakamura, T, Escolar, E. G., Yoshiwaki, M., Kojima, Y., Yabuta, Y., Kato, Y., Yamamoto, T., Hiraoka, Y., and Saitou, M. **Resolution of the curse of dimensionality in single-cell RNA sequencing**

data analysis. ***bioRxiv***: URL : https://doi.org/10.1101/2022.05.02.490246 (The RECODE source code: https://yusuke-imoto-lab.github.io/RECODE/index.html)
Single-cell RNA sequencing (scRNA-seq) determines gene expression in numerous individual cells. However, scRNA-seq data are high-dimensional with substantial technical noise. Upon analysis, such noise engenders statistical problems known as the curse of dimensionality (COD). Based on high-dimensional statistics, this work formulates a noise reduction method, RECODE (resolution of the curse of dimensionality), for high-dimensional data with random sampling noise. RECODE eliminates COD in scRNA-seq data with unique molecular identifiers. RECODE recovers expression values for all genes, including lowly expressed genes, realizing precise delineation of cell-fate transitions/identification of rare cells with all gene information. RECODE exhibits superior performance in cell-clustering and single-cell analysis over imputation methods. RECODE is parameter-free, data-driven, deterministic, and high speed, and its applicability is predictable based on the variance normalization performance (relevant to **Focus Areas 1** and **2**).

*[10] Bioethics for promoting human stem-cell research and human biology
*18. Sawai, T., Sakaguchi, H., Thomas, E., Takahashi, J., and Fujita, M. **The Ethics of Cerebral Organoid Research: Being Conscious of Consciousness.** ***Stem Cell Rep.***, 13, 440-447, 2019.
This work reviews the latest developments in cerebral organoid research, and examines the ethical issues that may arise regarding the relationship between cerebral organoids and consciousness. The novelty of this article is in its answering the question "What type of consciousness in cerebral organoids would make them ethically problematic?" This study also points 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, this work proposes that in the future, philosophers, bioethicists, and scientists will jointly examine the ethical issues involved in studies attempting to connect brain organoids to other neural tissues as well as studies attempting to transplant brain organoids to animals. **Note that this was the first article on bioethics to be published in *Stem Cell Reports*** (relevant to **Focus Area 5**).

*19.Sawai, T., Minawaka, T., Pugh, J., Akatsuka, K., Yamashita, J.K., and Fujita, M. **The moral status of human embryo-like structures: potentiality matters? The moral status of human synthetic embryos.** ***EMBO Rep.*****, 21**, e50984, 2020.
Research in early human development has undergone rapid progress during the past years, in part owing to new methods for the *in vitro* culture of human embryos and for the generation of embryo-like structures. However, these methods raise new ethical issues regarding the creation and use of human embryo-like structures, the moral status of which is uncertain. In particular, they raise questions about the moral significance of the potential of such embryo-like structures to develop into a human fetus and a mature human being. This potential to develop into human beings is one of the major points of contention in the ethical debate regarding human embryonic stem cell research and whether it is morally acceptable to destroy human embryos for research. This work addresses the question of how consistency demands a comparable argument for human embryo-like structures and discusses the implications for future research in human embryonic development (relevant to **Focus Area 5**).

20. Lovell-Badge, R. (1/47), Fujita, M. (13/47), Saitou, M. (38/47), et al. **ISSCR guidelines for stem cell research and clinical translation: The 2021 update.** ***Stem Cell Rep.***, 16, 1398-1408, 2021.
This is a white paper summarizing the major updates of the ISSCR Guidelines for Stem Cell Research and Clinical Translation based on discussions among international experts on stem cells, ethics, and law, including **Fujita** and **Saitou** from ASHBi, over a nearly two-year period. The updated guidelines maintain the recommendation of rigorous independent review for human stem cell, embryo, and related research activities, calling it the specialized scientific and ethics oversight process, and add clear criteria and practical guidance for its oversight. Newly added areas of research are "stem cell-based embryonic models," "chimeras and chimeric embryos," "organoids," "human embryo research beyond 14 days," "germline genome editing," and "mitochondrial replacement technologies" (relevant to **Focus Area 5**).

Appendix 1-2 List of Papers of Representative of Interdisciplinary Research Activities

* List **up to 10 papers** underscoring each interdisciplinary research activity and give brief accounts (within 10 lines).
* 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 the same. If a paper has many authors, underline those affiliated with the Center.
* If a paper has many authors (say, more than 10), all of their names do not need to be listed.

<Math-biology fusion papers>

1. M. Nagano, B. Hu, S. Yokobayashi, A. Yamamura, F. Umemura, M. Coradin, H. Ohta, Y. Yabuta, Y. Ishikura, I. Okamoto, H. Ikeda, N. Kawahira, Y. Nosaka, S. Shimizu, Y. Kojima, K. Mizuta, T. Kasahara, Y. Imoto, K. Meehan, R. Stocsits, G. Wutz, Y. Hiraoka, Y. Murakawa, T. Yamamoto, K. Tachibana, J. Peters, L. Mirny, B. Garcia, J. Majewski, M. Saitou. Nucleome programming for the foundation of totipotency in mammalian germline development. (2022) *The EMBO Journal*. *Accepted.*

In this paper, we performed comprehensive and in-depth nucleome analysis of mouse germ-cell development in vitro, encompassing pluripotent precursors, primordial germ cells, and spermatogonial stem cells. We show that the in vitro system recapitulates not only gene-expression and epigenetic properties, but also 3D genome-organization dynamics during germ-cell development in vivo. In particular, as a fusion research, we developed a mathematical method for reconstructing 3D chromatin structures and predicting their spatial organizations from Hi-C data, and verified the concept of gradual chromatin de-condensation along with germ-cell development. Motivated by this collaboration, we have started a new project to develop more general methods for comprehensively characterizing chromatin conformations using Hi-C and multi-contact 3C (MC-3C) data by means of topological data analysis and differential equations.

2. S. Seirin-Lee, K. Yamamoto, A. Kimura. The extra-embryonic space and the local contour are critical geometric constraints regulating cell arrangement. (2022) ***Development.*** *Accepted.*

In multicellular systems, cells communicate with adjacent cells to determine their positions and fates. Orientation of cell division, cell-cell interaction, and geometric constraints are three major factors that define cell arrangement, and especially, geometric constraints are difficult to reveal in experiments. In this study, we developed a multicellular morphology model so that precise geometric constraints can be incorporated. Our application of the model to embryos predicted that the amount of extra-embryonic space (ES), the empty space within the eggshell that is not occupied by embryonic cells, affects cell arrangement. The prediction was validated experimentally by increasing the ES in the C. elegans embryo. This finding provides a general concept that the amount of empty space can be a target for the regulation of cell arrangement, like the regulation of cell-cell interactions. This factor should be considered for multicellular systems including human being.

3. S. Iwanami, K. Ejima, K.S. Kim, K. Noshita, Y. Fujita, T. Miyazaki, S. Kohno, Y. Miyazaki, S. Morimoto, S. Nakaoka, Y. Koizumi, Y. Asai, K. Aihara, K. Watashi, R. N. Thompson, K. Shibuya, K. Fujiu, A.S. Perelson, S. Iwami, T. Wakita. Detection of significant antiviral drug effects on COVID-19 with reasonable sample sizes in randomized controlled trials: A modeling study, ***PLOS Medicine***, 18(7):e1003660 (2021).

Development of an effective antiviral drug for COVID-19 is a global health priority. Although several candidate drugs have been identified through in vitro and in vivo models, consistent and compelling evidence from clinical studies is limited. The lack of evidence from clinical trials may stem in part from the imperfect design of the trials. We investigated how clinical trials for antivirals need to be designed, especially focusing on the sample size in randomized controlled trials. Here, we found that estimated association in observational studies can be biased due to large heterogeneity in viral dynamics among infected individuals, and significant effect in randomized controlled trials may be difficult to be detected due to small sample size. The sample size can be dramatically reduced by recruiting patients immediately after developing symptoms. We believe this is the first study

investigated the study design of clinical trials for antiviral treatment using the viral dynamics model.

4. T. Ichinomiya, I. Obayashi, and Y. Hiraoka. Protein folding analysis using features obtained by persistent homology. *Biophysical Journal* 118 (2020), 2926-2937.

Understanding the protein-folding process is an outstanding issue in biophysics, however, the large freedom of atomic motion hinders the elucidation of this process. In this study, we developed a novel method to characterize the protein structure based on persistent homology and applied it to molecular dynamics simulations of chignolin. The most notable feature of our method makes it possible to precisely capture the topology of the protein, thereby unraveling folding process. We revealed two stable states and one saddle state, corresponding to the native, misfolded, and transition states, respectively, and also clarified the dynamics between them. Our method serves as a promising tool to understand the protein-folding process. Furthermore, the developed method is also used in the ASHBi fusion research with Saitou Group about Hi-C data analysis for 3D epigenomics.

5. A. Oyama, Y. Hiraoka, I. Obayashi, Y. Saikawa, S. Furui, K. Shiraishi, S. Kumagai, T. Hayashi, and J. Kotoku. 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, Article number: 8764 (2019).

We have evaluated the accuracy for classification of hepatic tumors by characterization of T1-weighted magnetic resonance (MR) images using topological data analysis with machine learning models. This study assessed non-contrast-enhanced fat-suppressed three-dimensional T1-weighted images of 150 hepatic tumors. The lesions included 50 hepatocellular carcinomas (HCCs), 50 metastatic tumors (MTs), and 50 hepatic hemangiomas (HHs) found respectively in 37, 23, and 33 patients. In the classification of HCC and MT (resp. HCC and HH, HH and MT), we obtained the highest accuracy of 85% (resp. 84%, 74%) when degree 1 (resp. degree 1, degree 2) persistence images were used. Our methods using topological data analysis allow for classification of the three hepatic tumors with considerable accuracy, and thus will be useful when applied for computer-aided diagnosis with MR images.

<Ethics-biology fusion papers>

6. Lovell-Badge R, Anthony E, Barker RA, Bubela T, Brivanlou AH, Carpenter M, Charo RA, Clark A, Clayton E, Cong Y, Daley GQ, Fu J, Fujita M, Greenfield A, Goldman SA, Hill L, Hyun I, Isasi R, Kahn J, Kato K, Kim J-S, Kimmelman J, Knoblich JA, Mathews D, Montserrat N, Mosher J, Munsie M, Nakauchi H, Naldini L, Naughton G, Niakan K, Ogbogu U, Pedersen R, Rivron N, Rooke H, Rossant J, Round J, Saitou M, Sipp D, Steffann J, Sugarman J, Surani A, Takahashi J, Tang F, Turner L, Zettler PJ, Zhai X. ISSCR guidelines for stem cell research and clinical translation: The 2021 update. *Stem Cell Reports*. 2021; DOI: 10.1016/j.stemcr.2021.05.012.

In May 2021, the ISSCR Guidelines for Stem Cell Research and Clinical Translation was updated. This is a white paper summarizing the major updates. International experts on stem cells, ethics, and law were involved in the nearly two-year process of updating the guidelines, including Drs. Saitou and Fujita from ASHBi. The updated guidelines maintain the rigorous independent review of human stem cell and embryo research and related research activities, calling it the specialized scientific and ethics oversight process, and add clear criteria and practical guidance for its oversight. Newly added areas of research are "stem cell-based embryonic models," "chimeras and chimeric embryos," "organoids," "human embryo research beyond 14 days," "germline genome editing," and "mitochondrial replacement technologies."

7. Hyun I, Clayton EW, Cong Y, Fujita M, Goldman SA, Hill LR, Monserrat N, Nakauchi H, Pedersen RA, Rooke HM, Takahashi J, Knoblich JA. ISSCR guidelines for the transfer of human pluripotent stem cells and their direct derivatives into animal hosts. *Stem Cell Reports*. 2021; DOI: 10.1016/j.stemcr.2021.05.005.

The revised ISSCR Guidelines for Stem Cell Research and Clinical Translation contain scientific and

ethical guidance on the transplantation of human pluripotent stem cells and their direct derivatives into animal models. This paper is a white paper summarizing the recommendations made by the ISSCR subcommittee that drafted this section. We strongly recommended that research involving the transplantation of human stem cells or their neural or glial derivatives into the central nervous system of animals be reviewed by an animal research oversight committee with experts in stem cell and developmental biology as reviewers, as this may raise concerns regarding the moral status of the animals.

8. Sawai T, Hatta T, Akatsuka K, Fujita M. Public attitudes in Japan toward the creation and use of gametes derived from human-induced pluripotent stem cells. ***Future Science OA***. 2021; DOI: 10.2144/fsoa-2021-0066.

While research on in vitro gametogenesis using pluripotent stem cells is expected to provide biological insights into human development, there are concerns about ethical issues associated with the creation and clinical use of embryos for research purposes. In this paper, we conducted an online survey of 3,096 members of the general public to determine the extent to which they would allow the creation and use of gametes using iPS cells. The results revealed that 78.6% would accept the creation of gametes, 51.7% would accept fertilization of the created gametes, 25.9% would accept clinical use of the created fertilized embryos, and 21.4% would not accept the research itself. Opinions were divided on the creation of fertilized embryos, which is currently not allowed under Japanese guidelines. Future deregulation should be carefully considered.

9. Sawai T, Hayashi Y, Niikawa T, Shepherd J, Thomas E, Lee T-L, Erler A, Watanabe M, Sakaguchi H. Mapping the ethical issues of brain organoid research and application. ***AJOB Neuroscience***. 2021; DOI: 10.1080/21507740.2021.1896603.

Research on brain organoids is growing rapidly, and there are high expectations for their application in disease research and regenerative medicine. On the other hand, there are concerns that creating human brain organoids with more complex structures may lead to the development of consciousness or the acquisition of higher cognitive abilities by transplanting them into animal brains. This paper provides a comprehensive overview of issues surrounding consciousness and its evaluation, ownership of brain organoids, animal enhancement and dignity, and informed consent for donors.

10. Crane AT, Shen FX, Brown JL, Cormack W, Ruiz-Estevez M, Voth JP, Sawai T, Hatta T, Fujita M, Low WC. The American public is ready to accept human-animal chimera research. ***Stem Cell Reports***. 2020;15(4): 804-810. DOI: 10.1016/j.stemcr.2020.08.018.

This paper is a collaborative study with the University of Minnesota, which asked 430 members of the American public in an online survey to what extent they would allow animal aggregation embryo research. The survey results showed that 83% would allow the injection of human iPS cells into pig embryos, 71% would allow the creation of chimeric pigs with human pancreases, and 59% would allow their pancreases to be implanted in humans. These American levels of acceptance were higher than those of Japanese previously surveyed by Ethics G (Sawai T, et al. 2017). In Japan, the creation of chimeric animals by injecting human pluripotent cells into animal embryos is acceptable starting in 2019, while in the U.S., the NIH has suspended the allocation of federal funding for such research since 2015. Based on the results of this study and a review of scientific papers, the paper argues that it is time for the NIH to relax its research restrictions.

Appendix 1-3
Major Awards, Invited Lectures, Plenary Addresses (etc.) (within 2 pages)

*Prepare the information below during the period from the start of the center through March 2022.

1. Major Awards

*List main internationally-acclaimed awards received/unofficially announced in order from the most recent.
*For each, write the recipient's name, the name of award, and the date issued.
In case of multiple recipients, underline those affiliated with the center.

