February 2023

Summary of Research Center Project

* Compile in English withinA4 2 pages.

Center name: Institute for the Advanced Study of Human Biology

Host institution: Kyoto University

Head of host institution: Nagahiro Minato, President

Center director: Mitinori Saitou, Professor, Institute for Advanced Study

Administrative director: Tadashi Ogawa, Program-Specific Professor, Institute for Advanced Study

1) Overall Framework of the Center Project

The **Institute for the Advanced Study of Human Biology** will investigate the core concepts of human biology, including disease states, using multidisciplinary integrative strategies, and create a basis for developing innovative therapeutic opportunities. As of April 2023, the Institute will consist of 16 principal investigators (PIs): 13 PIs investigating key individual themes in human biology with a central focus on genome regulation/evolution and disease modeling, 3 PIs that will respectively direct essential interdisciplinary science between life sciences and mathematics (2 PIs) and between life sciences and humanities (1 PI), and 3 core head/supervisors organizing research development cores for cutting-edge single-cell genome information analysis, primate genome editing, and non-human primate phenotype analysis, respectively. The Institute will recruit a few additional PIs to accelerate its mission. The Institute will establish a link with international institutions such as the EMBL, McGill University, and Karolinska Institute, creating a stratified organization for research promotion and strengthening its international profile. Thus, the Institute will be at the forefront of the advanced study of human biology as well as life sciences for the coming decades and provide a foundation for medical innovations.

2) Content of Research

The Institute will target humans and non-human primates as major research subjects in an effort to elucidate the core concepts of human biology and disease states, through a multi-disciplinary science approach. The key goals are: 1) to achieve outstanding research in key individual themes in human biology in the area of reproduction, development, growth and aging as well as heredity and evolution; 2) to clarify the principles defining species differences and human traits; 3) to generate primate models for key gene functions and intractable diseases, particularly those affecting the central nervous system and kidney; 4) to reconstitute key human cell lineages and tissues *in vitro* and validate their properties based on integrative information; and 5) to contribute to establishing an ethical framework for conducting human biology research and create a philosophy to direct the values of the Institute's research outcomes.

3) Interdisciplinary Research

The Institute will establish two lines of interdisciplinary science that are highly integral to its mission and goals. First, the Institute will promote fusion between the life sciences and mathematics, such as topological data analysis and machine learning. The Institute will develop novel mathematical approaches to analyze multi-hierarchical large-scale omics data for gene expression, genome sequence and structure, and epigenetic profiles as well as high-content imaging data, in addition to performing comparative analyses of relevant biological contexts in humans and other key species, thereby elucidating the principles defining species differences and key human traits. Second, by integrating life sciences with the humanities,

the Institute will contribute to the creation of a world-standard bioethics for promoting human biology research and create a natural philosophy regarding the values of its key research outcomes (e.g., artificial gametes/cerebral cortexes, genome-edited monkeys).

4) International Research Environment

To promote the internationalization of the Institute, we will continue our efforts to recruit non-Japanese PIs from overseas. To do so, the Institute will assign non-Japanese PIs from the researcher pool of the University's next-generation researcher fostering projects (HAKUBI Project), which recruits promising talents from around the world. In addition, we will utilize the "ASHBi Foreign and Female Researcher Recruitment Support Program" to increase the ratio of non-Japanese and/or female researchers. Furthermore, we will also make efforts to recruit international graduate students utilizing both the "McGill-Kyoto International Collaborative Program" and the "ASHBi Financial Support Program for International Graduate Students". After recruitment, the Institute's administrative organization will provide practical support in resolving the problems associated with research to the non-Japanese/early-career researchers.

To enhance the international research exchange opportunities, we will pursue institutional collaborations with prominent international institutions, as well as organize international symposia, workshops, and seminars, inviting world-leading researchers.

5) Center Management and System Reform

The Director has the authority to make the final decision on key issues of the Institute through discussions with the Executive Board consisting of the director, two vice directors, a head of the Institute's core facility, and an administrative director. The institutional decisions are shared with the PI board comprising 16 PIs 1 co-PI, and the administrative director, to implement action plans for the Institute. The Administrative Office, managed by the Administrative Director, consists of the Administrative Management Unit and the Research Acceleration Unit. While the former is responsible for regular operation, the latter is unique and responsible for its flexible and problem-solving type support by unique experts. To maintain its competitive edge, the Institute has established three core facilities: the Single-cell Genome Information Analysis Core (SignAC), the Primate Genome Engineering Core (PRiME), and the Non-human Primate Phenotype Analysis Facility (NPAF). They are managed by a core head/supervisor and operated by expert researchers and skilled technicians.

KU will provide sufficient support for the Institute's sustainability after the WPI program. First, KU will provide 5 tenure positions by April 2024 (two were already provided by the end of 2021). Second, KU will make SignAC a university-wide shared facility and take responsibility of its personnel and operating costs. Third, the portion of indirect funding allocated to the university headquarters' will be allocated to the Institute as university support.