Date	Recipient's name	Name of award
2021/10/28	Takashi Hiiragi	EMBO member
2021/4/26	Motoko Yanagita	Kidney International "Reviewer of the Year(2020)"
2020/12/6	Guillaume Bourque	Canada Research Chair (Tier 1), Computational Genomics and Medicine
2020/11/2	Motoko Yanagita	57th Erwin von Bälz Prize (2nd Prize), Boehringer Ingelheim
2020/7/7	Mitinori Saitou	EMBO Associate Member
2020/6/26	Mitinori Saitou	The ISSCR 2020 Momentum Award
2020/4/30	Guillaume Bourque	Research Scholars Emeritus, Fonds de Recherche en Santé du Québec
2020/4/6	Mitinori Saitou	Imperial Prize and Japan Academy Prize, Japan Academy
2020/3/11	Mitinori Saitou	Uehara Prize 2019
2020/1/29	Mitinori Saitou	Asahi Prize 2019
2019/11/28	Seishi Ogawa	56th Erwin von Bälz Prize (1st Prize), Boehringer Ingelheim
2019/10/27	Tadashi Isa	Honorary Fellow of Indian Academy of Neuroscience (IAN)
2018/11/8	Mitinori Saitou	Academic Award of the Mochida Memorial Foundation
2018/5/15	Seishi Ogawa	Medal of Honor with Purple Ribbon

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

*List up to 20 main presentations in order from most recent.
*For each, write the lecturer/presenter's name, presentation title, conference name and date(s)

Date(s)	Lecturer/ Presenter's name	Presentation title	Conference name
2022/3/29	Ken-ichi Amemori	Computational and Physiological Approaches to the Primate Anxiety Connectome	Computational connectome: SPP-2041 Meeting, (ONLINE, FIAS)
2022/3/26	Seishi Ogawa	Life history of breast cancer inferred from phylogenies	The 3rd International Cancer Symposium
2022/2/26	Motoko Yanagita	Kidney Tissue Inflammation and Fibrosis	World Congress of Nephrology' 22 (ONLINE, International Society of Nephrology)
2021/12/9-11	Sungirm Seirin-Lee	Mathematical equation of multifarious eruptions in urticaria	2021 GA2LEN UCARE Urticaria Conference (Hiroshima, Japan)
2021/10/14	Yasuhiro Murakawa	Functional characterization of human disease pathways using high-resolution chromatin contact maps	Immuno UK: In-Person (ONLINE, Oxford Global)

2021/6/26	Misao Fujita	“Ethics of Human Brain Organoid Research from the Perspective of Social Science Survey” (web)	ISSCR Annual Meeting 2021 (ONLINE, ISSCR)
2021/3/3	Cantas Alev	Towards reconstituting human somitogenesis in vitro	3rd SY-Stem Symposium on Stem Cell Research (Vienna, Austria)
2021/2/2	Hideki Ueno	Generation and plasticity of memory Tfh cells in humans	The Royal Society: T cell/B cell collaboration in autoimmunity (ONLINE, The Royal Society)
2020/10/21	Takashi Hiiragi	Self-organization in mouse development	Kavli Institute for Theoretical Physics conference (ONLINE, UC Santa Barbara)
2020/6/24	Misao Fujita	Stakeholder views – How scientists and various publics view brain organoid research and who should be making decisions on its regulation?	ISSCR 2020 VIRTUAL (ONLINE, ISSCR)
2020/2/3	Tadashi Isa	Neurobiology of recovery after brain and spinal cord injury in macaque models	NIH, Neuroscience Seminar Series, NIH, (Bethesda, USA)
2019/11/7	Motoko Yanagita	Erythropoietin-Producing Cells in Kidney Fibrosis	Kidney Week 2019, American Society of Nephrology (Washington DC, USA)
2019/6/15	Seishi Ogawa	Clonal hematopoiesis in Aplastic anemia	24th Congress of European Hematology Association (Amsterdam, Netherlands)
2019/5/16	Tadashi Isa	Large-scaled network reorganization for recovery after spinal cord injury	The Salk Institute Weekly Seminar (San Diego, USA)
2019/5/13	Guillaume Bourque	Unmasking transposable elements in regulation and disease	The Royal Society: Crossroads between transposons and gene regulation (London, UK)
2019/4/15	Yasuaki Hiraoka	Topological data analysis in materials science.	Workshop “Data Driven Dynamics: Algebraic Topology, Combinatorics and Analysis”, (Montreal, Canada)
2019/3/30	Mototsugu Eiraku	Self-organization of patterned functional tissues from pluripotent stem cells	119th International Titisee Conference:Tissue formation and regeneration: from molecules to models, (Lake Titisee, Germany)
2018/10/29	Takashi Hiiragi	Self-organisation in mouse development	19th International Conference for Systems Biology, (Lyon, France)
2018/9/24	Mitinori Saitou	Mechanism and In Vitro Reconstitution of Human germ cell development	From Stem Cells to Human Development 2018, (Surrey, UK)
2018/6/20	Mitinori Saitou	Mechanism and Reconstitution In Vitro of Germ Cell Development in Mice, Monkeys, and Humans	ISSCR Annual Meeting 2018 (Melbourne, Australia)

Appendix 1-4 2021 List of Center's Research Results

Refereed Papers

- List only the Center's papers published in 2021. (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 20), 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.

A. WPI Papers

1. Original Articles

1) Akatsuka, K., Hatta, T., Sawai, T., & **Fujita, M.** (2021). Public attitudes in Japan toward the reproductive use of gametes derived from human-induced pluripotent stem cells. ***Future Science Oa****, 7*(10). doi:10.2144/fsoa-2021-0065

2) Amemori, S., Graybiel, A. M., & **Amemori, K.** (2021). Causal Evidence for Induction of Pessimistic Decision-Making in Primates by the Network of Frontal Cortex and Striosomes. ***Frontiers in Neuroscience****, 15*. doi:10.3389/fnins.2021.649167

3) Chen, C. Y., Matrov, D., Veale, R., Onoe, H., Yoshida, M., Miura, K., & **Isa, T.** (2021). Properties of visually guided saccadic behavior and bottom-up attention in marmoset, macaque, and human. ***Journal of Neurophysiology****, 125*(2), 437-457. doi:10.1152/jn.00312.2020

4) Fujii, Y., Sato, Y., Suzuki, H., Kakiuchi, N., Yoshizato, T., Lenis, A. T., Maekawa, S., Yokoyama, A., Takeuchi, Y., Inoue, Y., Ochi, Y., Shiozawa, Y., Aoki, K., Yoshida, K., Kataoka, K., Nakagawa, M. M., Nannya, Y., Makishima, H., Miyakawa, J., Kawai, T., Morikawa, T., Shiraishi, Y., Chiba, K., Tanaka, H., Nagae, G., Sanada, M., Sugihara, E., Sato, T. A., Nakagawa, T., Fukayama, M., Ushiku, T., Aburatani, H., Miyano, S., Coleman, J. A., Homma, Y., Solit, D. B., Kume, H., & **Ogawa, S.** (2021). Molecular classification and diagnostics of upper urinary tract urothelial carcinoma.

***Cancer Cell**, 39*(6), 793-+. doi:10.1016/j.ccell.2021.05.008

5) Handa, T., Mori, K. P., Ishii, A., Ohno, S., Kanai, Y., Watanabe-Takano, H., Yasoda, A., Kuwabara, T., Takahashi, N., Mochizuki, N., Mukoyama, M., **Yanagita, M.**, & Yokoi, H. (2021). Osteocrin ameliorates adriamycin nephropathy via p38 mitogen-activated protein kinase inhibition. ***Scientific Reports**, 11*(1). doi:10.1038/s41598-021-01095-8

6) Hirabayashi, S., Shirakawa, K., Horisawa, Y., Matsumoto, T., Matsui, H., Yamazaki, H., Sarca, A. D., Kazuma, Y., Nomura, R., Konishi, Y., Takeuchi, S., Stanford, E., Kawaji, H., **Murakawa, Y.**, & Takaori-Kondo, A. (2021). APOBEC3B is preferentially expressed at the G2/M phase of cell cycle. ***Biochemical and Biophysical Research Communications**, 546*, 178-184. doi:10.1016/j.bbrc.2021.02.008

7) Horiuchi, S., Wu, H. C., Liu, W. C., Schmitt, N., Provot, J., Liu, Y., Bentebibel, S. E., Albrecht, R. A., Schotsaert, M., Forst, C. V., Zhang, B., & **Ueno, H.** (2021). Tox2 is required for the maintenance of GC T-FH cells and the generation of memory T-FH cells. ***Science Advances**, 7*(41). doi:10.1126/sciadv.abj1249

8) Hoyer, K., Hablesreiter, R., Inoue, Y., Yoshida, K., Briest, F., Christen, F., Kakiuchi, N., Yoshizato, T., Shiozawa, Y., Shiraishi, Y., Striefler, J. K., Bischoff, S., Lohneis, P., Putter, H., Blau, O., Keilholz, U., Bullinger, L., Pelzer, U., Hummel, M., Riess, H., **Ogawa, S.**, Sinn, M., & Damm, F. (2021). A genetically defined signature of responsiveness to erlotinib in early-stage pancreatic cancer patients: Results from the CONKO-005 trial. ***Ebiomedicine**, 66*, 103327. doi:10.1016/j.ebiom.2021.103327

9) Hyun, I., Clayton, E. W., Cong, Y. L., **Fujita, M.**, Goldman, S. A., Hill, L. R., Monserrat, N., Nakauchi, H., Pedersen, R. A., Rooke, H. M., Takahashi, J., & Knoblich, J. A. (2021). ISSCR guidelines for the transfer of human pluripotent stem cells and their direct derivatives into animal hosts. ***Stem Cell Reports**, 16*(6), 1409-1415. doi:10.1016/j.stemcr.2021.05.005

10) Ichijo, R., Kabata, M., Kidoya, H., Muramatsu, F., Ishibashi, R., Abe, K., Tsutsui, K., Kubo, H., Iizuka, Y., Kitano, S., Miyauchi, H., Kubota, Y., Fujiwara, H., Sada, A., **Yamamoto, T.**, & Toyoshima, F. (2021). Vasculature-driven stem cell population coordinates tissue scaling in dynamic organs. ***Science Advances***, 7(7), eabd2575. doi:10.1126/sciadv.abd2575

11) Ide, K., Matsuoka, N., & **Fujita, M.** (2021). Ethical Aspects of Brain Organoid Research in News Reports: An Exploratory Descriptive Analysis. ***Medicina-Lithuania**, 57*(6). doi:10.3390/medicina57060532

12) Io, S., Kabata, M., Iemura, Y., Semi, K., Morone, N., Minagawa, A., Wang, B., Okamoto, I., Nakamura, T., Kojima, Y., Iwatani, C., Tsuchiya, H., Kaswandy, B., Kondoh, E., Kaneko, S., Woltjen, K., **Saitou, M.**, **Yamamoto, T.**, Mandai, M., & Takashima, Y. (2021). Capturing human trophoblast development with naive pluripotent stem cells in vitro. ***Cell Stem Cell**, 28*(6), 1023-+. doi:10.1016/j.stem.2021.03.013

13) Ishikura, Y., Ohta, H., Sato, T., Murase, Y., Yabuta, Y., Kojima, Y., Yamashiro, C., Nakamura, T., **Yamamoto, T.**, Ogawa, T., & **Saitou, M.** (2021). In vitro reconstitution of the whole male germ-cell development from mouse pluripotent stem cells. ***Cell Stem Cell**, 28*(12), 2167-+. doi:10.1016/j.stem.2021.08.005

14) Jayakumar, V., Nishimura, O., Kadota, M., Hirose, N., Sano, H., **Murakawa, Y.**, Yamamoto, Y., Nakaya, M., **Tsukiyama, T.**, Seita, Y., Nakamura, S., Kawai, J., Sasaki, E., **Ema, M.**, Kuraku, S., Kawaji, H., & Sakakibara, Y. (2021). Chromosomal-scale de novo genome assemblies of Cynomolgus Macaque and Common Marmoset. ***Scientific Data**, 8*(1). doi:10.1038/s41597-021-00935-6

15) Jo, N., Zhang, R., **Ueno, H.**, **Yamamoto, T.**, Weiskopf, D., Nagao, M, Yamanaka, S., & Hamazaki, Y. (2021). Aging and CMV Infection Affect Pre-existing SARS-CoV-2-Reactive $CD8^+$ T Cells in Unexposed Individuals. ***Frontiers in Aging**, 2*. doi:10.3389/fragi.2021.719342

16) Karunakaran, K. B., Amemori, S., Balakrishnan, N., Ganapathiraju, M. K., & **Amemori, K.** (2021). Generalized and social anxiety disorder interactomes show distinctive overlaps with striosome and

matrix interactomes. ***Scientific Reports**, 11*(1). doi:10.1038/s41598-021-97418-w

17) Katagiri, N., Hitomi, H., Mae, S. I., Kotaka, M., Lei, L., **Yamamoto, T.**, Nishiyama, A., & Osafune, K. (2021). Retinoic acid regulates erythropoietin production cooperatively with hypoxia-inducible factors in human iPSC-derived erythropoietin-producing cells. ***Scientific Reports**, 11*(1). doi:10.1038/s41598-021-83431-6

18) Kato, R., Hayashi, T., Onoe, K., Yoshida, M., Tsukada, H., Onoe, H., **Isa, T.**, & Ikeda, T. (2021). The posterior parietal cortex contributes to visuomotor processing for saccades in blindsight macaques. ***Communications Biology**, 4*(1). doi:10.1038/s42003-021-01804-z

19) Kato, R., Zeghbib, A., Redgrave, P., & **Isa, T.** (2021). Visual instrumental learning in blindsight monkeys. ***Scientific Reports**, 11*(1). doi:10.1038/s41598-021-94192-7

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21) Kawakami, R., Matsui, M., Konno, A., Kaneko, R., Shrestha, S., Shrestha, S., Sunaga, H., Hanaoka, H., Goto, S., Hosojima, M., Kabasawa, H., Obokata, M., Koitabashi, N., Matsui, H., Sasaki, T., Saito, A., **Yanagita, M.**, Hirai, H., Kurabayashi, M., & Iso, T. (2021). Urinary FABP1 is a biomarker for impaired proximal tubular protein reabsorption and is synergistically enhanced by concurrent liver injury. ***Journal of Pathology**, 255*(4), 362-373. doi:10.1002/path.5775

22) Klimkowska, M., Nannya, Y., Gran, C., Mansson, R., Douagi, I., **Ogawa, S.**, Nahi, H., & Tobiasson, M. (2021). Absence of a common founder mutation in patients with cooccurring myelodysplastic syndrome and plasma cell disorder. ***Blood**, 137*(9), 1260-1263. doi:10.1182/blood.2020007555

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24) Koshimizu, Y., Isa, K., Kobayashi, K., & Isa, T. (2021). Double viral vector technology for selective manipulation of neural pathways with higher level of efficiency and safety. ***Gene Therapy**, 28*(6), 339-350. doi:10.1038/s41434-020-00212-y

25) Li, X. Y., Kim, W., Arif, M., Gao, C. X., Hober, A., Kotol, D., Strandberg, L., Forsstrom, B., Sivertsson, A., Oksvold, P., Turkez, H., Grotli, M., Sato, Y., Kume, H., **Ogawa, S.**, Boren, J., Nielsen, J., Uhlen, M., Zhang, C., & Mardinoglu, A. (2021). Discovery of Functional Alternatively Spliced PKM Transcripts in Human Cancers. ***Cancers**, 13*(2). doi:10.3390/cancers13020348

26) Li, X. Y., Kim, W., Juszczak, K., Arif, M., Sato, Y., Kume, H., **Ogawa, S.**, Turkez, H., Boren, J., Nielsen, J., Uhlen, M., Zhang, C., & Mardinoglu, A. (2021). Stratification of patients with clear cell renal cell carcinoma to facilitate drug repositioning. ***iScience**, 24*(7). doi:10.1016/j.isci.2021.102722

27) Liao, Y. P., Urayama, S., **Isa, T.**, & Fukuyama, H. (2021). Optimal Model Mapping for Intravoxel Incoherent Motion MRI. ***Frontiers in Human Neuroscience**, 15*. doi:10.3389/fnhum.2021.617152

28) Lovell-Badge, R., Anthony, E., Barker, R. A., Bubela, T., Brivanlou, A. H., Carpenter, M., Charo, R. A., Clark, A., Clayton, E., Cong, Y. L., Daley, G. Q., Fu, J. P., **Fujita, M.**, Greenfield, A., Goldman, S. A., Hill, L., Hyun, I., Isasi, R., Kahn, J., Kato, K., Kim, J. S., Kimmelman, J., Knoblich, J. A., Mathews, D., Montserrat, N., Mosher, J., Munsie, M., Nakauchi, H., Naldini, L., Naughton, G., Niakan, K., Ogbogu, U., Pedersen, R., Rivron, N., Rooke, H., Rossant, J., Round, J., **Saitou, M.**, Sipp, D., Steffann, J., Sugarman, J., Surani, A., Takahashi, J., Tang, F. C., Turner, L., Zettler, P. J., & Zhai, X. M. (2021). ISSCR Guidelines for Stem Cell Research and Clinical Translation: The 2021 update. ***Stem Cell Reports**, 16*(6), 1398-1408. doi:10.1016/j.stemcr.2021.05.012

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2. Review Articles

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156) Nakamura, T., Fujiwara, K., **Saitou, M.**, & Tsukiyama, T. (2021). Non-human primates as a model for human development. ***Stem Cell Reports**, 16*(5), 1093-1103. doi:10.1016/j.stemcr.2021.03.021

157) Obayashi, I., Nakamura, T., & **Hiraoka, Y.** (2021). Persistent Homology Analysis for Materials Research and Persistent Homology Software: HomCloud. ***Journal of the Physical Society of Japan***, accepted.

3. Proceedings N/A
4. Other English articles N/A

Appendix 2　FY 2021 List of Principal Investigators

NOTE:

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

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

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

<Results at the end of FY2021> **Principal Investigators Total: 18**

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	51	Professor Kyoto University Institute for Advanced Study, Kyoto University	MD, PhD Cell Biology, Developmental Biology	90%	Oct.30, 2018	Usually stays at the center and participates in the center's activities as Center Director and Executive Board member	
Cantas ALEV	47	Associate Professor Institute for the Advanced Study of Human Biology (ASHBi) Kyoto University	MD, PhD Developmental Biology	100%	Jul.1, 2019	Usually stays at the center and participates in the center's activities	
Ken-ichi AMEMORI	48	Associate Professor Institute for the Advanced Study of Human Biology (ASHBi) Kyoto University	PhD Neuroscience	100%	Sep. 1, 2020	Usually stays at the center and participates in the center's activities	
Guillaume BOURQUE	45	Professor Human Genetics, McGill University	PhD Bioinformatics, Genomics, Epigenomics	25%	Oct.30, 2018	Stays at Kyoto University 3 times per year for 3-4 weeks (total ~11 weeks)	Has recruited Co-PI and a Foreign researcher at the Center
Mototsugu EIRAKU	47	Professor Laboratory of Developmental System, Institite for Frontier Life and Medical Sciences, Kyoto University	PhD Developmental Biology	70%	Oct.30, 2018	Usually stays at the center and participates in the center's activities	
Masatsugu EMA	53	Professor Department of Stem Cells and Human Disease Models Research Center for Animal Life Science, Shiga University of Medical Science	PhD Developmental Biology, Developmental Engineering	70%	Oct.30, 2018	Usually stays at the center and participates in the center's activities	

		<Results at the end of FY2021>					Principal Investigators Total: 18
Misao FUJITA	52	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	54	Group Leader Developmental Biology, European Molecular Biology Laboratory	MD, PhD Developmental Biology	20%	Oct.30, 2018	Stays at the center every 2-3 months and participates in the center's activities	Setting up the laboratory, recruiting co-PI
Vice director Yasuaki HIRAOKA	44	Professor Kyoto University Institute for Advanced Study, Kyoto University	PhD Applied Mathematics	70%	Oct.30, 2018	Usually stays at the center and participates in the center's activities as Vice Director and Executive Board member	
Vice director Tadashi ISA	61	Professor Graduate School of Medicine, Kyoto University	MD, PhD Neuroscience	80%	Oct.30, 2018	Usually stays at the center and participates in the center's activities as Vice Director and Executive Board member	
Yasuhiro MURAKAWA	39	Professor Kyoto University Institute for Advanced Study, Kyoto University	MD, PhD Human Genomics, Medical Science, Systems Biology	100%	Sep. 1, 2020	Usually stays at the center and participates in the center's activities	
Seishi OGAWA	59	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	
Sungrim SEIRIN-LEE	44	Professor Institute for the Advanced Study of Human Biology (ASHBi) Kyoto University	PhD Mathematical Biology and Medicine, Mathematical modeling, Applied Mathematics	100%	Oct.1, 2021	Usually stays at the center and participates in the center's activities	
Tomoyuki TSUKIYAMA	38	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	

		<Results at the end of FY2021>				Principal Investigators Total: 18	
Hideki UENO	54	Professor Graduate School of Medicine, Kyoto University	MD, PhD Immunology	95%	Oct.30, 2018	Stays at the center every 2-3 months and participates in the center's activities	Has recrutied a Co-PI at the Center
Ryo YAMAMOTO	46	Associate Professor Institute for the Advanced Study of Human Biology (ASHBi) Kyoto University	MD, PhD Hematology	100%	Apr. 1, 2020	Usually stays at the center and participates in the center's activities	
Head of the Single-cell Genome Information Analysis Core Takuya YAMAMOTO	44	Associate Professor, Department of Life Science Frontiers, Center for iPS Cell Research & Application, Kyoto University	PhD Molecular Biology, Bioinformatics	80%	Oct.30, 2018	Usually stays at the center and participates in the center's activities as Executive Board member	
Motoko YANAGITA	52	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 his/her work for the center vis-à-vis his/her total working hours.

Principal investigators unable to participate in project in FY 2021

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

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age)
Sungrim Seirin-Lee (44)
Affiliation and position (Position title, department, organization, etc.)
ASHBi, Professor

Academic degree and specialty
PhD(Environmental Science), Mathematical modeling

Effort **100 %**
* Percentage of time that the principal investigator will devote to working for the center vis-à-vis his/her total working hours.

Research and education history
Mathematical biology(modeling) for cell biology, developmental biology and medicine; Pattern formation; Applied mathematics

- **Ph.D of Environmental Science** (April 2008 – March 2010): Graduate School of Environmental Science, Okayama University, Japan (including **study-abroad** to Center for Mathematical Biology, Mathematical Institute, University of Oxford, UK during Nov. 2008 - Sep. 2009). *2- year early completion of a PhD by 4 publications of SCI papers as lead author.*
- **Master of Environmental Science** (April 2006 – March 2008): Graduate School of Environmental Science, Okayama University, Japan
- **Master of Mathematical Science** (March 2000 – February 2002): Department of Mathematics, Graduate School, Pusan National University, Korea
- **Bachelor of Science** (March 1996 – February 2000): Department of Mathematics, College of Natural Sciences, Pusan National University, Korea

Achievements and highlights of past research activities
Achievements
(1) International influence * Describe the kind of attributes listed below.
a) Recipient of international awards :
b) Member of a scholarly academy in a major country
- 2014-Current: Society of mathematical Biology (United States)
- 2021-Current: Society for Industrial and Applied Mathematics(United States)

c) Guest speaker or chair of related international conference and/or director or honorary chairman of a major international academic society in the subject field
Workshop Organizer: Total number is **24** (including **12** international meetings).
Selected lists
- Mini-symposium, Diverse quantitative approaches integrating data and modelling in development and medicine, SMB annual meeting 2021, June 13-17, 2021 (with A. Dawes (Ohio State Univ.))
- Mini-symposium "Mathematical modeling and numerical methods for complex interface problem in life science", SIAM Conference for Life Sciences 2020, Los Angeles, US, 8-11 June, 2020 ((with L. Zhang (Peking University) & Prof. X. Zhao(The George Washington University))
- A3 International Workshop on mathematical and life sciences, (1)Beijing, 9-12th May 2019, (2)Hiroshima, 17-20th May 2018, (3) NIMS Daejeon Korea, 12-14th May 2017. (with Jae-kyeong Kim, KAIST, and Lei Zhang, Beijing University)
- Mini-symposium, Cell polarity and pattern formation, JSMB&SMB joint conference 2018, Sydney 7-12th July 2018. (with Y. Morishita, RIKEN)
- ECMTB2016 (European Conference on Mathematical and Theoretical Biology and Annual Meeting of The Society for Mathematical Biology)・Mini-symposium「Mathematical biology and robotics」, Nottingham, UK, 11 JUL-15 JUL, 2016.

- Mini-symposium「Turing!! Turing?? on morphogenesis via experimental and theoretical approaches 」: 8th European Conference on Mathematical and Theoretical Biology and Annual Meeting of The Society for Mathematical Biology, Kraków, Poland, June 28 - July 2, 2011.

All lists can be found in
https://sites.google.com/site/seirin711lee/activiti

Oral Presentations:

Total number of presentations is **117** (including **47** invited talks in the international meetings among **76** invited talks).
All lists can be found in https://sites.google.com/site/seirin711lee/publications/presentations?authuser=0

d) Editor of an international academic journal
- Journal of Theoretical Biology (Editorial board member, Elsevier),
- PLOS One (Academic editor, PLOS)

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

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

[1] Oct. 2021-Mar. 2027; JST (Japan Science and Technology Agency), **CREST** 「形と皮膚科学を繋ぐ数理情報システム制御医学の創出 (Creation of systematic mathematical medicine that connects shape and skin diseases)」(246,000,000 JPY) JPMJCR2111

[2] Nov. 2020-Mar. 2021: JST (Japan Science and Technology Agency), **CREST**'s Specific issue research grant (**特定課題調査研究**)* 「形と皮膚科学を繋ぐ数理情報システム制御医学の創出 (Creation of systematic mathematical medicine that connects shape and skin diseases)」(3,000,000 JPY) JPMJCR2016

[3] April 2019-Mar. 2024: Grant-in-Aid for Scientific Research (B) (**KAKENHI B**), 「非対称細胞分裂の統合的解明及び大域的数理モデリング手法の開発 (Integrated elucidation of asymmetric cell division and development of global mathematical modeling methods)」 (16,700,000 JPY) JP19H01805

[4] April 2018-Mar. 2021: Fund for the Promotion of Joint International Research (**KAKENHI 国際共同研究加速基金**(国際共同研究強化)), 「細胞の空間制御による時間制御の仕組み解明及びパターン形成の新たな理論創出 (Elucidation of the mechanism of temporal regulation by spatial control of cells and creation of a new theory of pattern formation)」 (13,500,000 JPY) JP17KK0094

[5] Oct. 2016- Mar. 2020: **JST** (Japan Science and Technology Agency), **PRESTO**, 「動的変形空間による細胞機能決定機構の解明及び *In vitro* 実験への検証 (Elucidation of the mechanism of cell function determination by dynamic deformation space and its validation for in vitro experiments)」(30,000,000 JPY) JPMJPR16E2.

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

[1] PK Maini, TE Woolley, RE Baker, EA Gaffney, S. Seirin-Lee, Turing's model for biological pattern formation and the robustness problem, ***Interface focus*** (2012) 2 (4), 487-496 (Citation:210)

[2] S Seirin Lee, EA Gaffney, NAM Monk, The influence of gene expression time delays on Gierer–Meinhardt pattern formation systems, ***Bulletin of mathematical biology*** (2010)72 (8), 2139-2160(Citation:58)

[3] S Seirin Lee, EA Gaffney, RE Baker, The dynamics of Turing patterns for morphogen-regulated growing domains with cellular response delays, ***Bulletin of mathematical biology***(2011) 73 (11), 2527-

2551(Citation:39)
[4] S. Seirin Lee, T Shibata, Self-organization and advective transport in the cell polarity formation for asymmetric cell division, ***Journal of Theoretical Biology***(2015) 382, 1-14(Citation:16)
[5] S. Seirin Lee*, Lateral Inhibition-Induced Pattern Formation Controlled by the Size and Geometry of the Cell. ***Journal of Theoretical Biology*** (2016)404, 51-65. (Citation:14)
[6] S. Seirin-Lee*, Y. Yanase, S. Takahagi, M. Hide*(* Co-corresponding authors), Multifarious Eruptions of Urticaria Solved by A Simple Mathematical Equation. ***PLOS Computational Biology*** (2020)16(1): e1007590. (***Press Released***) (Citation:7)
[7] S. Seirin-Lee*, Fumitaka Osakada, Junichi Takeda, Satoshi Tashiro, Ryo Kobayashi, Takashi Yamamoto, Hiroshi Ochiai*(*Equal contribution), Role of dynamic nuclear deformation on genomic architecture reorganization. ***PLOS Computational Biology*** (2019) 15 (8): e1007289. (***Press Released***) (Citation:11)
[8] S. Seirin-Lee*, M. Nomata, M. Mukunoki, Mathematical modeling and regionality-based optimal policy to reduce empty houses, *Akiya*, in Japan. ***Japan Journal of Industrial and Applied Mathematics*** (2020) *37:365-382.* (***Press Released***) (Citation:0)
[9] S. Seirin-Lee*, K. Yamamoto, A. Kimura*, The extra-embryonic space and the local contour are critical geometric constraints regulating cell arrangement (2022) ***Development***. (*Accepted,* ***Press release*** 予定)

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

JSPS A3 program 日中韓「生命科学分野」の日本代表

COMMITTEE in Academic Society

- 2021-2022 Director member of The Japan society for industrial and applied mathematics (JSIAM) 日本応用数理学会理事
- 2017-2020 Steering Committee of JSMB(Japanese Society of Mathematical Biology), 日本数理生物学会 運営委員
- 2019-2020 Scientific Committee of JSMB(Japanese Society of Mathematical Biology), 日本数理生物学会 学術委員

Appendix 3-1 FY 2021 Records of Center Activities

1. Researchers and other center staffs, satellites, partner institutions

1-1. Number of researchers and other center staffs

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

a) Principal Investigators

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

(number of persons)

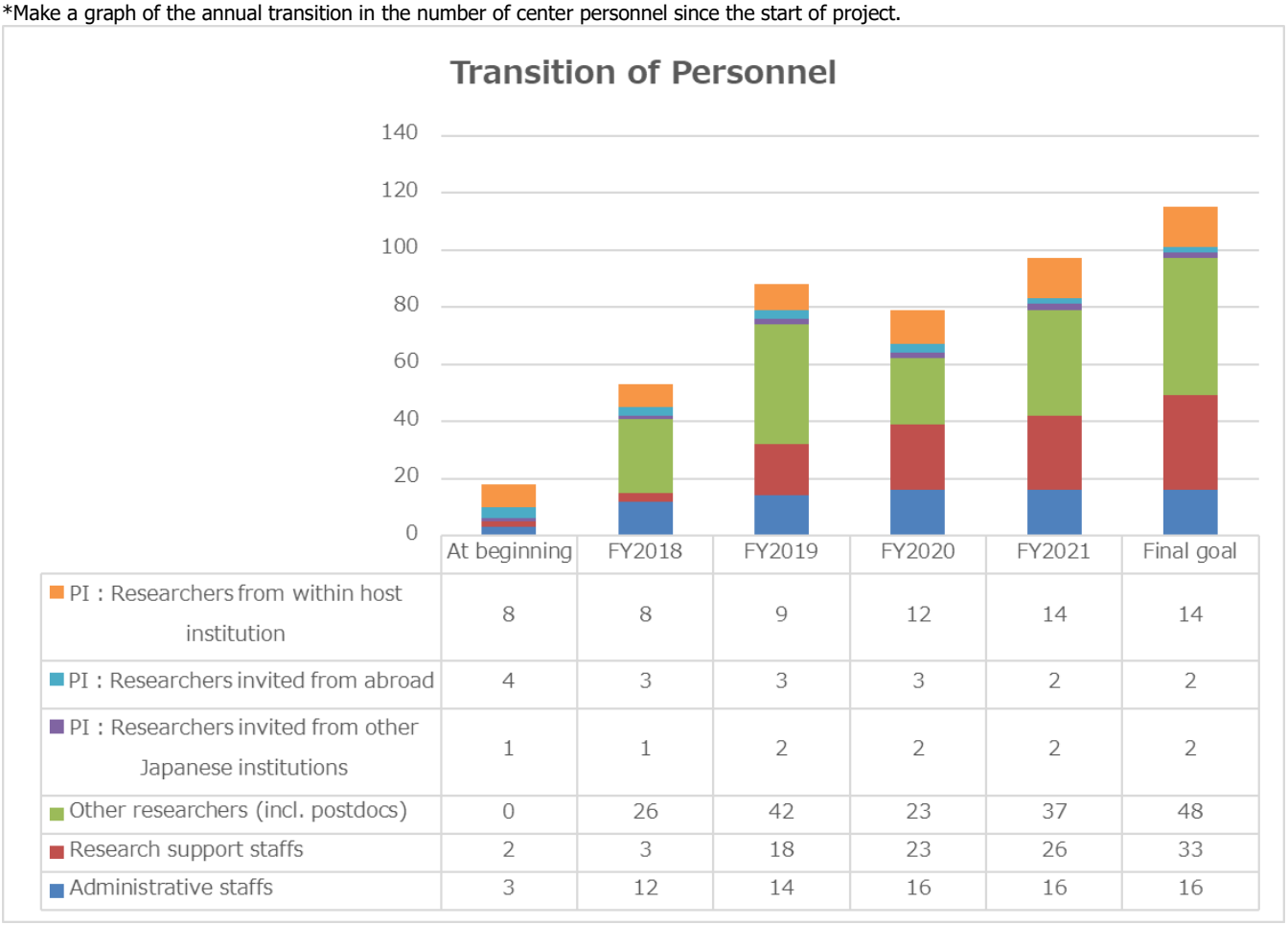
	At the beginning of project	At the end of FY 2021	Final goal (Date: Mar, 2024)
Researchers from within the host institution	8	14	14
Researchers invited from abroad	4	2	2
Researchers invited from other Japanese institutions	1	2	2
Total principal investigators	13	18	18

b) Total members

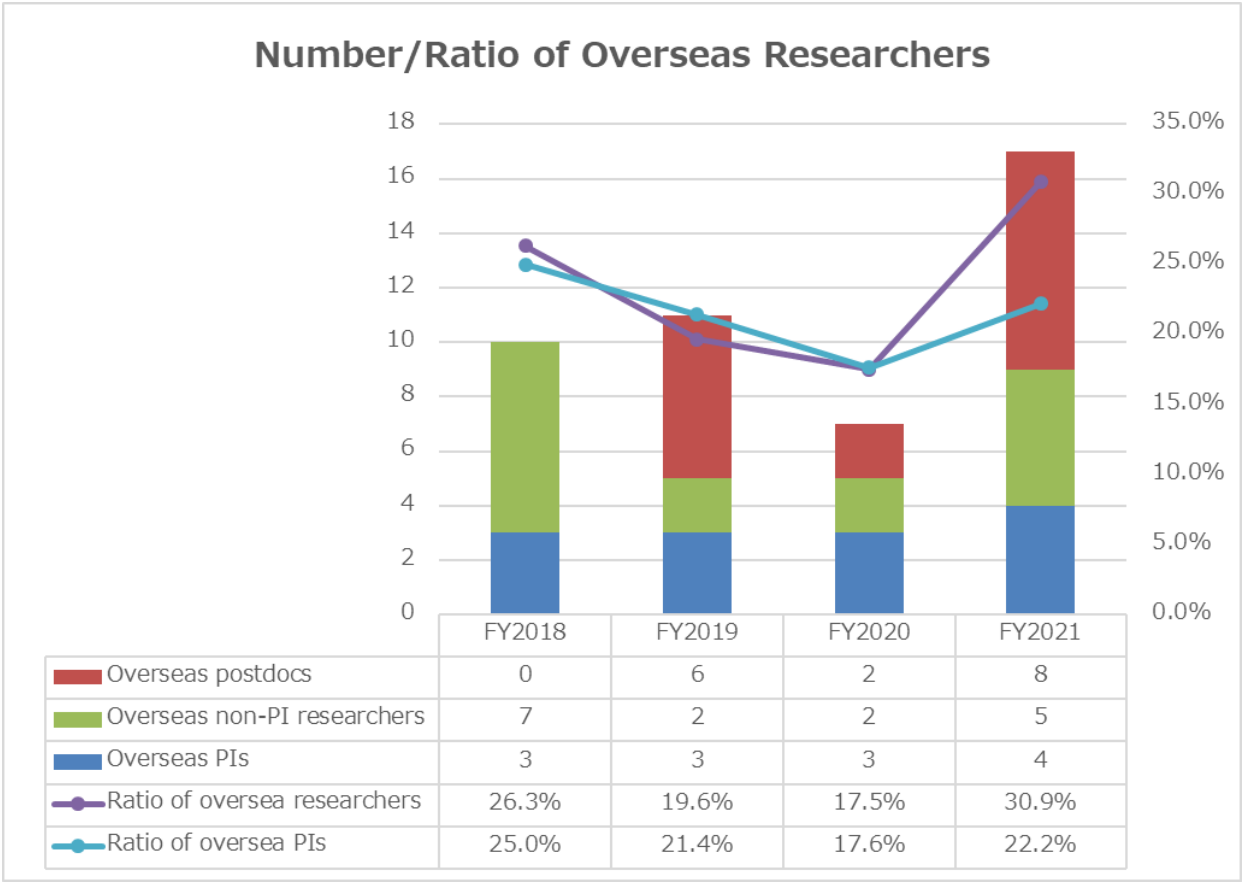
	At the beginning of project		At the end of FY 2021		Final goal (Date: Mar, 2024)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	13		55		66	
Overseas researchers	4	31	17	31	20	30
Female researchers	3	23	14	25	20	30
Principal investigators	13		18		18	
Overseas PIs	4	31	4	22	4	22
Female PIs	3	23	3	17	3	17
Other researchers	0		21		19	
Overseas researchers	0	#DIV/0!	5	24	4	21
Female researchers	0	#DIV/0!	5	24	3	16
Postdocs	0		16		29	
Overseas postdocs	0	#DIV/0!	8	50	12	41
Female postdocs	0	#DIV/0!	6	38	14	48
Research support staffs	2		26		33	
Administrative staffs	3		16		16	
Total number of people who form the "core" of the research center	18		97		115	

Appendix 3-2　Annual Transition in the Number of Center Personnel

*Make a graph of the annual transition in the number of center personnel since the start of project.