February 2023

Research Center Project

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Center name: Institute for the Advanced Study of Human Biology

Host institution: Kyoto University

Head of host institution: Nagahiro Minato, President

Prospective center director: Mitinori Saitou, Professor, Institute for Advanced Study

Prospective administrative director: Tadashi Ogawa, Program-Specific Professor, Institute for Advanced Study

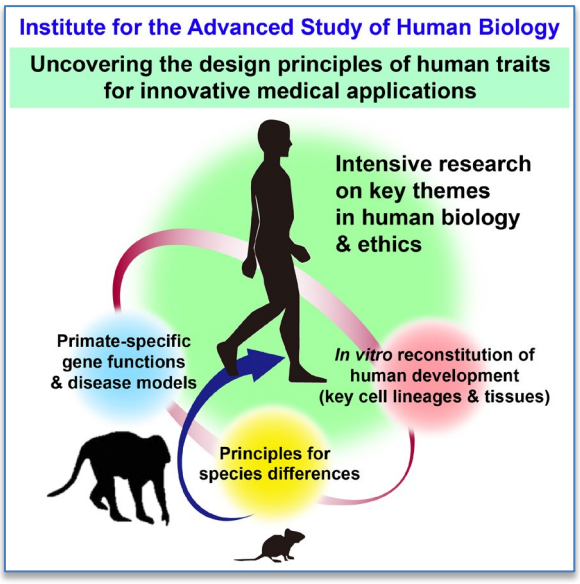
1) Overall Framework of the Center Project

* Cleary and concisely describe your center's mission statement as a WPI center, its identity, and its goals toward achieving the objectives of the WPI program.

The mission of the **Institute for the Advanced Study of Human Biology** is to investigate the core concepts of human biology, including disease states, using multidisciplinary integrative strategies, and create a foundation of knowledge for developing innovative therapies (Figure: page 1).

The goals of the Institute are:

1) to promote the study of human biology, with a focus on genome regulation.
2) to clarify the principles defining 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*.
5) to contribute to formalizing an international ethics standard for human biology research.



To realize these goals, the Institute will create and promote the advanced study for "human biology", in order to be at the forefront of life science in the coming decades. Although recent advances in genome science have allowed successive identifications of gene mutations responsible for many diseases, a benchmark strategy for exploring human gene functions has been lacking. By creating an advanced study of human biology, this will provide the necessary foundation for the future development of innovative medical interventions.

Despite the obvious importance and urgent need, due to technical/ethical difficulties, there are as of yet no scientific institutes among the world's leading countries that is primarily focused on human biology. Therefore, the Institute for the Advanced Study of Human Biology will assume a distinguished identity and play a leading role in fundamental research in human biology and its applications worldwide.

2) Content of Research

2) -1 Research fields

* Write in your target research field(s)
* Describe the importance of the target research field(s), including the domestic and international R&D trends in that research domain and neighboring field(s), and describe the scientific and/or social significance of the field(s).
* Describe the value of carrying out research in the field(s) as a WPI center (e.g., Japan's advantages in the subject fields, the project's international appeal as an initiative that challenges world-level science issues, and the future prospects of the research)
* List up to 5 centers either in Japan or overseas that are advancing research in fields similar to the center's field(s), and evaluate research levels between your center and those centers.

Target Research Fields

The target research field of the Institute is **Human Biology**. The Institute will investigate critical themes in human biology in the area of reproduction, development, growth and aging, as well as heredity and evolution, with a strong intense focus on **genome regulation** and **disease modeling**. Specifically, using humans and non-human primates as major research subjects, the Institute will explore germ-cell development, early embryonic development, brain development/growth/pathogenesis, kidney development/growth/pathogenesis, stem cell aging and tumorigenesis, and lymphocyte development/aging, as well as epigenetic inheritance and primate-specific transposable elements.

The Institute will perform interdisciplinary research in **the fused domains between life sciences and mathematics involving geometric data analysis (GDA), topological data analysis (TDA), probabilistic data analysis (PDA), and modeling between life sciences and humanities/social sciences (bioethics** and **philosophy on life)**, respectively, and will implement three research development cores for **multi-hierarchical genome information analysis at the single-cell level, cutting-edge genome editing in primates**, and **non-human primate phenotype analysis**, respectively. The interdisciplinary research program and the research development cores will be integral to the research programs of all principal investigators (PIs), thereby creating a system for the Institute to deliver a highly coherent research program.

The Importance of the Target Research Fields

Elucidating the core concepts of human biology, including diseased states, is fundamental in life science and has direct relevance not only to our primitive quest on human evolution, but also to applications in medicine and the wellbeing of our society. Using a diverse array of model organisms, including the mouse, tremendous research efforts have been made and substantial amounts of knowledge have been accumulated on the mechanism that supports an organismal life cycle. On the other hand, such knowledge has often been difficult or unsuccessfully translated to human biology due to species differences in the regulations of key biological pathways. **We consider that the time has come for us to directly address what it is to be human. This is also because much of the outcomes from drug discovery research in model organisms, such as mice, have not been replicated in human clinical trials.** We would like to point out two prominent examples:

First, during human evolution, remarkable changes have been achieved in the organization and size of the central nervous system (CNS), with expansion of the cerebral cortex being the most prominent. For example, primates, but not rodents, have developed an outer subventricular zone (OSVZ), which is a critical zone for the expansion of the cerebral cortex in primates. The cerebral cortex regulates context-dependent behaviors in a flexible manner, whereas the subcortical systems regulate innate and reflex-like behaviors. Primates depend more on the cortical functions, while rodents depend more on the subcortical systems.