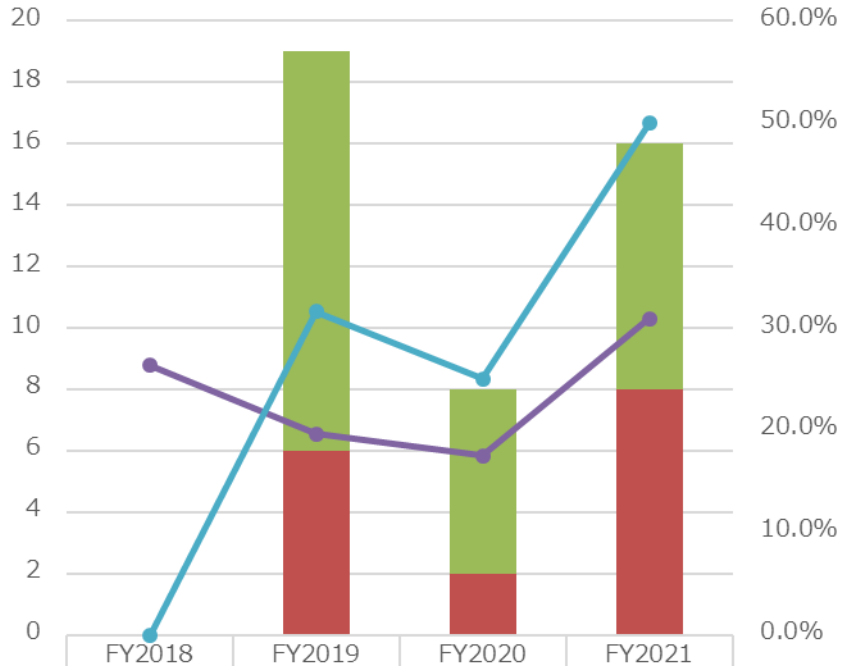


	At beginning	FY2018	FY2019	FY2020	FY2021	Final goal
PI : Researchers from within host institution	8	8	9	12	14	14
PI : Researchers invited from abroad	4	3	3	3	2	2
PI : Researchers invited from other Japanese institutions	1	1	2	2	2	2
Other researchers (incl. postdocs)	0	26	42	23	37	48
Research support staffs	2	3	18	23	26	33
Administrative staffs	3	12	14	16	16	16



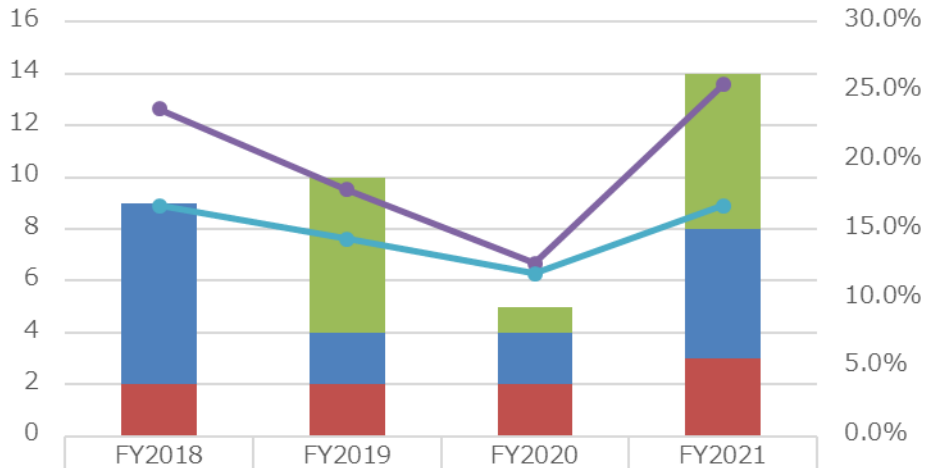
	FY2018	FY2019	FY2020	FY2021
Overseas postdocs	0	6	2	8
Overseas non-PI researchers	7	2	2	5
Overseas PIs	3	3	3	4
Ratio of oversea researchers	26.3%	19.6%	17.5%	30.9%
Ratio of oversea PIs	25.0%	21.4%	17.6%	22.2%

Number/Ratio of Overseas Postdoc



	FY2018	FY2019	FY2020	FY2021
Japanese postdocs	0	13	6	8
Overseas postdocs	0	6	2	8
Ratio of oversea researchers	26.3%	19.6%	17.5%	30.9%
Ratio of female postdocs	0.0%	31.6%	25.0%	50.0%

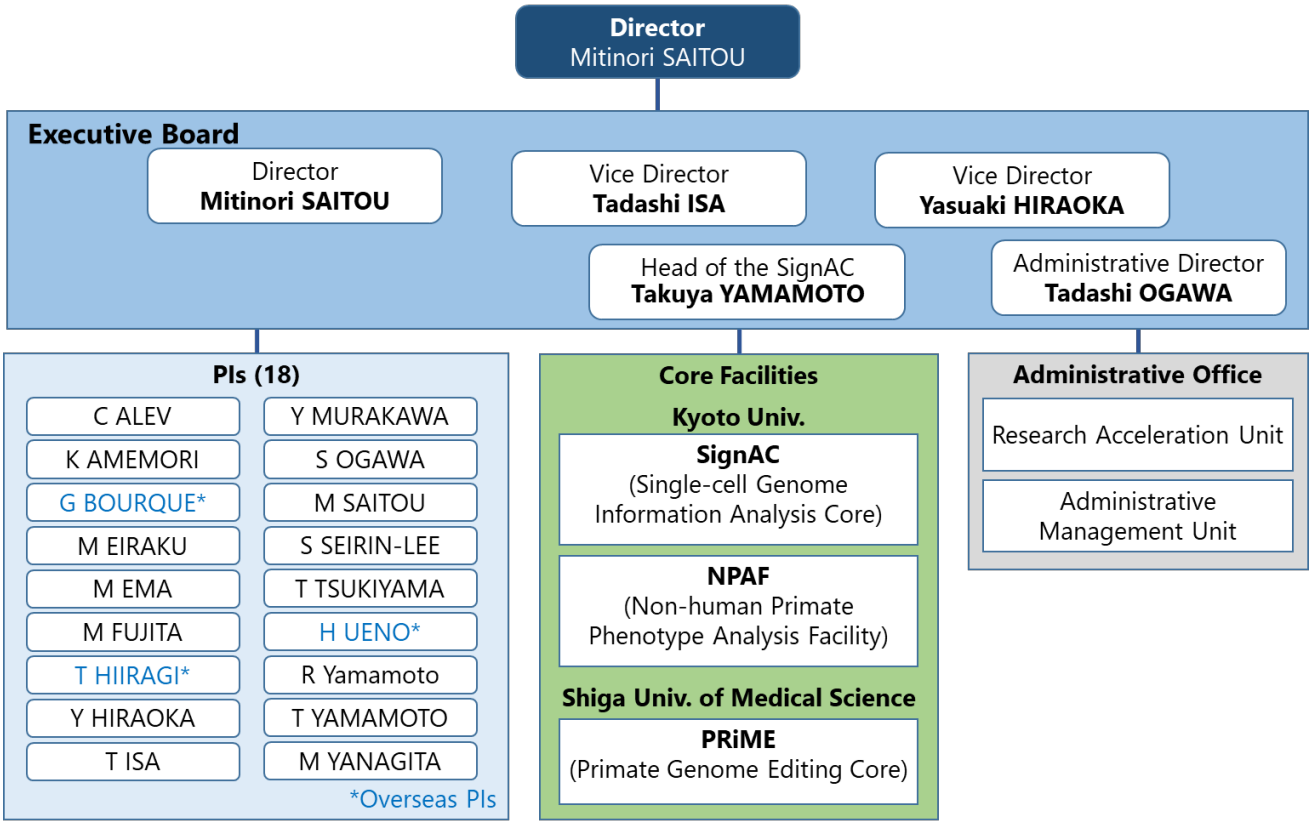
Number/Ratio of Female Researchers



	FY2018	FY2019	FY2020	FY2021
Female postdocs	0	6	1	6
Female non-PI researchers	7	2	2	5
Female PIs	2	2	2	3
Ratio of female researchers	23.7%	17.9%	12.5%	25.5%
Ratio of female PIs	16.7%	14.3%	11.8%	16.7%

Appendix 3-3　Diagram of Management System

- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any 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).



Appendix 3-4　Campus Map

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

Appendix 3-5 Project Expenditures in FY2021

1) Overall project funding

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

(Million yens)

Cost items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total costs	Amount covered by WPI funding
Personnel	Center director and administrative director	29	4
	Principal investigators (no. of persons):15	145	45
	Other researchers (no. of persons):38	191	171
	Research support staff (no. of persons):28	68	68
	Administrative staff (no. of persons):23	77	31
	Subtotal	510	319
Project activities	Research startup cost	35	24
	Fusion research startup cost	29	16
	Cost of satellite organizations (no. of satellite organizations):1	78	78
	Cost of international symposiums	7	2
	Rental fees for facilities	23	23
	Cost of utilities	8	4
	Cost of operating and maintenance of Core Facility	54	39
	Cost of workshops, seminars and Young Researcher Foster programs	4	3
	Cost of outreach activities	8	7
	Cost of maintenance contracts, communication, copy machine rental and maintenance fee)	28	19
	Cost of consumables, small equipments	43	25
	Other costs	0	0
	Subtotal	317	240
Travel	Domestic travel costs	0	0
	Overseas travel costs	1	0
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):0		
	Travel cost for scientists on transfer (no. of domestic scientists):0 (no. of overseas scientists):1	1	0
	Subtotal	2	0
Equipment	Cost of laboratory maintenance (repair work, etc.)	48	45
	Cost of research equipments in SignAC and open laboratory equipments maintenance	219	96
	Subtotal	267	141
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1	14	
	KAKENHI	214	
	Commissioned research projects, etc.	786	
	Joint research projects	111	
	Ohers (donations, etc.)	123	
	Subtotal	1248	0
Total		2344	700

Costs (Million yens)

WPI grant in FY 2021	700
Costs of establishing and maintaining facilities	30
Establishing new facilities	0
Repairing facilities	30
(Number of facilities: 1 , about 2,010 m²)	
Others	0
Costs of equipment procured	112
High-throughput long-read sequencer(1)	40
Live imaging microscope with a wide field of view for long-term culture(1)	15
Single cell library preparation system(1)	14
Others	43
	0

*1. Funding sources that include government subsidies (including Enhancements promotion expenses (機能強化促進経費), 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.

2) Costs of satellites

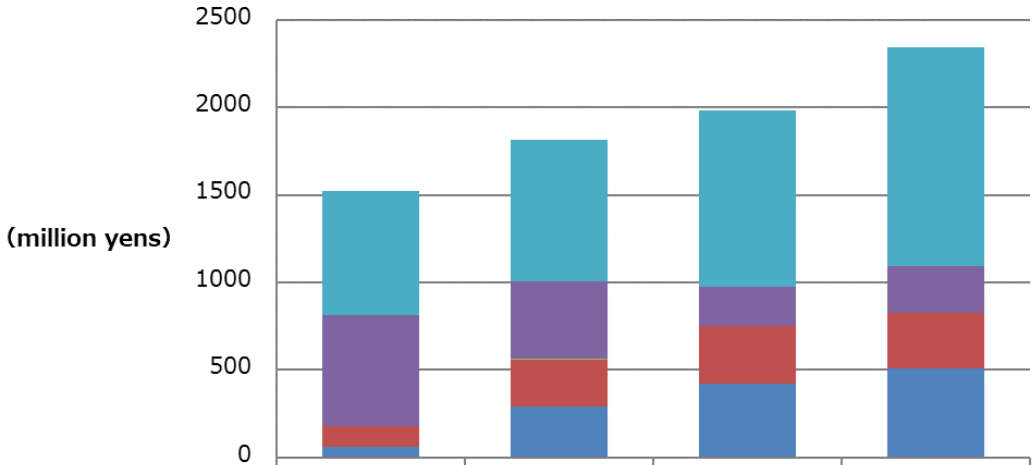
(Million yens)

Cost items	Details	Total costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):2		
	Other researchers (no. of persons):2		
	Research support staff (no. of persons):1		
	Administrative staff (no. of persons):0		
	Subtotal	35	23
Project activities	Subtotal	20	20
Travel	Subtotal	0	0
Equipment	Subtotal	34	34
Research projects	Subtotal	45	0
Total		134	77

Appendix 3-6　Annual Transition in the Amounts of Project Funding

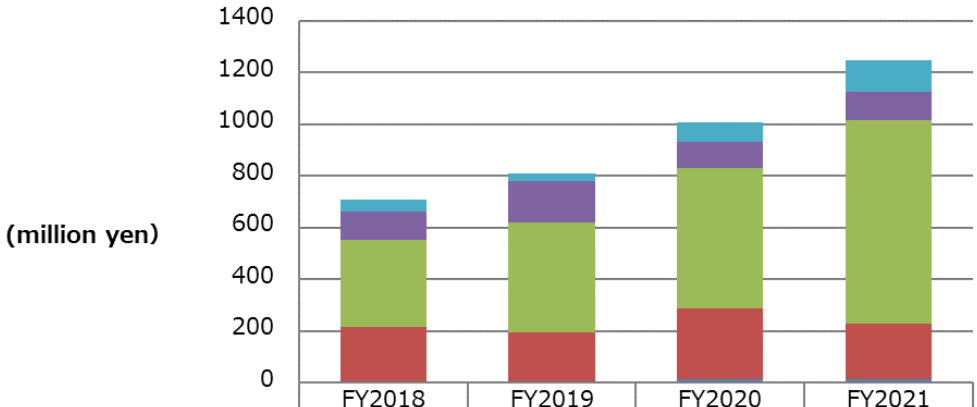
*Make a graph of the transition in the number of overall project funding.

Transition of Project Expenditures



	FY2018	FY2019	FY2020	FY2021
Research Projects	709	810	1007	1248
Equipment	633	440	225	267
Travel	2	7	3	2
Project Activities	117	264	331	317
Personnel	61	293	419	510

Transition of Research Project Expenditures



	FY2018	FY2019	FY2020	FY2021
Ohers (donations, etc.)	48	31	75	123
Joint research projects	108	159	103	111
Commissioned research projects, etc.	338	427	543	786
KAKENHI	215	190	274	214
Project supported by other government subsidies, etc. *1	0	3	12	14

*1 Definition is as shown in Appendix 3-5 (Project Expenditures)

- Describe external funding warranting special mention. Include the name and total amount of each grant.

FY2018
- Name: KAKENHI Grant-in-Aid for Specially Promoted Research, JSPS
  Total Amount: 110,000,000 JPY (acquired by Mitinori Saitou)
- Name: Project for Cancer Research and Therapeutic Evolution (P-CREATE), AMED
  Total Amount: 68,856,154 JPY (acquired by Seishi Ogawa)
- Name: Donation, Pythias Fund
  Total Amount: 47,447,296 JPY (acquired by Mitinori Saitou)

FY2019
- Name: Collaboration Research, TMK Project
  Total Amount: 88,864,901 JPY (acquired by Motoko Yanagita)
- Name: Project for Cancer Research and Therapeutic Evolution (P-CREATE), AMED
  Total Amount: 81,539,500 JPY (acquired by Seishi Ogawa)
- Name: KAKENHI Grant-in-Aid for Specially Promoted Research, JSPS
  Total Amount: 77,700,000 JPY (acquired by Mitinori Saitou)

FY2020
- Name: AMED-CREST, AMED
  Total Amount: 89,798,800 JPY (acquired by Seishi Ogawa)
- Name: KAKENHI Grant-in-Aid for Specially Promoted Research, JSPS
  Total Amount: 89,600,000 JPY (acquired by Mitinori Saitou)
- Name: AMED-CREST, AMED
  Total Amount: 63,327,000 JPY (acquired by Hideki Ueno)

FY2021
- Name: KAKENHI Grant-in-Aid for Specially Promoted Research, JSPS
  Total Amount: 78,000,000 JPY (acquired by Mitinori Saitou)
- Name: Translational and Clinical Research Core Centers, AMED
  Total Amount: 73,277,517 JPY (acquired by Seishi Ogawa)
- Name: Brain/MINDS, AMED
  Total Amount: 67,140,000 JPY (acquired by Tadashi Isa)

Appendix 4-1 FY 2021 Status of Collaboration with Overseas Satellites

- If satellite and partner institutions have been established, fill in required items of the form below.

1. Satellites and partner institutions

- List the satellite and partner institutions in the table below (including the domestic satellite institutes).
- Indicate newly added and deleted institutions in the "Notes" column.

<Satellite institutions>

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

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes

- If overseas satellite institutions have been established, fill in required items on the form below. If overseas satellite institutions have not been established, it is not necessary to complete the form.

2. Coauthored Papers

- List the refereed papers published in FY 2021 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 1-4. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1-4 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2022 and not described in Appendix 1-4.

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

1)
2)
3)
4)

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

1)
2)
3)
4)

3. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2021. 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
FY2021					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2021					

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
FY2021					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2021					

Appendix 4-2 FY 2021 Visit Records of Researchers from Abroad

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

Total: 69

	Name	Age	Affiliation		Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
			Position title, department, organization	Country				
1	Fuchou Tang		Professor, BIOPIC, College of Life Sciences, Peking University Associate Director, Beijing Advanced Innovation Center for Genomics (ICG)	China	PhD Stem Cell Biology	Has received - 2017 Bayer Investigator Award - 2016 NSFC, Distinguished Young Investigator Award - 2015 Guxiaocheng Lecture Award, Ray Wu Fouddation - 2015 Listed as Top 10 China's Scientific Advances in 2014 - 2013 NSFC, Excellent Young Investigator Award	Apr 06, 2021	Participation as invited lecturer, ASHBi Seminar
2	Bertie Göttgens		Professor, Molecular Haematology and Deputy Director of the Cambridge Stem Cell Institute	UK	PhD Haematology	Has received -2014 Fellow of the Academy of Medical Sciences -2010 McCulloch and Till Award	Apr 19, 2021	Participation as invited lecturer, ASHBi Distinguished Seminar
3	Jan-Michael Peters	59	Scientic Director, Research Institute of Molecular Pathology, Vienna	Austria	PhD Cell/Molecular Biology	Has received - 2012 Member of Austrian Academy of Sciences - 2011 Wittgenstein Prize - 2007 Binder Innovation Prize - 2005 Boehringer Ingelheim Research & Development Award - 2002 Novartis Research Prize - 2002 EMBO member - 2001 Roche Research Prize for Cell Biology - 2001 EMBO Young Investigator Award - 1994 Falcon Prize of German Society for Cell Biology - 1992 Junior Scientist Award of Society for Promotion of Molecular Biology	May 28, 2021	Participation as invited lecturer, ASHBi Distinguished Seminar
4	Marnie Blewitt		Professor, Bellberry-Viertel Senior Medical Research Fellow Walter and Eliza Hall Institute, University of Melbourne	Australia	PhD Developmental Biology	Has received - 2017 Bellberry-Viertel Senior Medical Research Fellowship - 2015 Lorne Genome Women in Science Award - 2013 Financial Review Top 100 Women of Influence Award - 2009 L'Oreal Australia For Women in Science Fellowship - 2009 Australian Academy of Science Ruth Stephens Gani Medal - 2006 Genetics Society of Australia DG Catcheside Prize	Aug 27, 2021	Participation as invited lecturer, ASHBi Seminar
5	Bruno Reversade	44	IMB & IMCB, A*STAR, Singapore Amsterdam UMC, Netherlands Koç University, Turkey	Netherlands	PhD Mendelian Genetics	Has received - 2021 Inaugural UIBR investigator, A*STAR - 2016 The Award for Leading, Educating & Nurturing Talent, A*STAR - 2016 ISDSO Award, International Society of Differentiation - 2012 EMBO Young Investigator 2006 David Sigman Award, UCLA	Sep 03, 2021	Participation as invited lecturer, ASHBi Seminar

	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				
6	Dora Angelaki		Professor, New York University,	USA	PhD, Neuroscience	Has received - 2014 Member, National Academy of Sciences - 2014 Member, American Academy of Arts and Sciences - 2012 Pradel Research Award in Neuroscience, NAS - 2011 Grass Lectureship, Society of Neuroscience - 2006 Hallpike-Nylen medal, Bárány Society - 1996 Presidential Early Career Award for Scientists and Engineers	Sep 10-15, 2021	Participation as invited lecturer, JANUBET Neurobiology School
7	Wim Vanduffel		Professor, KU Leuven	Belgium	PhD, Neuroscience	Has received - 2018 Academia Europaea member - 2011 Prize Janine en Jacques Delruelle - 1986 Laureate Jan Kets Zoo Antwerp	Sep 10-15, 2021	Participation as invited lecturer, JANUBET Neurobiology School
8	Clifford Kentros		Professor, Kavli Institute of Systems Neuroscience, Norwegian University of Science and Technology	Norway	PhD, Neuroscience	Professor of Medicine and leader of the Kentros research group at the Kavli Institute of Systems Neuroscience, NTNU	Sep 10-15, 2021	Participation as invited lecturer, JANUBET Neurobiology School
9	Menno Witter	69	Professor, Kavli Institute for Systems Neuroscience Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology	Norway	PhD, Neuroscience	Also - Director of the Norwegian Research School in Neuroscienc Has received - Member, the Royal Norwegian Society of Sciences and Letters - 2016 Olav Thon Foundation International Research Award	Sep 10-15, 2021	Participation as invited lecturer, JANUBET Neurobiology School
10	Wolfram Schultz	77	Professor, Cambridge University	UK	PhD, Neuroscience	Has received - 2019 Lashley Award (Am Philosoph Soc) - 2018 Gruber Prize - 2017 Brain Prize - 2014 EMBO Fellow - 2013 Zülch Prize - 2010 EJN FENS Award - 2009 Fellow, the Royal Society - 2005 Ipsen Prize - 2002 Golden Brain Award - 1997 Theodore-Ott-Prize - 1984 Ellermann Prize	Sep 10-15, 2021	Participation as invited lecturer, JANUBET Neurobiology School
11	Peter Strick	75	Thomas Detre Professor and Chair, Department of Neurobiology; Director, Systems Neuroscience Institute, Pittsburgh University	USA	PhD, Neuroscience	Has received - 2012 Member National Acaemy of Sciences - 2004 Member, American Academy of Arts and Sciences - 1999 Fellow, American Association for the Advancement of Science - 1986 Javits Neuroscience Investigator Award, NIH-NINDS - 1979 C.J. Herrick Award	Sep 10-15, 2021	Participation as invited lecturer, JANUBET Neurobiology School
12	Okihide Hikosaka		Distinguished Investigator, LSR, National Eye Institute, NIH	USA	PhD, Neuroscience	Has received - 2018 Gruber Foundation Neuroscience Prize - 2015 Golden Brain Award, Minerva Foundation - 2011 Member, American Academy of Arts and Sciences - 1999 Tokizane Toshihiko Memorial Award - 1989 Tsukahara Memorial Award	Sep 10-15, 2021	Participation as invited lecturer, JANUBET Neurobiology School

	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				
13	Douglas P. Munoz		Professor, Canada Research Chair in Neuroscience, Queen's University, Canada	Canada	PhD Neuroscience	Canada Research Chair in Neuroscience - 2001 Aesculiapian Society Teaching Award - 1999 Premier's Research Excellence Award - 1997 Basmejian Award - 1993 Fellow, Alfred P. Sloan Foundation	Sep 10-15, 2021 Jan 05, 2022	Participation as invited lecturer, JANUBET Neurobiology School Participation as an invited lecturer, ASHBi Distinguished Seminar
14	Yutaka Yoshida		Professor, Burke Neurological Institute, Weill Cornell Medicine	USA	PhD, Neuroscience	Has received - 2009 Basil O'Connor Starter Scholar Research Award of March of Dimes - 2009 Trustee Grant Award from Cincinnati Children's Hospital Medical Center - 2003 HFSP Long term Fellowship - 1998 American Association for Cancer Research-ITOEN Young Investigator Award	Sep 10-15, 2021 Mar14-17, 2022	Participation as invited lecturer, JANUBET Neurobiology School Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
15	Christiana Bjørkli		Norwegian University of Science and Technology	Norway	PhD student	PhD student at the Norwegian University of Science and Technology	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
16	Katrine Sjaastad Hanssen		Norwegian University of Science and Technology	Norway	PhD student	PhD student at the Norwegian University of Science and Technology	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
17	Marial Letizia Potenza		Norwegian University of Science and Technology	Norway	PhD student	PhD student at the Norwegian University of Science and Technology	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
18	Vikas Kumar Tiwari		All India Institute of Medical Sciences	India	PhD student	PhD student at the All India Institute of Medical Sciences	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
19	Asgeir Kobro-Flatmoen		Norwegian University of Science and Technology	Norway	PhD, Neuroscience	Researcher at the Norwegian University of Science and Technology	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
20	Hyunchan Lee		LSR, National Eye Institute, NIH	USA	PhD, Neuroscience	Researcher at the NIH	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
21	Gabriela Costello		LSR, National Eye Institute, NIH	USA	PhD, Neuroscience	Researcher at the NIH	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
22	Kazutaka Maeda		LSR, National Eye Institute, NIH	USA	PhD, Neuroscience	Researcher at the NIH	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
23	Stefan Blankvoort		LSR, National Eye Institute, NIH	USA	PhD, Neuroscience	Researcher at the NIH	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
24	Xuefei Yu		LSR, National Eye Institute, NIH	USA	PhD, Neuroscience	Researcher at the NIH	Sep 10-15, 2021	Participation as student, JANUBET Neurobiology School
25	Peter Boor	43	Professor, Department of Translational nephropathology, at RWTH Aachen University	Germany	MD, PhD Nephrology	Has received - 2020 Franz Volhard Prize - 2019 Bernd Tersteegen-Award	Oct 27, 2021	Participation as invited lecturer, NEPHROLOGY EXPERT SEMINAR
26	Rafael Kramann	41	Professor of Medicine and Chair of Nephro-Cardiology, at RWTH Aachen University	Germany	MD, PhD Nephrology	Has received - 2021 Thodor Frerichs Prize - 2019 Franz Volhard Prize - 2014 Fellow of the American Society of Nephrology - 2014 Stanley Shaldon Award for Young Investigators - 2011 German Society of Nephrology Award for Young Investigators	Nov 05, 2021	Participation as invited lecturer, ASHBi Distinguished Seminar

	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	Aida Andrés		Associate Professor, Division of Biosciences, University College London	UK	PhD Evolutionary Biology	Formerly a group leader the Max Planck Institute for Evolutionary Anthropology, her group focuses how organisms adapt to their environment by analysing genomes, both modern and ancient, to infer how natural selection mediates genetic adaptations.	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
28	James Briscoe		Group Leader, The Francis Crick Institute	UK	PhD Developmental Biology	Has received - 2019 Fellow of the Royal Society - 2019 Fellow of the Academy of Medical Sciences - 2018 Editor in Chief of Development, the Company of Biologists - 2009 EMBO member - 2008 EMBO Gold Medal - 2001 EMBO Young Investigator	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
29	J. Gray Camp	40	Institute of Molecular and Clinical Ophthalmology Basel	Switzerland	PhD Developmental Biology	Has received - GSCN 2017 Publication of the Year Award	Nov 8-10, 2021 Mar 14-17, 2022	Participation as invited speaker, ASHBi Symposium 2021 International Symposium on Development and Plasticity of Neural Systems
30	Anne Goriely		Professor of Human Genetics, Radcliffe Department of Medicine, University of Oxford	UK	PhD Human Genetics	Has received - 2020 Wellcome Investigator Award	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
31	Anne Grapin-Botton	54	Group Leader & Director, Max Planck Institute of Molecular Cell Biology and Genetics, Dresden	Germany	PhD Developmental Biology	Has received - 2018 HFSP fellowship and several awards and grants	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
32	Henrik Kaessmann		ZMBH Research Group Leader, Center for Molecular Biology, Heidelberg University	Germany	PhD Comparative Genomics	Recipient of - 2021 Award for Outstanding Research Achievements (Heidelberg University) - 2014 Cloëtta Prize, Max Cloëtta Foundation - 2014 Jürg Tschopp Life Science Prize, Univ. of Lausanne - 2014 EMBO member - 2010 Friedrich Miescher Award - 2008 Basic Life Science Award, Univ. of Lausanne - 2005 EMBO Young Investigator Award - 2004 Heinz Maier Leibnitz young investigator award, Max Planck Society	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
33	Janet Kelso	47	Head, Bioinformatics research group, Max-Planck Institute for Evolutionary Anthropology in Leipzig	Germany	PhD Bioinformatics	Co-Editor-in-chief of the journal Bioinformatics, Board of the International Society of Computational Biology Has received - 2016 ISCB fellow - 2010 Newcomb Cleveland Prize - 2004 L'Oréal-UNESCO Awards for Women in Science	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
34	Diana Laird		Associate Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, UCSF	USA	PhD Developmental Biology	Recipient of - NIH Director's New Innovator Award - W.M. Keck Foundation Award	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
35	Prisca Liberali		Group Leader, Friedrich Miescher Institute for Biomedical Research Assistant Professor, University of Basel	Switzerland	PhD Developmental Biology	Recipient of - 2021 Friedrich Miescher Award - 2019 EMBO Young Investigator	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021

	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				
36	Claire Rougeulle	53	Group Leader & Deputy Director, Epigenetics and Cell Fate Center, Université de Paris, France Professor, Ecole Polytechnique	France	PhD Developmental Biology	Recipient of - 2022 Chevalier dans l'Ordre National du Mérite - 2021 Antoine Lacassagne Prize, Collège de France - 2019 CNRS Silver Medal - 2016 EMBO member - 2007 CNRS Bronze Medal	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
37	Davor Solter	81	Max Planck Society Visiting International Professor Siriraj Center for Excellence in Stem Cell Research, Mahidol University Medical School, Bangkok	USA	PhD Developmental Biology	Emeritus Director of Max Planck Institute Has received - 2022 Mendel Medal, Genetics Society - 2018 Canada Gairdner International Award - 2006 Rosenstiel Award - 1998 March of Dimes Prize in Developmental Biology - 1994 American Academy of Arts and Sciences - 1994 EMBO member - 1992 Academia Europaea member - 1991 Member, Max-Planck Society	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
38	Azim Surani	76	Director of Germline and Epigenetics Research Wellcome Trust/CRUK Gurdon Institute, University of Cambridge	UK	PhD Developmental Biology	Has received - 2022 Mendel Medal, Genetics Society - 2018 Canada Gairdner International Award - 2007 Rosenstiel Award - 2014 ISSCR McEwen Award for Innovation - 2010 Royal Medal - 2010 Mendel Lectures - 2006 Rosenstiel Award - 2001 Gabor Medal - 2001 Fellow of the Academy of Medical Sciences - 1994 EMBO member - 1990 Fellow of of the Royal Society	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
39	Barbara Treutlein	40	Professor, Quantitative Developmental Biology, ETH Zürich D-BSSE, Switzerland	Switzerland	PhD Quantitative Developmental Biology	Has received - 2020 Young Investigator Award, GSCN - 2019 EMBO Young Investigator - 2019 Dr. Susan Lim Award, ISSCR - 2018 NYSCF Investigator Award - 2016 Friedmund Neumann Prize, Schering Foundation	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
40	James Turner		Assistant Research Director & Principal Group Leader, The Francis Crick Institute	UK	PhD Developmental Biology	Has received - 2021 Fellow of the Academy of Medical Sciences - 2019 EMBO member - 2014 Wain Medal, - ERC Consolidator award	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021