Consequently, after damage to the motor cortex, rodents still can walk, while primates cannot. Rodent models for basal ganglia disorders, such as Parkinson's disease or dystonia, exhibit quite different phenotypes from those of human patients. Furthermore, there is a marked difference in cognitive functions, especially those involving the dorsolateral prefrontal cortex, which exhibits executive functions and is absent in rodents. Such differences in the CNS limit the value of rodent models of neurodegenerative or psychiatric disorders. As a result, during the past decades, drug development for these disorders has faced serious problems, with many of the drug candidates developed in rodent models proving ineffective in preclinical trials and many mega-pharma companies withdrawing from drug development for these diseases.

Second, the kidney is a critical organ that maintains homeostasis of the body fluid. It is becoming increasingly clear that rodent models are insufficient for understanding the pathology of human kidney diseases. For example, diabetic nephropathy is the main cause of end-stage renal failure. However, none of the rodent models recapitulate all key features of human diabetic nephropathy. Accordingly, drugs that are effective in treating rodent models are often invalid in treating human diseases. Another example is acute kidney injury (AKI), a condition in which kidney function declines rapidly. Although various drugs have shown effectiveness in the pre-clinical trials using AKI mouse models, no treatment for human AKI has been developed so far. Thus, mouse models may not replicate human diseases and may not be suitable for establishing drug efficacy in human diseases.

Therefore, the current rodent models show clear limitations as systems to recapitulate accurately human biology, especially related to diseases, due to species differences, most likely in most tissues/organs. Accordingly, human biology requires the use of human materials. However, such materials, particularly those related to human development, are technically and ethically difficult to obtain. We therefore need to create systematic and ethically appropriate opportunities for access to human materials, and for the use of non-human primates as human models. However, it is important to note that even the macaques (e.g., rhesus and cynomolgus monkeys), which are the closest to humans among the models available for experimentation, have evolved independently from humans over ~25 million years. **Hence, in order to significantly promote human biology beyond current practices, it is imperative to perform parallel investigations into humans and non-human primates while elucidating the principles underlying the emergence of species differences in order to better extrapolate the knowledge from model organisms to humans. Indeed, in a broader context, a major challenge for the life sciences in the 21st century will be to understand the mechanistic basis of species differences - the diversity of life forms driven by evolution.**

Direct investigation of human traits requires human or non-human primate materials. To carry out research using such materials with the public's trust, appropriate regulations and understanding of public values are indispensable. In recognition of this imperative, on May 2, 2018, *Nature* announced that it would include ethicists among the peer reviewers for articles that use materials such as human embryos and germ cells. The emphasis placed on the role of bioethics in human biology will continue to grow in the future. There are several elements of research findings anticipated at this Institute (artificial human gametes, cerebral organoids, genome-edited monkeys, etc.) about which society's existing values are ill-equipped to make judgments regarding their moral statuses. For example, whether human gastruloids and fertilized human embryos created for experiments from artificial gametes demand the same ethical considerations as surplus embryos resulting from fertility treatment is a philosophical question on the brink of becoming a real-world

problem. Moreover, while the research use of human and non-human primate materials is indispensable for elucidating human life, it must be complemented by strict ethical considerations. Thus, it will be essential and very timely to implement a **Group for Bioethics and Philosophy** and create a fused domain between life sciences and humanities/social sciences in the Institute.

In light of all the above, we consider that the target research fields of the Institute will be of fundamental importance in life science in the coming decades.

The Value of Carrying out Research in the Field(s) as a WPI Center

In order to realize the outstanding and ambitious goal of establishing the advanced study of human biology as a forefront life science in the coming decades, it will be essential for a critical mass of scientific experts to come together and to perform their research and exchange ideas in a coherent fashion. The establishment of a WPI center by attracting scientists with outstanding potential from Kyoto University and relevant institutions in Japan and overseas is an ideal means to achieve such goals, by creating an intellectually interactive, highly interdisciplinary, collaborative and productive environment.

Currently, access to human materials is more limited in Japan than in other countries. On the other hand, Japan has a clear advantage over Europe and the USA in terms of access to non-human primates. While creating systematic opportunities for access to human materials, the Institute will simultaneously implement the **Primate Genome Engineering Core** as a domestic satellite at the **Research Center for Animal Life Science, Shiga University of Medical Science, which maintains one of the largest primate colonies and most advanced reproductive technologies both in Japan and worldwide (~700 cages, isolation of ~40 oocytes per week)**. In collaboration with **Mitinori Saitou**, the Research Center for Animal Life Science has already established expertise in the developmental engineering of cynomolgus monkeys and published multiple key papers (*Nature*, **537**, 57-62, 2016; *Dev. Cell*, **39**, 169-185, 2016; *Cell Stem Cell*, **17**, 178-194, 2015; *Cell Stem Cell*, **21**, 517-532, 2017; *Sci. Rep,* **6**:24868, 2016); such activity is unique to this Institute, both in Japan and around the world. Thus, it is timely and advantageous for the Institute to implement the **Primate Genome Engineering Core** and expand on research using non-human primates. Moreover, **the Primate Genome Engineering Core will tightly coordinate and perform collaborative efforts with the Division of Marmoset Research at the Central Institute for Experimental Animals, creating an opportunity to promote primate genome-editing research in Japan to a world-class status.**

Five Centers in Fields Similar to the Center's Field(s)

The Institute for the Advanced Study of Human Biology will be very timely and assume a unique position at the forefront of the field of human biology worldwide. There is a rapid, increasing interest in studying human biology, including human developmental biology. For instance, one of the top journals in developmental biology, *Development*, has recently generated a new subsection dedicated to Human Development and established a regular meeting on Human Development since 2014 (From stem cells to human development: to which **Mitinori Saitou** was invited in 2018). **The Wellcome Trust has recently prepared a new initiative, the (HDBI)** (in which **Takashi Hiiragi** is involved)**, at a cost of £10m**. These activities are primarily **Human Developmental Biology Initiative** driven by the recognition that the current lack of success in regenerative medicine stems from the lack of fundamental knowledge in human developmental

biology. An improved understanding of human developmental biology should thus form a strong basis for the success of stem-cell-based regenerative medicine. **Further, although recent advances in genome science have allowed for successive identifications of gene mutations causative for many diseases, there is still no benchmark strategy for exploring the functions of human genes. However, there is, as of yet, no scientific institute among the world's leading countries that is primarily focused on human biology. Therefore, we believe that the advanced study of human biology will create such a strategy, providing a foundation for the development of innovative medical interventions.**

In terms of developmental biology, one of the world-leading institutes would be **the Gurdon Institute** at the University of Cambridge, UK (to which **Takashi Hiiragi** belongs as of October 2018). However, the primary focus of that institute is developmental biology and cancer, and research on human biology is dependent on each lab and, therefore, rather limited. **EMBL** has also recently established a new outstation in **Barcelona** dedicated to tissue biology and disease modeling. However, their studies are so far limited to stem cell cultures or organoids without reference to basic human biology. **The Francis Crick Institute** in London has a prominent interest in human health and disease. However, their primary aim is to understand fundamental biology with a particular emphasis on interdisciplinary collaboration; as such, they are not necessarily focused on human biology. Moreover, due to their large size and high diversity, it makes it difficult to coordinate their research efforts and focus on human biology. **The Curie Institute** in Paris is a leading scientific institution in France and collaborates actively with hospitals in Paris. However, there is no coordinated effort for human biology in this large institute. In the US, while there are many "stem cell institutes" (e.g., the **Harvard Stem Cell Institute**), their research activity is not necessarily coordinated with research in basic human biology, and such research is carried out on an individual lab basis.

Taken together, these facts indicate that the Institute for the Advanced Study of Human Biology will play a unique and world-leading role in the fundamental research of human biology.

2)-2 Research Objectives and Plans

* Describe in a clear and easy-to-understand manner by the general public the research objectives that your project seeks to achieve by the end of its grant period (in 5 years). In that process, what world-level scientific and/or technological issues are you seeking to solve? What will be the expected impact of the scientific advances you aim to achieve on society in the future?
* Describe concretely your research plan to achieve these objectives and any past achievements related to your application.

Research Objectives

The Institute's objective is to create a scientific basis for elucidating what it is to be human, including our diseased states. Accordingly, the Institute will continue to explore humans and non-human primates as major research subjects and clarify the mechanisms underlying the acquisition of human traits and disease states. Over the next five years, the key focus areas of the Institute will continue to be the following:

1) to promote the study of human biology, with a focus on genome regulation.
2) to clarify the principles that define 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*.
5) to contribute to formalizing an international ethics standard for human biological research.

With this, the Institute's research will not only uncover how human beings have evolved, but also create a foundation for delineating the etiologies of many intractable diseases and the development of innovative therapies, and thereby a basis for a healthy start to life and a healthy aging society.

Research Plans

As of April 2023, the Institute will consist of with 16 PIs. These will include 13 PIs investigating key individual themes in human biology in the areas of reproduction, development, growth and aging, as well as heredity and evolution **(Life Science Groups)**, and 3 PIs leading the interdisciplinary sciences and 2 PIs in the three research development cores. Together, these units will continue to allow the Institute to achieve a coherent research program focused on its goal of advanced study of human biology (Figure: page 7).

The two lines of interdisciplinary research and three research development cores are as follows:

Yasuaki Hiraoka (Vice Director), a world-leading mathematician in topological data analysis (TDA) and applied mathematics, and **Sungrim Seirin-Lee**, an expert in mathematical modeling, will lead the **Mathematical Science Groups**. **Hiraoka's** group will develop novel methodologies for analyzing multi-hierarchical, large-scale omics data based on mathematics such as TDA and PBA to clarify the principles for the emergence of species differences as well as to infer spatial gene expression properties. **Seirin-Lee's** group will develop methodologies for modeling and analyzing tissue patterning at multi-hierarchical scales. Together, these groups aim to formulate a "data representation theory" for promoting human biology using multi-hierarchical, large-scale omics/imaging data.