	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				
41	Christopher Walsh		Bullard Professor, Pediatrics and Neurology, Harvard Medical School Chief, Genetics and Genomics, Boston Children's Hospital Investigator, Howard Hughes Medical Institute Associate Member, Broad Institute	USA	MD, PhD NeuroBiollogy	Member of the National Advisory Mental Health Council, American Association of Physicians, the American Association for the Advancement of Sciences, the National Academy of Medicine, the American Academy of Arts and Sciences, and the National Academy of Sciences Has received - 2021 Gruber Neuroscience Prize - Jaocob Javits Neuroscience Investigator Award, NINDS - Dreifuss-Penry Epilepsy Award, American Academy of Neurology - Denny-Brown and Jacoby Awards, American Neurological Association - Penfield Award, Middle Eastern Medical Assembly - Clinical Research Award, American Epilepsy Society - Pruzansky Award, American College of Medical Genetics - Perl-Neuroscience Award, University of North Carolina	Nov 8-10, 2021	Participation as invited speaker, ASHBi Symposium 2021
42	David Archard	71	Emeritus Professor, Queen's University Belfast	UK	Ph Philosophy and Applied Ethics	Also - Chair of the Nuffield Council on Bioethics - Honorary Vice-President of the Society for Applied Philosophy - Member and Deputy Chair of the Human Fertilization and Embryology Authority - Chair of the Nuffield Council on Bioethics	Nov 12, 2021	Participation as invited lecturer, ASHBi Bioethics-Biology Fusion Workshop
43	Sarah Chan		Chancellor's Fellow, Usher Institute, Edinburgh University	UK	PhD Ethics	Also - Director, Mason Institute for Medicine, Life Sciences and Law - Co-Principal Investigator, Centre for Biomedicine, Self and Society - Ethics Advisory Committee member, Genomics England and Scottish Genomes Partnership Has received - 2018 Fellow, the Royal Society of Edinburgh	Nov 12, 2021	Participation as invited lecturer, ASHBi Bioethics-Biology Fusion Workshop
44	Naomi Moris		Group Leader, Francis Crick Institute	UK	PhD Stem Cell Biology	Has received - 2017 Junior Research Fellowship, Newnham College, Cambridge	Nov 12, 2021	Participation as invited lecturer, ASHBi Bioethics-Biology Fusion Workshop
45	Julian Savulescu		Director of the Oxford Uehiro Centre for Practical Ethics; Uehiro Professor of Practical Ethics; Fellow of St Cross College, University of Ocford	UK	PhD, practical ethics	Has received - 2018 Daniel M. Wegner Theoretical Innovation Prize - 2014 Doctoris Honoris Causa from the University of Bucharest - 2009 ‘Thinker’ Award in the top 100 Australian Future Leaders - 2009 Monash University Distinguished Alumni - 2005 ASMR Gold Medalist	Nov 12, 2021	Participation as invited lecturer, ASHBi Bioethics-Biology Fusion Workshop
46	Jun Wu		Assistant Professor, Department of Molecular Biology, University of Texas Southwestern Medical Center, Hamon Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center	USA	PhD Stem Cell Biology	Has received - 2021 Robertson Stem Cell Investigator, NYSCF - 2018 Virginia Murchison Linthicum Scholar in Medical Research, UTSW - 2017 CPRIT Scholar: First-Time, Tenure-Track Faculty Members Program	Dec 01, 2021	Participation as invited speaker, MBSJ Symposium

	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				
47	Mari Ohnuki		Post-Doc Anthropology and Human Genomics, Department Biology II Ludwig Maximilians University Munich	Germany	PhD	Postdoc of the Wolfgang Enard's Anthropology and Human Genomics at the Ludwig Maximilians University Munich.	Dec 17, 2021	Participation as invited lecturer, ASHBi Seminar
48	Takanori Takebe	35	Director for Commercial Innovation, Center for Stem Cell and Organoid Research and Medicine (CuSTOM), Cincinati Children's Hospital Associate Professor, UC Department of Pediatrics Professor, Institute of Research, Division of Advanced Research, TMDU	USA	MD PhD Gastroenterology Hepatology and Nutrition, Developmental Biology	Board of directors of ISSCR Has received - 2020 New Innovator Award, NIH - 2019 JSPS Prize - 2019 Japan Academy Medal - 2016 Robertson Stem Cell Investigator Award, NYSCF	Jan 07, 2022	Participation as invited lecturer, ASHBi Seminar
49	Janet Rossant	71	Chief of Research Emeritus, Senior Scientist, The Hospital for Sick Children	Canada	PhD, Stem Cell Biology	Has received - 2018 L'Oréal-UNESCO For Women in Science Award - 2015 Gairdner Wightman Award - 2013 Ross G. Harrison Medal - 2008 Foreign Associate, National Academy of Sciences - 2000 Fellow, Royal Society - 1993 Fellow, Royal Society of Canda	Feb 02, 2022	Participation as invited lecturer, ASHBi Distinguished Seminar
50	Lawrence S.B. Goldstein	66	Professor Emeritus, UC San Diego Scientific Director, Sanford Consortium for Regenerative Medicine	USA	PhD Neoroscience	Has received - 2020 National Academy of Sciences member - 2009 Public Service Award, American Society for Cell Biology - 2008 Fellow of American Academy of Arts and Sciences - Senior Scholar Award, Ellison Medical Foundation - American Cancer Society Faculty Research Award - The Loeb Chair in Natural Sciences	Mar 02, 2022	Participation as invited lecturer, "Fetal Tissue Research: Science and Ethics at the Frontiers in the United States and Europe"
51	R. Alta Charo, J.D.	64	Knowles Professor Emerita of Law & Bioethics, University of Wisconsin-Madison	USA	PhD Law and Bioethics	Also - lead co-chair of the 4S unit of the new Dept of Defense biotechnology manufacturing innovation institute Has received - 2020 Fellow of American Academy of Arts and Sciences - 2013 Adam Yarmolinsky Medal - 2006 National Academies' Institute of Medicine (IOM) member	Mar 02, 2022	Participation as invited lecturer, "Fetal Tissue Research: Science and Ethics at the Frontiers in the United States and Europe"
52	Roger A Barker		Professor and Honorary Consultant Neurologist, Department of Clinical Neuroscience and Wellcome-MRC Cambridge Stem Cell Institute, University of Cambridge, UK.	UK	PhD Neurology	Also - Consultant Neurologist at Addenbrooke's Hospital - Director of the UK Regenerative Medicine Platform - Vice President, the World Parkinson Coalition Has received -2015 Fellow of the Academy of Medical Sciences	Mar 04, 2022	Participation as invited lecturer, "Fetal Tissue Research: Science and Ethics at the Frontiers in the United States and Europe"

	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				
53	Susan Chuva de Sousa Lopes		Associate Professor, Developmental Biology, Department of Anatomy and Embryology, Leiden University Medical Cente	Netherland	PhD Developmental Biology	Also - Member of Taskforce preparing SciSpacE Roadmaps Human Physiology for European Space Agency (ESA) - Elected member of the Special Interest Group “Stem Cells”, ESHRE Has received - 2021 Academia Europaea member - 2020 2020 Aspasia award, NWO - 2019 VICI-laureate, NWO - 2017 De Snoo-van’t Hoogerhuijs Foundation award - 2011 Aspasia award, NWO - 2006 VENI-laureate, NWO - 2006 De Snoo-van’t Hoogerhuijs Foundation award	Mar 04, 2022	Participation as invited lecturer, "Fetal Tissue Research: Science and Ethics at the Frontiers in the United States and Europe"
54	Steven Lisgo		HDBR Resource Manager, Institute of Genetic Medicine, Newcastle University	UK	PhD	As a HDBR Resource manager of MRC-Wellcome Trust Human Developmental Biology Resource (HDBR), he takes care of the ongoing collection of human embryonic and fetal material ranging from 3 to 20 weeks of development.	Mar 04, 2022	Participation as invited lecturer, "Fetal Tissue Research: Science and Ethics at the Frontiers in the United States and Europe"
55	Mu-ming Poo	73	Director, Institute of Neuroscience, Chinese Academy of Sciences	China	PhD, Neuroscience	Has received - 2016 Gruber Prize in Neuroscience - 2011 Outstanding Science and Technology Achievement Prize, Chinese Academy of Sciences - 2010 Qiushi Excellent Scientist Award, China - 2009 Member, National Academy of Sciences U.S. - 2005 Peoples Republic of China International Science & Technology Cooperation Award - 2002 Ray Wu Society Award - 2001 Ameritec Prize - 2001 Fellow of the American Association for the Advancement of Science - 2000 Academician, Academia Sinica. Taiwan	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
56	Ole Kiehn	64	Professor, University of Copenhagen / Karolinska Institute	Demnark	PhD, Neuroscience	Has received - 2022 Brain Prize - 2014 EMBO member - 2013 Academia Europea member - 2012 Member, The Royal Swedish Academy of Sciences - 2010 Member of the The Royal Danish Academy of Sciences and Letters - 2004 Has received international Schellenberg Prize in spinal cord research - 1996 Recipent of Anna Brochardt Prize	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems

	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				
57	Martin Schwab	72	Professor, University of Zurich Professor emeritus ETH Zurich Institute of Regenerative Medicine	Switzerland	PhD, Neuroscience	Has received - 2018 Honorary Medal of Eurospine - 2016 Schellenberg Prize - 2007 Betty and David Koetser Prize - 2002 International Prize for Translational Neuroscience of the Gertrud Reemtsma Foundation and the Max-Planck-Society - 2001 Member, Swiss Academy of Medical Sciences - 2000 Kilby International Award - 1999 Eduard Buchner Prize - 1996 1st Christopher Reeve Research Medal, UC Irvine - 1995 Victor Hamburger Award - 1994 The Wakeman Award - 1994 Marcel Benoist Swiss Science Prize	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
58	Zhigang He		Professor, Harvard Medical School	USA	PhD, Neuroscience	Also Klingenstein Fellow in Neuroscience, a John Merck Scholar, and a McKnight Scholar Has received - 2021 Member, National Academy of Medicine (NAM) - 2020 Greenberg End Blindness Visionary Prize - 2019 Reeve-Irvine Research Medal - 2005 Ameritec Prize for paralysis research	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
59	Mark Tsuzynski		Professor, University of California, San Diego Founding Director, UCSD Translational Neuroscience Institute	USA	PhD, Neuroscience	Has received - 2015 Reeve-Irvine Medal - 2013 Jacoby Award, American Neurological Association - 2013 Fellow, American Neurological Association - 2012 Eleced, The Dana Alliance for Brain Initiatives - 2012 Zenith Award, Alzheimer's Association - 2008 Adelson Award, American Society for Neurorehabilitation - 2008 Ted Bullock Award, UCSD Neuroscience Program - 2004 Visionary Award, Glenner Alzheimer's Association - 2002 Barbara Haugh Alzheimer's Disease Research Award - 2001 Ariens Kappers Medal - 2001 Spinal Cord Injury Research Award - 2000 Sanberg Memorial Award for Brain Repair - 1998 Member, American Neurological Association - 1995 Silvio O. Conte Research Award	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
60	Victor Borrell		Professor, Institute of Neuroscience Alicante	Spain	PhD, Neuroscience	Also - Executive Board Member, Spanish Society for Developmental Biolog - Deputy Director, Institute of Neurosciences in Alicante Has received - Young Investigator Award, Spanish Society of Neuroscience - Alberto Sols Award - 2007 HFSPO Career Development Award - 2002 Extraordinary Prize of Doctoral Thesis, U. Barcelona	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems

	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				
61	Jonas Friesen		Professor, Karolinska Institute	Sweden	PhD, Neuroscience	Has received - 2017 Eric K. Fernström Foundation Grand Nordic Prize	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
62	Hongjun Song		Professor, University of Pennsylvania	USA	PhD, Neuroscience	Has received - 2020 Member, National Academy of Medicine (NAM) - 2017 Jacob Javits Neuroscience Investigator Award, NIH - 2008 Young Investigator Award from the Society for Neuroscience - Rising Star Award from the International Mental Health Research Organization	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
63	Freda Miller		Associate Director, Professor, University of British Columbia	Canada	PhD, Neuroscience	Has received - Fellow, Royal Society of Canada - International Research Scholar, Howard Hughes Medical Institute - Fellow, American Association for the Advancement of Science	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
64	Arnold Kriegstein		Professor, UCSF Weill Institute for Neurosciences	USA	PhD, Neuroscience	Has received - 2017 NINDS Outstanding Investigator Award - 2011 Solomon A. Berson Medical Alumni Achievement - 2011 Javits Neuroscience Investigator Award - 2008 Member, the National Academy of Medicine - 1999 Javits Neuroscience Investigator Award	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
65	Juergen Knoblich	58	Scientific Director (interim), Professor, IMBA Full Professor for Synthetic Biology, Medical University of Vienna	Austria	PhD, Neuroscience	Has received - 2020 Member, Pontifical Academy of Sciences - 2020 Board of Directors, ISSCR - 2015 Sir Hans Krebs Medal (FEBS) - 2013 Member, Austrian Academy of Sciences - 2012 Erwin Schroedinger Prize (ÖAW) - 2012 Academia Europaea member - 2009 Wittgenstein Prize (FWF) - 2003 Early Career Award, ELSO - 2002 EMBO member - 2001 Young Investigator Award, EMBO - 2001 Anniversary Award of the Federation of the European Biochemical Societies (FEBS)	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
66	Pierre Vanderhaeghen	54	Professor, VIB-KU Leuven	Belgium	PhD, Neuroscience	Has received - 2021 Remedios Caro Almela Prize - 2020 Generet Award for Rare Diseases - 2013 AXA Foundation Distinguished Permanent Chair in Neuroscience - 2013 Solvay Prize for Neuroscience Research - 2011 Francqui Prize - 2011 Solvay Prize for Neuroscience Research - 2009 Prize of the Foundation Roger de Spoelberch - 2009 EMBO member - 2008 Pierre Clerdent Foundation Prize for Research on Brain Diseases - 2006 UCB Award for Neuroscience - 2000 Emile Defay Fund Research Award	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems

	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				
67	Karl Deisseroth	50	D.H. Chen Professor, Stanford University Professor of Bioengineering and Psychiatry, Stanford University Investigator, Howard Hughes Medical Institute	ISA	MD PhD, Neuroscience	Has received - 2021 Lasker Basic Medical Research Award - 2020 Heineken Prize - 2019 Alpert Award - 2019 Member, National Academy of Engineering - 2018 Leibinger Prize - 2018 Kyoto Prize - 2018 Rumford Prize, AAAS - 2018 Eisenberg Prize - 2018 Canada Gairdner International Award 2018 - 2017 NOMIS Foundation Distinguished Scientist Award - 2017 Else Kröner Fresenius Prize - 2017 Redelsheimer Award - 2017 Harvey Prize in Human Health - 2016 McGovern Award in Science and many more	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
68	Sebastian Jessberger		Professor, University of Zurich	Switzerland	PhD, Neuroscience	Has received - 2016 Robert Bing Prize - 2013 Friedrich Götz prize - 2012 EMBO Young Investigator	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems
69	Magdalena Götz	60	Professor, University of Munich	Germany	PhD, Stem cell biology	Has received - 2018 Schellenberg Prize of Wings for Life Foundation - 2017 Prize of the Roger de Spoelbergh Foundation - 2017 Member of the Bavarian Academy of Sciences - 2016 Roger de Spoelberch Foundation Award - 2015 German Stem Cell Network Female Scientist Award - 2015 Carl-Zeiss Award of the German Society for Cell Biology - 2014 Ernst Schering Prize - 2013 Remedios Caro Almela Prize - 2010 Federal Cross of Merit on Ribbon - 2008 Hans und Ilse Breuer Award - 2008 Member, Leopoldina Academy - 2007 Gottfried-Wilhelm Leibniz Award - 2007 Familie Hansen Award - 2006 EMBO member - 2006 Academia Europaea member	Mar 14-17, 2022	Participation as invited speaker, International Symposium on Development and Plasticity of Neural Systems

Appendix4-3 Postdoctoral Positions through Open International Solicitations

* In the column of number of applications and number of selection, put the total number (upper), the number and percentage of overseas researchers in the < > brackets (lower).

Fiscal year	number of applications	number of selection
FY 2018	0	19
	< 0, 0 %>	<5, 26%>
FY 2019	48	9
	<34, 71%>	<3, 33%>
FY 2020	48	12
	<39, 81%>	<4, 33%>
FY 2021	39	15
	< 31, 79%>	< 8, 53%>

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Appendix 4-4 Status of Employment of Postdoctoral Researchers

Enter the information below during the period from the start of the center through the end of FY 2021.

- For each person, fill in the spaces to the right. More spaces may be added.
- Leave "Position as of April 2022" blank if unknown.
- Enter the host institution name and the center name in the footer.

Japanese Postdocs

Employment period	Position before employed at WPI center		Next position after WPI center		Position as of April 2022*	
	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located
FY2018~2020	Assistant Professor, CiRA, Kyoto University	Japan	Assistant Professor, CiRA, Kyoto University	Japan	Senior Lecturer, CiRA, Kyoto University	Japan
FY2018~2020	Program Specific Assistant Professor, iCeMS, Kyoto University	Japan	Assistant Professor, CiRA, Kyoto University	Japan	General Manager, Internal Medicine, Tanaka Oushin Clinic	Japan
FY2018~2020	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan
FY2018~2019	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Assistant Professor, Department of Embryology, Nara Medical University	Japan	Assistant Professor, Department of Embryology, Nara Medical University	Japan
FY2018~2020	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Program-Specific Researcher, KUIAS, Kyoto University	Japan
FY2018~2020	Program-Specific Researcher, Graduate School of Engineering, Osaka University	Japan	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Program-Specific Researcher, KUIAS, Kyoto University	Japan
FY2018~2020	Assistant Research Staff, Graduate School of Medicine, Kyoto University	Japan	N/A, G CUBE CO., LTD.	Japan		
FY2020	Student, Graduate School of Medicine, Tokyo University	Japan	N/A	N/A		
FY2020	Program-Specific Researcher, KUIAS, Kyoto University	Japan	Program-Specific Researcher, KUIAS, Kyoto University	Japan	Program-Specific Researcher, KUIAS, Kyoto University	Japan
FY2020	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan
FY2020	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan
FY2020	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan
FY2020	Researcher (part-time), Graduate School of Medicine, Kyoto University	Japan	Postdoc, Aarhus University	Denmark	Postdoc, Aarhus University	Denmark
FY2020	Research Scientist, RIKEN Center for Biosystems Dynamics Research	Japan	Associate Professor, Department of Mathematics, Faculty of Science, Hokkaido University	Japan	Associate Professor, Department of Mathematics, Faculty of Science, Hokkaido University	Japan
FY2020	Program-Specific Researcher, inFront, Kyoto University	Japan	Assistant Professor, inFront, Kyoto University	Japan	Assistant Professor, LiMe, Kyoto University	Japan
FY2020	JSPS PD, inFront, Kyoto University	Japan	Researcher, Kyoto Prefectural University of Medicine	Japan	Researcher, Kyoto Prefectural University of Medicine	Japan
FY2020~2021	Assistant Professor, CiRA, Kyoto University	Japan	Associate Professor, Graduate School of Humanities and Social Sciences, Hiroshima University	Japan	Associate Professor, Graduate School of Humanities and Social Sciences, Hiroshima University	Japan
FY2018~2020	Researcher (part-time), Graduate School of Medicine, Kyoto University	Japan	N/A	Japan		

Employment period	Position before employed at WPI center		Next position after WPI center		Position as of April 2022*	
	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located
FY2020	Researcher (part-time), Graduate School of Medicine, Kyoto University	Japan	Program-Specific Associate Professor, The Hakubi Center for Advanced Research, Kyoto University	Japan	Program-Specific Associate Professor, The Hakubi Center for Advanced Research, Kyoto University	Japan
FY2020	Program-Specific Researcher, Pediatrics, Kyoto University Hospital	Japan	N/A	Japan		
FY2020	Researcher (part-time), Graduate School of Medicine, Kyoto University	Japan	N/A	Japan		
FY2020	Administrative Staff, Ritsumeikan University	Japan	N/A	Japan		
FY2020	Ph.d. Student, Tokyo University	Japan	Research Associate, Department of Urology, Faculty of Medicine, The University of Tokyo Hospital	Japan	Research Associate, Department of Urology, Faculty of Medicine, The University of Tokyo Hospital	Japan
FY2020	Ph.d. Student, Graduate School of Medicine, Kyoto University	Japan	Researcher (part-time), Graduate School of Medicine, Kyoto University	Japan	Researcher (part-time), Graduate School of Medicine, Kyoto University	Japan
FY2020~2021	JSPS DC1, inFront, Kyoto University	Japan	Non-Researcher, Medical Affairs, Ono Pharmaceutical Co., Ltd	Japan	Non-Researcher, Medical Affairs, Ono Pharmaceutical Co., Ltd	Japan
FY2021	Postdocotral Fellowship, IFOM the FIRC Institute of Molecular Oncology	Italy	Assistant Professor, School of Medicine, Tohoku University	Japan	Assistant Professor, School of Medicine, Tohoku University	Japan
FY2021	Junior Investigator, Research Center for Genome & Medical Sciences, Tokyo Metropolitan Institute of Medical Science	Japan	Specially Appointed Researcher, CoMIT, Osaka University	Japan	Specially Appointed Researcher, CoMIT, Osaka University	Japan

Overseas Postdocs

Employment period	Position before employed at WPI center		Next position after WPI center		Position as of April 2022*		Nationality
	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located	Position title, organization	Country where the organization is located	
FY2018~2020	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan	Assistant Professor, Graduate School of Medicine, Kyoto University	Japan	USA
FY2018~2020	Program-Specific Researcher, Graduate School of Medicine, Kyoto University	Japan	Visiting Researcher, School of Natural Sciences and Health, Tallinn University	Estonia	Staff Scientist, National Institute of Mental Health	USA	Estonia
FY2018~2021	Program Specific Assistant Professor , Graduate School of Medicine, Kyoto University	Japan	Researcher (part-time), ASHBi, Kyoto University	Japan	Researcher (part-time), ASHBi, Kyoto University	Japan	China
FY2020	Researcher and Project Co-leader, Shenzhen Digital Life Institute, iCarbonX	China	Field Application Specialist, Bio-Techne China	China			China
FY2021	Ph.d. Student, Graduate School of Biomedical Sciences, Tokushima university	Japan	Reseracher, Graduate School of Medicine, Kobe University	Japan	Reseracher, Graduate School of Medicine, Kobe University	Japan	Bangladesh

Appendix4-5　List of the Cooperative Research Agreements with Overseas Institutions

*Prepare the information below during the period from the beginning of the Center through March 2022.

N/A

Appendix4-6 Holding International Research Meetings

* Indicate up to two of most representative international research conferences or symposiums each financial year and give the number of participants using the table below.

FY2018-FY2019: 3 meetings

Date	Meeting title and Place held	Number of participants
Mar 11 2019	ASHBi Kickoff Symposium at Shirankaikan, Kyoto University	From domestic institutions: 146 From overseas institutions: 5
23 Aug 2019	1st ASHBi Mathematical Workshop at Seminar room, 2F, KUIAS main building, Kyoto University	From domestic institutions: 76 From overseas institutions: 2

FY2020: 0 meetings*

Date	Meeting title and Place held	Number of participants
Nov 9-11 2020	POSTPONED to 26-29 Apr 2022 EMBO Workshop (co-organized by ASHBi) "Molecular mechanisms of developmental and regenerative biology"	Invited speakers: *original* From domestic institutions: *5* From overseas institutions: 19
Mar 8-11 2021	POSTONED to 14-17 Mar 2022 The International Symposium on Development and Plasticity of Neural Systems (co-organized by ASHBi)	Invited speakers: *original* From domestic institutions: *22* From overseas institutions: *18*

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

FY2021: 4 meetings

Date	Meeting title and Place held	Number of participants
Nov 8-10 2021	ASHBi Symposium 2021 "Human Development, Genetics and Evolution" (online)	From domestic institutions: 201 From overseas institutions: 78
Mar 14-17 2022	The International Symposium on Development and Plasticity of Neural Systems (online)	From domestic institutions: 306 From overseas institutions: 173

Appendix 5 List of Achievements of Center's Outreach Activities between FY 2018 – 2021

* Using the table below, show the achievements of the Center's outreach activities from FY2018 through FY2021 (number of activities, times held).
*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 below, 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

Activities	FY2018 (number of activities, times held)	FY2019	FY2020	FY2021
PR brochure, pamphlet	5	6	2	4
Lectures, seminars for the general public	1	2	1	1
Teaching, experiments, training for elementary, secondary and high school students	N/A	N/A	N/A	2
Participating, exhibiting in events	N/A	2	3	2
Press releases	7	9	13	19
Publications of the popular science books	N/A	N/A	N/A	1
Others (Flyers)	1	27	33	42
Others (Website development)	1	1	1	2
Others (Social media open)	N/A	N/A	3	1
Others (Multimedia)	N/A	N/A	2	N/A
Others (Outreach events to industry)	N/A	N/A	N/A	3
Others (Major visit to ASHBi)	N/A	3	1	N/A
Others (TV programs)	N/A	N/A	N/A	3

Appendix 5 List of Media Coverage of Projects Carried out between FY 2018 – 2021

* Select main items of press releases, media coverage, and reports for FY 2018-2021 (especially by overseas media)

1) Japan

No.	Date	Type of the media (e.g., newspaper, magazine, television)	Description
1	Sep. 21, 2018	newspaper 8	[Asahi Shimbun Sep.21, The Kyoto Shimbun Sep.21, Sankei Shimbun Sep.21, Chunichi Simbun Sep.21, Nihon Keizai Shimbun Sep.21, Nikkann Kogyo Simbun Sep.21, Mainichi Shimbun Sep.21, Yomiuri Shimbun Sep.21] - Introduction of the recent research result published in *Science* by Prof. Saitou
2	Nov. 22, 2018	newspaper 2	[Nikkan Kogyo Shimbun Nov.22, Mainichi Shinbun Nov.23] - Introduction of the research result published in *Science Advances* by Prof. Eiraku
3	Jan. 3, 2019	newspaper 6	[Asahi Shimbun Jan.3, The Kyoto Shimbun Jan.3, Sankei Shimbun Jan.3, Nihon Keizai Shimbun Jan.3, Mainichi Shimbun Jan.6, Yomiuri Shimbun Jan.7] - Introduction of the research result published in *Nature* by Prof. S. Ogawa
4	Jan. 22, 2019	newspaper 2	[Yomiuri Shimbun Jan.22, The Kyoto Shimbun Jan.25] - Introduction of the research result published in *Kidney International* by Prof. Yanagita
5	Mar. 11, 2019	television 1	[NHK Kyoto] ASHBi Kickoff Symposium at Kyoto University.
6	Mar. 12, 2019	newspaper 1	[The Kyoto Shimbun] Establishment of new institute(ASHBi) at Kyoto University and its research goals.
7	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 ("Bioartificial islet transplantation," a curative treatment for type 1 diabetes, comes into sight - Regulations on “animal assembly embryo" research eased significantly in Japan; Center for iPS Cell Research and Application, Kyoto University) - Introduction of the recent research result published in *Cell Stem Cell* by Fujita Group

8	16 Sep 2019	newspaper 1	[Nikkan Kogyo Shimbun] - Introduction of the research result published in *Journal of Neuroscience* by Isa Group
9	28 Oct 2019	newspaper 1	[NIKKEI] - Introduction of the research result published in *Cell Reports* by Yamamoto Group
10	20 Dec 2019	newspaper 1	[The Kyoto Shimbun] - Introduction of the research result published in *Nature* by Ogawa Group
11	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 (Colonic epithelium affected with ulcerative colitis found to harbor carcinogenic inhibitory mutations in the IL-17 pathway - Kyoto University) - Introduction of the research result published in *Nature* by Ogawa Group
12	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 (Genes mutate three times faster than normal - Intractable intestinal disease and carcinogenesis relationship) - Introduction of the research result published in *Nature* by Ogawa Group
13	01 Jan 2020	newspaper 1	[Asahi Shimbun] - Introduction of the Asahi Prize for Prof. Saitou
14	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
15	08 Jan 2020	jounal 1	[Nature Highlight] 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 (Genetics: clonal selection patterns in normal and inflammation-associated tumor tissues) - Introduction of the research result published in *Nature* by Ogawa Group
16	24 Jan 2020	newspaper 1	[Yomiuri Shimbun Jan. 24] - Introduction of the recent research result published in *Nature* Communications by Ema Group

17	24 Jan 2020	newspaper 1	[Yomiuri Shimbun] - Introduction of the recent research result published in *Nature Communications* by Ema Group
18	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―京大 (Elucidating How Oogenesis Begins in Mouse Germ Cells -Kyoto University) - Introduction of the research result published in *Science* by Saitou Group
19	14 Feb 2020	television 1	[NHK Kyoto] - Introduction of the research result published in *Science* by Saitou Group
20	14 Feb 2020	news website 1	[The Kyoto Shimbun] - Introduction of the research result published in *Science* by Saitou Group
21	16 Feb 2020	news website 1	[NIKKEI] 卵母細胞への成長、詳細な仕組み解明 (Elucidating the detailed mechanism of growth into oocytes) - Introduction of the research result published in *Science* by Saitou Group
22	16 Feb 2020	news website 1	[医療NEWS (Medical News)] 世界初、生殖細胞が卵母細胞に分化する仕組みを解明－京大 (World's first clarification of how germ cells differentiate into oocytes - Kyoto University) - Introduction of the research result published in *Science* by Saitou Group
23	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
24	02 Apr 2020	newspaper 2	[Nikkan Kogyo Shimbun Apr.2, NIKKEI Apr. 6] - Introduction of the research result published in *Nature* by Alev Group

25	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
26	20 May 2020	newspaper 2	[Nikkan Kogyo Shimbun May.29, Kyoto Shimbun Jun.3] - Introduction of the research result published in *Kidney International* by Yanagita Group
27	13 Oct 2020	newspaper 1	[Nikkan Kogyo Shimbun Nov.23] - Introduction of the research result published in *Journal of the American Society of Nephrology* by Yanagita Group
28	20 Jan 2021	news website 1	[Business Insider Japan Jan.20] - Interview article with Mitinori Saitou
29	23 Jan 2021	newspaper 1	[Kyoto Shimbun] - Introduction of Assis. Prof. Sawai (Fujita Group)
30	21 Mar 2021	television 1, newspaper 2	[Asahi Shimbun Mar. 18, NHK Mar.21] - Comments for the research papers on Nature about iPS cell by Prof. Saitou. [Yomiuri Shimbun Mar.21] Comment for same papers by Assist. Prof. Sawai
31	16 Apr 2021	newspaper 1	[Yomiuri Shimbun] - Comments for a paper about growth of chimeric embryos of Assis. Prof. Sawai (Fujita Group)
32	17 Jun 2021	news website 1	[Techplus] - Introduction of the recent research result published in Cancer Cell by Ogawa Group
33	22 Jun 2021	newspaper 1	[Asahi Shimbun] - Comments for revision of the 14-days-rule of Prof. Saitou
34	07 Jul 2021	newspaper 1	[Yomiuri Shimbun] - Introduction of the recent research result published in PLoS Medicine by Prof. Iwami

35	26 Aug 2021	newspaper 1	[Mainichi Shimbun] - Introduction of the recent research result published in PLoS Medicine by Prof. Iwami
36	09 Sep 2021	newspaper 14	[Kyoto Shimbun, Asahi Shimbun, Mainichi Shimbun, Yomiuri Shimbun, Nikkan Kogyo Shimbun, Kyodo Tsushin, Jiji Tsushin, Tokyo Shimbun, Kumamoto Nichinichi Shimbun, Kochi Shimbun, Saga Shimbun, Kobe Shimbun, To'o Nippou, Ehime Shimbun] - Introduction of the recent research result published in Cell Stem Cell by Saitou Group
37	09 Sep 2021	television 3	[NHK, Kanasai TV, ABC] - Introduction of the recent research result published in Cell Stem Cell by Saitou Group
38	16 Sep 2021	newspaper 1	[Mainichi Shimbun] - Introduction of the recent research result published in Blood Cancer Discovery by Ogawa Group
39	16 Sep 2021	newspaper 1	[Nihon Keizai Shimbun] - Introduction of Prof. Yanagita and HAKUBI Project of Kyoto University
40	28 Oct 2021	newspaper 1	[Asahi Shimbun] - Introduction of the recent research result published in eLife by Prof. Iwami
41	29 Oct 2021	television 1	[TV Asahi] - Introduction of the research activities of Prof. Ueno
42	02 Nov 2021	newspaper 1	[Kyoto Shimbun] - Introduction of the recent research result published in Journal of the American Society of Nephrology by Yanagita Group
43	10 Nov 2021	news website 1	[Nikkei Biotech] - Introduction of the recent research result published in Journal of the American Society of Nephrology by Yanagita Group
44	22 Nov 2021	newspaper 1	[Mainichi Shimbun] - Comments for after effect of COVID-19 by Prof. Ueno
45	26 Nov 2021	newspaper 1	[Kyoto Shimbun] - Introduction of the recent research result published in Journal of Clinical Investigation by Yanagita Group
46	06 Dec 2021	newspaper 1	[Chubu Keizai Shimbun] Introduction of the research activities of Prof. Murakawa
47	24 Dec 2021	news website 1	[Nikkei Business] - Introduction of Seishi Ogawa's research activities
48	06 Jan 2022	newspaper 2	[Kyoto Shimbun, Kyodo Tsushin] - Comment for a paper of Oxford University by Assist. Prof. Sawai (Fujita Group)
49	18 Mar 2022	news website 1	[Yomi Doctor] - Interview with Prof. Yanagita

2) Overseas

No.	Date	Type of the media (e.g., newspaper, magazine, television)	,
1	Sep. 20, 2018	news website 1	[Washington Post] "The 'game-changing' technique to create babies from skin cells just stepped forward" - Introduction of the recent research result published in Science by Prof. Saitou
2	Sep. 21, 2018	news website 1	[Chincago Tribune] "'Game-changing' technique to create babies from regular cells just stepped forward" - Introduction of the recent research result published in Science by Prof. Saitou
3	Sep. 24, 2018	news website 1	[Smithsonian.com] "'Scientists Create Immature Human Eggs Out of Blood Cells For the First Time" - Introduction of the recent research result published in Science by Prof. Saitou
4	Oct. 14, 2018	news website 1	[The Guardian] "Reproduction revolution: how our skin cells might be turned into sperm and eggs" - Introduction of the recent research result published in *Science* by Prof. Saitou
5	Nov. 21, 2018	news website 1	[Phys.org] "Team uncovers the underlying mechanisms of 3-D tissue formation" - Introduction of the research result published in *Science Advances* by Prof. Eiraku
6	Nov. 23, 2018	news website 1	[Cell Science] "Cellular Mechanosensing Key for 3D Formation" - Introduction of the research result published in *Science Advances* by Prof. Eiraku
7	Jan. 2, 2019	news website 1	[genomeweb]"Cancer Driver Gene Mutations Rise with Age in Otherwise Normal Esophageal Tissue" - Introduction of the research result published in *Nature* by Prof. S. Ogawa
8	Jan. 30, 2019	news website 1	[One Zero by Medium] "Inside the Experiment That Could End Infertility" - Interview of Prof. Saitou and an introduction of a new technology to create egg and sperm cells from iPS cells published in *Science* .
9	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