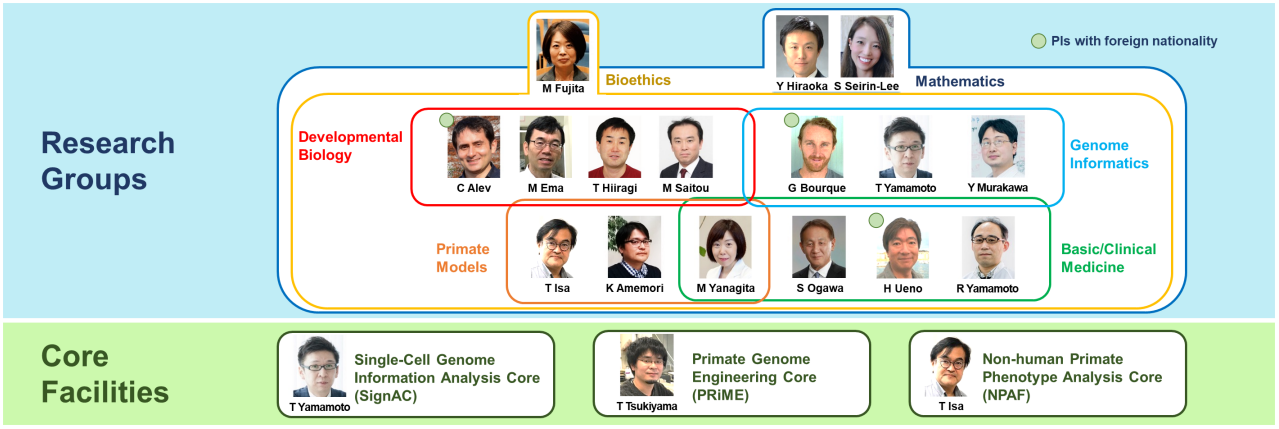
Misao Fujita, an expert in bioethics using an empirical approach, will lead the **Bioethics and Philosophy Group**. This group will formalize the ethics for the appropriate use of human materials (human fetal tissues and early postmortem tissues) and create an ethical standard and philosophy to direct the values of the Institute's research outcomes (e.g., artificial gametes, artificial cerebral cortexes, genome-edited monkeys). For more details on their activities, see section 3) Interdisciplinary Research.

Takuya Yamamoto, an expert in genome information analysis, will lead the **Single-Cell Genome Information Analysis Core**. The core will develop further cutting-edge analytical tools for acquiring large-scale multi-hierarchical datasets for gene expression, genome sequence, structure, and epigenetic profiles at the single-cell level, supporting the research of all groups. In addition, **Yamamoto** will also develop innovative methodologies for the 3D (whole mount) spatial transcriptome analysis and combine them with comprehensive genome-wide datasets, contributing to the exploration of the principles for the emergence of species differences.

Tomoyuki Tsukiyama, who is an expert in primate genetic engineering based at the **Research Center for Animal Life Science, Shiga University of Medical Science (the domestic satellite of the Institute)**, will lead the **Primate Genome Engineering Core**. The core will ensure a stable supply of embryos/adult tissues of cynomolgus monkeys and, by further developing cutting-edge genome-editing technologies, will continue to generate **genome-edited cynomolgus monkeys** for exploring primate-specific gene functions and establishing relevant disease models, thereby serving an integral function for the researchers at the Institute. So far, the target genes include those responsible for **brain functions in primates** and for **kidney development and growth, processes that are significantly divergent between primates and rodents, for which drug screening has been largely unsuccessful in rodent models** (see "The Importance of the Target Research Fields"). Specifically, these genes include

DISC1 (**Isa**: a gene responsible for schizophrenia), *PKD1* (**Tsukiyama** and **Ema**: a gene responsible for polycystic kidney), and *NPHP1* (**Yanagita**: a gene causative for nephronophthisis type 1). With the progression of the Institute's research, the core will target new candidates in primate-specific traits and disease development. Furthermore, the Institute will establish close relations with the **Division of Marmoset Research at the Central Institute for Experimental Animals**, which is a key center for generating gene-edited marmosets, thereby further promoting top-level research for primate genome editing in Japan and the rest of the world.

Tadashi Isa, is an expert of neural network and psychosis model studies in primates, will lead **Non-human primate Phenotype Analysis Facility (NPAF)**. This facility will analyze the phenotypic aspects of genome-edited macaque monkeys; behaviors including social interactions, brain, and other physiological functions.



The life science groups will consist of four research platforms (Developmental Biology: **Alev**, **Ema**, **Hiiragi**, **Saitou**; Genome Informatics: **Bourque**, **Murakawa**, **T. Yamamoto**; Primate Models/Macaque Genome Engineering: **Amemori**, **Isa**; Basic/Clinical Medicine: **S. Ogawa**, **Ueno**, **R. Yamamoto**, **Yanagita**) that will focus on key areas of human biology, namely reproduction, development, growth, and aging as well as heredity and evolution.

Cantas Alev, an expert in developmental biology and a pioneer in the field of *in vitro* reconstitution of segmentation clock and somitogenesis, will reconstitute key human mesoderm-derived tissues *in vitro* as well as generate *in vitro* models of human and non-human primate embryogenesis. This will shed light on the regulation of human development and differentiation at the genome level and help identify human/primate-specific features of embryonic development and organogenesis. **Alev's** group will also contribute to establishing the ethical standards related to *in vitro* model systems of human and non-human primate embryonic development.

Masatsugu Ema, an expert in primate embryology, will elucidate the mechanisms of human disease, including that of ADPKD (autosomal dominant polycystic kidney disease), with genetically modified monkeys and will explore cellular and molecular mechanisms unique to early development in primates. This will include the mechanism of trophectoderm differentiation and the invasion of trophectoderm into endometrium, which is a fundamental process during embryonic development. **Ema's** group will also develop novel techniques to create genetically modified monkeys.

Takashi Hiiragi is an expert in developmental biology and has revealed a number of key principles for embryonic morphogenesis using multidisciplinary approaches based on live-imaging, mathematics, and biophysics. **Hiiragi's** group will aim to understand the mechanisms underlying primate development, in

comparison to that of the mouse, by focusing on spatiotemporal scaling across species during pre-implantation development and spatial coordination between morphogenesis and patterning, such as epiblast order emergence and coordinated morphogenesis with implantation into the uterus. These studies will extend our understanding of how early human embryogenesis occurs.

Mitinori Saitou (Director) is a world leader in germ cell biology and *in vitro* reconstitution of germ cell development in mice, monkeys, and humans. **Saitou's** group will develop ex vivo culture systems for differentiating human (h) and cynomolgus monkey (cy) primordial germ cells (PGCs)/oogonia into oocytes. Based on such systems, the group will develop *in vitro* systems to generate oocytes from PGC-like cells (PGCLCs) derived from h/cy induced pluripotent stem cells (iPSCs)/embryonic stem cells (ESCs), to reveal the mechanism underlying h/cy germ-cell development. **Saitou's** group will focus on the mechanism for the generation of genetic and epigenetic diversities through meiotic recombination and epigenetic reprogramming, respectively, and uncover species differences of such key processes among mice, monkeys and humans. Additionally, **Saitou's** group will clarify the mechanism for the evolution of human germ cell development based on comparative analyses with chimpanzee, orangutan, monkey, and mouse germ cell development.

Guillaume Bourque is an expert in comparative genome information analyses. **Bourque's** group will: 1) develop methods that use graphs and pangenomes for comparative epigenomic analyses. This will lead to the identification of genomic/epigenomic regions that are specific to the human lineage and thus contribute to our understanding of human evolution; 2) by leveraging lenti massively parallel reporter assay (lentiMPRA), identify causal mutations among the 7.6 million nucleotides that differ between human and chimpanzees that alter gene regulatory activity in neurons and chondrocytes, that distinguish humans from other primates; 3) analyze the function of transposable elements (TEs) that are evolved in the primate genome by identifying specific TE instances that are involved in cell differentiation and human evolution; 4) by using lentiMPRA, assess more than 700 thousands of human disease variants for their regulatory activity with a focus on disease variants associated with the liver and immune system.

Yasuhiro Murakawa is an expert in RNA biology of human diseases. By developing novel experimental methods and bioinformatics algorithms at both population and single-cell level, the Murakawa group will build a functional genomic atlas of transcriptional enhancers and novel genes encoded in the human genome. Furthermore, by integrating with large-scale human disease genomics, Murakawa's group will comprehensively elucidate the molecular pathogenesis and evolutionary mechanisms of human diseases, which will uncover novel therapeutic targets to create innovative future medicine.

Takuya Yamamoto (SignAC Head) will aim to uncover an overall picture of spatiotemporal RNA regulation and its biological significance. By utilizing cutting-edge sequencing technologies and methods for analyzing RNA regulation such as splicing, editing, polyA length, circulation, and various modifications, **T Yamamoto's** group will investigate the dynamics of intracellular RNA localization during cell fate conversion and pathogenesis.

Ken-ichi Amemori is an expert in neurobiology using non-human primates as human models. **Amemori's** group will explore the large-scale networks related to anxiety disorders (ADs) in non-human primates, which are highly conserved with those in humans. They will: 1) analyze inter-areal interactions of the AD-related network, with the investigation of the relationship between cognition and emotion; 2) examine the network function by recording neural activities from the AD-related circuitry; 3) manipulate AD-related pathways using chemogenetics approaches and elucidate its function; 4) perform single-nucleus RNA sequencing of the AD-related neuronal nuclei, examine the spatial distribution of the AD-related neurons, and develop novel genetic tools to manipulate the targeted cells' function, thereby establishing a critical

model for ADs.