10	26 Jun 2019	jounal 1	[Science] Embryo experiments take ‘baby steps’ toward growing human organs in livestock - Introduction of her comment by Prof. Fujita
11	28 Jun 2019	jounal 1	[Science] Taking ‘baby steps’ to human organs in livestock - Introduction of her comment by Prof. Fujita
12	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
13	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 ([Sciencenet.cn - news writing robot] Study reveals frequent mutations in NFKBIZ pathway in ulcerative colitis) - Introduction of the recent research result published in *Nature* by Ogawa Group
14	14 Jan 2020	news website 1	[News Break] - Introduction of ISSCR Momentum Award for Prof. Saitou
15	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
16	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 ([Sciencenet.cn - news writing robot] ZGLP1 is a determinant of oogenic fate in mice) - Introduction of the recent research result published in *Science* by Ogawa Group
17	01 Jun 2020	news website 2	[Scienmag Jun.1, 7th Space Jun.2] - Introduction of ISSCR Momentum Award Lecture by Porf. Saitou
18	Apr. 8-11, 2021	news website 18	[MadicalXpress, Infosurhoy, Sacience Daily, Sciencemag, New York Post, India Times Post, The Medical News, RT Arabic, Techgnology Networks, ABC.es, La Vos Degital, ABC Desevilla, Bioedge.org, Newsfeeds.Media, WhatsNew2Day, Techregister, Nachrichten Welt, ExpressDigest] - Introduction of the recent research result published in AJOB Neuroscience by Assis. Prof. Sawai (Fujita Group)

19	May. 26, 2021	newspaper 2	[El Mundo, La Repubblica] - Introduction of the recent research result published in AJOB Neuroscience by Assis. Prof. Sawai (Fujita Group)
20	May. 1, 2021	television 1	[BBC] - Introduction of the recent research result published in AJOB Neuroscience by Assis. Prof. Sawai (Fujita Group)
21	Feb. 21, 2022	magazine 1	[Science & Vie] - Introduction of the recent research result published in AJOB Neuroscience by Assis. Prof. Sawai (Fujita Group)
22	Apr. 8, 2021	blog 1	[TekCrispy] - Introduction of the recent research result published in AJOB Neuroscience by Assis. Prof. Sawai (Fujita Group)
23	Jul. 5-12, 2021	news website 18	[The Medical News, Doc Wire News, MedicalXpress, Scitech daily, UPI.com, Mirage News, Bioengineer.org, Science Mag, Daily Mail, NewsyPeople, The Amed Post, MSN, Technology Networks, American Council on Science and Health, Newsbreak, Ebiotrade] - Introduction of the recent research result published in Plos Medicine by Prof. Iwami
24	Jul. 7, 2021	blog 1	[Science Blog] - Introduction of the recent research result published in Plos Medicine by Prof. Iwami
25	Jul 29, Sep 16, Sep 19, 2021	news website 3	[Pourquoi Docteur, MedicalXpress, Science Daily] - Introduction of the recent research result published in Frontiers in Neuroscience by Amemori Group
26	Aug. 2, 2021	blog 1	[Psychology Today] - Introduction of the recent research result published in Frontiers in Neuroscience by Amemori Group
27	Sep 7, 16, 2021	news website 2	[Phys. org, Science Mag] - Introduction of the recent research result published in EMBO Reports by Assis. Prof. Sawai (Fujita Group)
28	Sep. 7, 2021	news website 2	[MedicalXpress, Mirage News] - Introduction of the recent research result published in Cell Stem Cell by Saitou Group
29	Sep 14, 16, 2021	news website 2	[MedicalXpress, Science Mag] - Introduction of the recent research result published in Scientific Reports by Isa Group
30	Oct 11, 15, 2021	news website 3	[Newsbreak, MedicalXpress, Mycom] - Introduction of the recent research result published in Science Advances by Ueno Group

31	Nov. 15, 2021	news website 1	[MedicalXpress] - Introduction of the recent research result published in Journal of the American Society of Nephrology by Yanagita Group
32	Apr. 1, 2022	blog 1	[Physician's Weekly] - Introduction of the recent research result published in Journal of the American Society of Nephrology by Yanagita Group
33	Dec 7-8, 2021	news website 4	[Science Mag, Bioengineer.org, MedicalXpress, The Medical News] - Introduction of the recent research result published in Journal of Clinical Investigation by Yanagita Group
34	Mar. 11, 2022	news website 1	[Phys.org] - Introduction of the recent research result published in Developmental Cell by Hiiragi Group
35	Feb 18-19, Apr 12, 2022	news website 4	[MedicalXpress, Today UK News, Newswise, Science Mag] - Introduction of the recent research result published in Neuroethics by Assis. Prof. Sawai (Fujita Group)
36	Feb 19, Apr 12, 2022	blog 2	[Bruce's blog, Science blog.com] - Introduction of the recent research result published in Neuroethics by Assis. Prof. Sawai (Fujita Group)
37	Mar. 25, 2022	news website 3	[GEN, Phys.org, Nouvelles du monde] - Introduction of the recent research result published in Nature Communications by Assoc. Prof. Inoue (Brouque Group)

Appendix6-1 Host Institution's Commitment (Fund, Personnel)

1. Contributions from host institution

(1) Fund, Personnel

* Regarding "Fund" entry, describe with reference to the items in the Progress Report (Jisseki-hokoku-sho) based on Article 12 of the Grant Guidelines (Kofu-yoko).

* Don't include competitive funding obtained by researchers (used as research project funding)

(FY 2018-2021)

<Fund> **(million yen)**

Fiscal Year	2018	2019	2020	2021
Personnel	43	145	167	191
Faculty members				
Full-time	29	82	98	103
Concurrent	3	11	9	29
Postdocs				
RA etc.				
Research support staffs	4	13	14	13
Administrative staffs				
Full-time	7	39	37	36
Concurrent			9	10
Project activities	9	61	66	77
Travel	0	2	0	2
Equipment	60	97	44	126
Research projects				
Total	112	305	277	396

<Personnel> **(person)**

Fiscal Year	2018	2019	2020	2021
Personnel	21	27	32	34
Faculty members				
Full-time	7	9	10	10
Concurrent	1	3	4	7
Postdocs				
RA etc.				
Research support staffs	1	1	2	1
Administrative staffs				
Full-time	12	14	14	14
Concurrent			2	2

Appendix6-1 Host Institution's Commitment

1. Contributions from host institution

(2) Provision of land and/or building(s), lab space, etc.

KU has provided two tenured faculty positions to ASHBi, and we have hired Yasuhiro Murakawa in October 2020 and Sungrim Seirin-Lee in November 2021 as tenured professors. KU allows ASHBi to take the headquarters' dividend, which is half of the total of the indirect funds from competitive grants acquired by ASHBi researchers. With this financial support, ASHBi was able to acquire approximately 148 million yen as indirect funds in FY2021. In addition, KU provided a special budget (approx. 100 million yen) to purchase a new 3rd-generation long-read sequencer (PacBio IIe) in FY2021.

Indirect fund support and Multiple-Year Budgeting for Indirect Funds

KU allocates half of the indirect funds associated with external funding to the departments and the other half to the university headquarters. For indirect funds acquired by PIs/researchers affiliated with ASHBi, the portion of university headquarters is allocated to ASHBi as university support.

In addition, KU allows ASHBi to introduce a multi-year budget for indirect funds. As a benefit, the Institute has been able to carry over indirect costs to the next fiscal year (maximum carryover amount is 40 million yen). This greatly increases the flexibility of ASHBi's budget planning.

Provision of land and/or building(s), lab space, etc.

Kyoto University has provided ASHBi with a building in the medical campus (Medical Campus Building B, ASHBi Main Building) to serve not only as a housing of overseas and early career PIs, but also as an interaction hub for the KU Graduate School of Medicine and KU Hospital.

The first floor of the 2,010 m^2 space provided to ASHBi houses facilities and organizations that play a central role in the interaction of researchers within/outside ASHBi: the SignAC core facility, offices of mathematics and bioethics for interdisciplinary studies, a lounge, seminar room, the Director's room, the Administrative Director's room, and the administrative office. The lounge functions as a place with its relaxing atmosphere, has become an ideal spot to gather and discuss for ASHBi members across research disciplines, not only to serve as a resting place. The second and third floors consist of labs and office space for overseas PIs and early-career PIs. These areas have been designed to have a shared style in order to maximize the efficient use of resources and maximize interactions among the PI groups.

2. System under which the center's director is able to make substantive personnel and budget allocation decisions

In April 2016, KU created a new organizational structure called the Kyoto University Institute for Advanced Study (KUIAS), which has been organized as an international research hub hosting the WPI centers as its core components. KUIAS is designated with special privileges and therefore has a high degree of autonomy. Under the KUIAS's umbrella, the directors of the respective WPIs can exercise strong leadership and implement better top-down management.

The Institute director has the authority to make the final decision on important matters concerning the operations at the Institute. The Executive Board consists of director **Saitou**, vice directors **Isa** and **Hiraoka**, SignAC core head **Yamamoto**, and administrative director **T Ogawa**. Executive board meetings are regularly held twice a month (it was once a week until March 2019). The Executive Board meetings discuss and make decisions with regards to the research direction of the Institute, personnel affairs, budgetary concerns, as well as proposals and requests made by the ASHBi PIs and its members.

The PI board, consisting of all 18 PIs of the Institute, one co-PI (**Inoue**), and the administrative director, meets monthly to deliberate the matters proposed by the Executive Board and make concrete decisions and action plans and share various information concerning the Institute.

3. Support for the center director in coordinating with other departments at host

institution when recruiting researchers, while giving reasonable regard to the educational and research activities of those departments

Collaboration with the KU graduate school of medicine
Starting from FY2020, ASHBi has been collaborated with the KU Graduate School of Medicine to co-host the "Developmental Biology/Cell Biology/Systems Biology Course". The course offers cross-disciplinary discussions and is held as a monthly seminar that includes two lectures: one by a young researcher (30 min) and the other by an invited researcher (1 hour). In FY2020, 3 ASHBi PIs: **Alev**, **Hiraoka**, and **R Yamamoto** hosted the seminar; in FY2021, **Amemori**, **Murakawa**, and **Seirin-Lee** hosted the seminar. This collaboration with the Graduate School of Medicine gives the Institute an opportunity to approach and recruit more graduate students from KU.

Joint PhD program between KU and McGill University
The joint PhD program, "Kyoto-McGill International Collaborative Program in Genomic Medicine" was established in October 2018 between the KU Graduate School of Medicine and McGill University. The ASHBi PI **Bourque** is one of the main organizers at McGill University. By utilizing this program, ASHBi has so far accepted three foreign students (May 2019 – July 2020, November 2020 – October 2021, and November 2021 – present).

4. Revamping host institution's internal systems to allow introducing of new management methods
(e.g., English-language environment, merit-based pay, cross appointment, top-down decision making unfettered by conventional modes of operation)

SignAC as a good practice model for a university-wide core facility
As a successful model of a core facility, SignAC is expected to play a central role in the university-wide core facility concept envisioned in KU's future plan. The unique feature of SignAC is that this core facility is constantly updating its analytical technology by having its own research staff (Tsujimura and one postdoc). This gives SignAC a strong competitive edge compared with other core facilities. KU appreciates this competitive edge and plans to use SignAC as a good practice to develop university-wide core facilities.

Furthermore, in December 2020, SignAC joined the **"Innovative Support Alliance for Life Science (iSAL)"** at KU, a unified platform of core facilities from various departments related to life science studies. Using the online management system of iSAL for equipment reservation and payment, SignAC now provides smooth access to its facilities even for researchers outside of ASHBi. Starting in May 2022, five instruments and DNA/RNA sequencing analysis services will be made available to researchers inside and outside the University through iSAL. Thus, an increasing number of researchers will be able to utilize the SignAC facility.

ASHBi administrative office
The administrative office, also known as the **"ASHBi Office"**, provides the administrative support of the ASHBi. The Office consists of the **"Administrative Management Unit"** and the **"Research Acceleration Unit"**, and is managed by the administrative director **T Ogawa**. While the former unit is responsible for regular operation (e.g. general affairs, personnel, and accounting services), the latter unit is responsible for flexible and problem-solving type support. For example, the Research Acceleration Unit provides support for planning the Institute's events (e.g. international symposium and retreat), creating a support program to address an institute-wide issue (e.g. internationalization of the Institute's researchers), and promoting the foreign researcher activities. In addition, this unit organizes seminars to foster young researchers.

To fulfill the above roles, the Unit has hired four experts. **Spyros Goulas** is a former scientific editor at Cell Press (Journal Name: Developmental Cell) and is expected to support the Institute's members (especially young researchers) to develop and improve their abilities in writing their research papers. **Tomoki Shimizu** is appointed as the public relations manager and is responsible for increasing the Institute's visibility through international news releases. **Makoto Shida** is hired as an industry-academia collaboration manager and is also responsible for strengthening the ability to obtain grants. **Hiromi Inoue** has five years of experience as a lab manager specializing in life sciences at UCSF. She utilizes this experience to support the Institute's management. She is also responsible for strengthening

the visualization of research results.

Research Acceleration Programs for fostering foreign/early-career researchers
As mentioned earlier, the Research Acceleration Unit actively organizes seminars in English for foreign/early-career researchers to help them acquire the necessary knowledge and skills for their research activities.

For example, in FY2022, **Goulas** will hold a series of seminars on scientific paper writing and how to publish papers. Early-career researchers tend to have difficulties in developing their research stories in their papers. The seminar will be designed to develop their ability for allowing editors and reviewers to better understand their research story and their significance. In addition, **Shida** has held seminars on how to write effective grant proposals. Some application guidelines for Japanese research grants (such as KAKENHI) and doctoral fellowships (such as JSPS DC1 and DC2 fellowships) are not available in English. Therefore, he has translated the useful information into English and convey it to the participants in his seminars.

These seminars are open to universities and research institutions throughout Japan. The four seminars held over the past year have been attracted 502-878 registrants from 40-51 institutions.

Effective Support for foreign researchers by the ASHBi Office
ASHBi provides support for foreign researchers and their families in obtaining visas and entering Japan, in close cooperation with the overseas research support staff at KUIAS. The Institute assist them in obtaining and applying for the necessary documents at the Japanese Embassy. ASHBi's English-speaking secretary in charge of foreign PIs and foreign researchers also provides assistance in finding housing, opening bank accounts, applying for tax credits, and so on.

When a foreign researcher is hired as an overseas PI at the ASHBi, the Institute provides 30 million yen to cover the start-up costs for two years and 22.5 million yen per year for personnel costs to hire his/her team members. We also provide 270 m2 of office space and 530 m2 of lab space, shared by two overseas PIs and 4 early-career PIs.

When setting up a new laboratory, it is necessary to purchase supplies and hire laboratory members. However, the complicated administrative procedures of Japanese universities can be an obstacle for foreign researchers. Therefore, ASHBi has prepared an illustrated manual in English that explains basic administrative procedures such as hiring and purchasing equipment in an easy-to-understand manner. ASHBi has also established a consultation platform operated by ASHBI's URA and English-speaking secretary. When a foreign PI/researcher faces a problem, the URA discusses it with the foreign PI/researcher and consults with the relevant department to find a solution. The URA shares the solution with the secretary so that the next time the same problem arises, the secretary can handle it himself/herself.

5. Utilities and other infrastructure support provided by host institution

(*In addition to those listed in the item 1. "Contributions from host institution")

Support by the Graduate School of Medicine on animal facility etc.
For ASHBi's overseas and early career PI groups to effectively start research at ASHBi, Graduate School of Medicine, in collaboration with KUIAS, has allocated some space in the animal facility for ASHBi. This has allowed ASHBi researchers to conduct necessary animal experiments without establishing an independent animal facility of its own. Furthermore, ASHBi is allowed to use the regulatory approval process for animal experiments as well as the ethical approval process for use of hESCs, human samples and human gene analyses provided by the Graduate School of Medicine. These support has greatly lifted the burdens to pursue human biology research at ASHBi.

6. Support for other types of assistance

Collaboration with KURA on individual grant writing support
In addition to the Research Acceleration Programs, **Shida** has been working closely together with KURA, KU's URA office, to provide individual support to ASHBi's early career PIs and researchers. By combining KURA's abundant supporting experience and **Shida**'s close relationship with the ASHBi researchers, the

researchers have been able to utilize the support in successfully obtaining external funding such as JSPS's Grants-in-aid for Scientific Research type S, C, Wakate and JST's Fusion Oriented Research for disruptive Science and Technology.

Appendix6-2 The Host Institution's Mid-term Plan

* Excerpt the places in the host institution's "Mid-term objectives" and/or "Mid-term plan" that clearly show the positioning of the WPI center within its organization.

Overview of Medium-Term Goals and Plans

Medium-Term Goals	Medium-Term Plans
2. Goals Related to Research	2. Measures for Achieving the Goals Related to Research
(1) Goals Related to Research Standards and Results	(1) Measures for Achieving the Goals Related to Research Standards and Results [21] The university will establish the Kyoto University Institute for Advanced Study (KUIAS) as a leading international research hub. KUIAS will be organized around a world-leading research institute established under the World Premier International Research Center (WPI) initiative. The university will provide support for international research institutes, including efforts to strengthen the research system and expand the scope of iPS cell research.
(3) Goals Related to the Internationalization of Research	(3) Measures for Achieving the Goals Related to the Internationalization of Research [29] The university will establish and develop KUIAS and other world-class research institutes through flexible management and through organizational structures and research support functions that facilitate internationalization.