Tadashi Isa is a world leader of studies of primate neural networks. **Isa's** group will: 1) explore the mechanism for massive plasticity after the spinal cord injury in adult macaques, with a focus on a) when the re-routing occurs, b) do the re-routed corticospinal neurons really contribute to the recovery, c) what kind of gene regulatory network changes occur in the re-routed neurons and whether these changes contribute to the re-routing; 2) create a psychosis model in the macaques (*DISC1* knockout) and develop therapeutic strategies; 3) evaluate metacognition and its neural correlates in the blindsight monkeys; 4) develop therapeutic strategies against the gambling disorder by frontal cortex stimulation; 5) development early stage treatment strategies for Lewy body diseases. Thus, **Isa's** group will create a foundation for the study of gene functions in primate brain functions, generate critical disease models, and develop therapeutic strategies for those diseases.

Seishi Ogawa is an expert in the genome biology of cancer and has been identifying key mutations responsible for many types of cancers. **Ogawa's** group will clarify pathways through which successive aging-associated mutations lead to tumorigenesis. Target tissues include the mammary epithelium, esophagus, large intestine, and hematopoietic system. They will analyze ~100,000 single cells in incipient tumor lesions or in normal stem cells for their genome sequence and gene expression and delineate a comprehensive picture of clonal selection and evolution as a nascent step of tumorigenesis. To this end, they will develop a methodology to detect mutations and measure global gene expression simultaneously from single cells and to determine the pathways for clonal selection and evolution based on population genetics bioinformatics. **Ogawa's** group will also investigate the role of epigenetic mutations in cancer with a focus on hematologic malignancy.

Hideki Ueno (Vice Director from April 2023) is an expert of human immunology and a world leader in the field of human T follicular helper cells (Tfh). **Ueno's** group recently found human naïve $CD4^+$ T cells, which form the origin of $CD4^+$ T-cell subsets essential for the adaptive immune system, that was isolated from different specimens (e.g., cord blood, adult peripheral blood, tonsils, spleen, and liver), display a distinct differentiation trajectory and open chromatic landscape. This has led to the idea that naïve T cells are exposed to environmental elements and get "trained" to respond promptly to anticipated external antigens *in situ*. In this context, a fraction of naïve T cells might reside in tissues longer than initially anticipated. Accordingly, **Ueno's** group, by using single-cell (sc)RNAseq, scATACseq, scTCRseq, and single-cell spatial transcriptomics, will aim to define the heterogeneity of naïve CD4+ T cells present in different human tissues.

Ryo Yamamoto is an expert of hematopoietic stem cell (HSC) biology. Using single-cell transcriptomic and enhancer analysis, **R Yamamoto's** group will: 1) elucidate mechanisms underlying self-renewal and differentiation of HSCs using the mouse, cynomolgus, and human samples; 2) elucidate mechanisms of hematopoietic stem cell aging using the mouse, cynomolgus and human samples.

Motoko Yanagita is an expert in kidney biology and has made key contributions to understanding of the pathogenesis of many kidney diseases. **Yanagita's** group will: 1) explore the role of tertiary lymphoid tissues (TLTs) in the context of kidney disease pathogenesis, with a focus on a) intervention experiments on CD153-CD30 signaling, b) the identification of senescence-associated T cells (SAT cells) and age-associated B cells (ABCs), C) the role of TLTs in a wider range of human kidney diseases, d) establishment of non-invasive diagnostic methods for TLTs; 2) create a model of familial nephronophthisis in the macaques (*NPHP1* knockout) and develop therapeutic strategies; 3) identify primate-specific kidney injury-associated genes.

All the PIs are committed to creating a new chapter in the study of human biology on the basis of their

research focusing on key components of human biology.

Moreover, under the leadership of the director, to strengthen the interactions among PIs and the identity of the institute, we currently have five ongoing "Flagship Projects," which will facilitate the realization of the ASHBi's research objectives. The themes and brief contents of the five flagship projects are as follows:

1. Deconstructing and reconstructing early primate development

This is the flagship project of the "Developmental Biology Platform," and will focus on understanding the mechanism underlying pre-/post-implantation primate development and its reconstitution both *ex vivo* and *in vitro*, in order to provide critical insights into the mechanism of human development and stem cell-based regenerative medicine (relevant to **Focus Areas 1**, **2** and **4**).

2. Interdisciplinary primate-genomics research for developing new primate models of human disorders

This is the joint flagship project of the "Genome Informatics Platform" and "Primate Models/Macaque Genome Engineering Platform" and will consist of **a)** a systems biology study of anxiety disorders by an integrative approach that combines functional genomics and neuroscience and **b)** a systems biology study of the gene regulatory networks in the corticospinal motor neurons that accounts for the massive plasticity in the adult primate brain, which will be the basis for the development of innovative medical interventions. This project is also relevant to the project creating disease models using gene-knockout monkeys (*PKD1*, *NPHP1*, *DISC1* knockouts) (relevant to **Focus Areas 1**, **2** and **3**).

3. Age-associated genomic alterations of organ cells and their interplay with the immune system

This is the flagship project of the "Basic/Clinical Medicine Platform," and it 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 increased malignancy risk of cholangiocytes. The results of this project will unravel the cause of age-associated systems impairments and their consequences in humans. In addition, the Basic/Clinical Medicine platform will explore age-associated systemic alterations in diverse organs, including kidneys, creating a solid basis for further developing the flagship project (relevant to **Focus Area 1**).

4. Establishment of a new mathematics "data representation theory"

This is the flagship project of Mathematical Science Groups and will establish a new mathematical paradigm called "data representation theory". By combining optimal transport, topological data analysis, and pattern formation theory, the 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, which will contribute to the further innovation of both biology and mathematics (relevant to **Focus Area 2**).

5. Bioethics surrounding birth and death: philosophical and empirical approaches to defining the rules behind research use of human tissue

This is the flagship project of Bioethics and Philosophy Groups and 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 (relevant to **Focus Area 5**).

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

Thus, the Institute will delve into key areas of human biology and will be highly integrative with the activities of interdisciplinary science and research development cores, realizing a coherent progression of the field of advanced study of human biology.

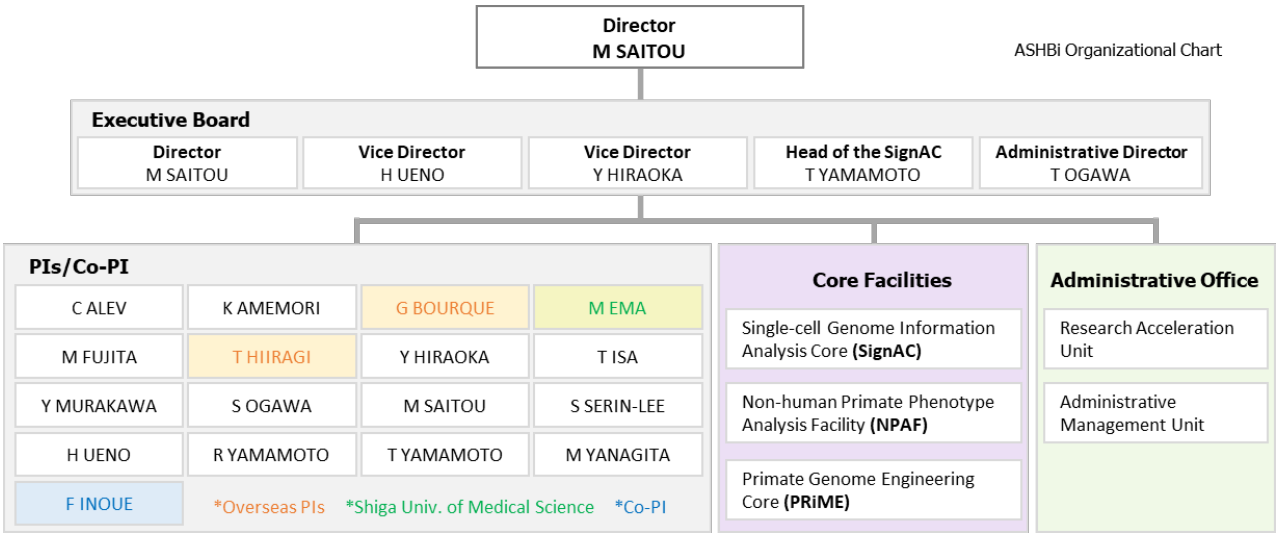
2)-3 System for advancing the research

* Describe the center's research organization (including its research, support and administrative components) and your concept for building and staffing the organization.
* Describe your concrete plan for achieving the center's final staffing goal, including steps and timetables.
* If the center will form linkage with other institutions, domestic and/or foreign, *by establishing satellite functions*, provide the name(s) of the partner institution(s), and describe their roles, personnel composition and structure, and the collaborative framework with the center project (e.g., contracts to be concluded, schemes for resource transfer).
* If the center will form linkage with other institutions, domestic and/or foreign, *without establishing satellite functions*, provide the names of the partner institutions and describe their roles and linkages within the center project.
* Appendix: "List of Principal Investigators" (to be attached)
* Appendix: "Composition of personnel in center" (to be attached)

THE INSTITUTE'S RESEARCH ORGANIZATION

The Institute consists of 16 PIs: 13 PIs are from KU (**Cantas Alev**, **Ken-ichi Amemori**, **Misao Fujita**, **Yasuaki Hiraoka**, **Tadashi Isa**, **Yasuhiro Murakawa**, **Seishi Ogawa**, **Mitinori Saitou**, **Sungrim Seirin-Lee**, **Hideki Ueno**, **Ryo Yamamoto**, **Takuya Yamamoto**, and **Motoko Yanagita**), 1 from Shiga University of Medical Science (**Masatsugu Ema**), and 2 from abroad (**Guillaume Bourque** and **Takashi Hiiragi**). One overseas PI has also hired a young researcher as a co-PI (Bourque group; **Fumitaka Inoue**), who works full-time at the Institute and runs the overseas PI group at the Institute.

The **Executive Board**, consists of the director (**Mitinori Saitou**), 2 vice directors (**Yasuaki Hiraoka** and **Hideki Ueno**), the core head of the SignAC (**Takuya Yamamoto**), and the administrative director (**Tadashi Ogawa**).



CORE FACILITIES AND THE INSTITUTE'S SATELLITE

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

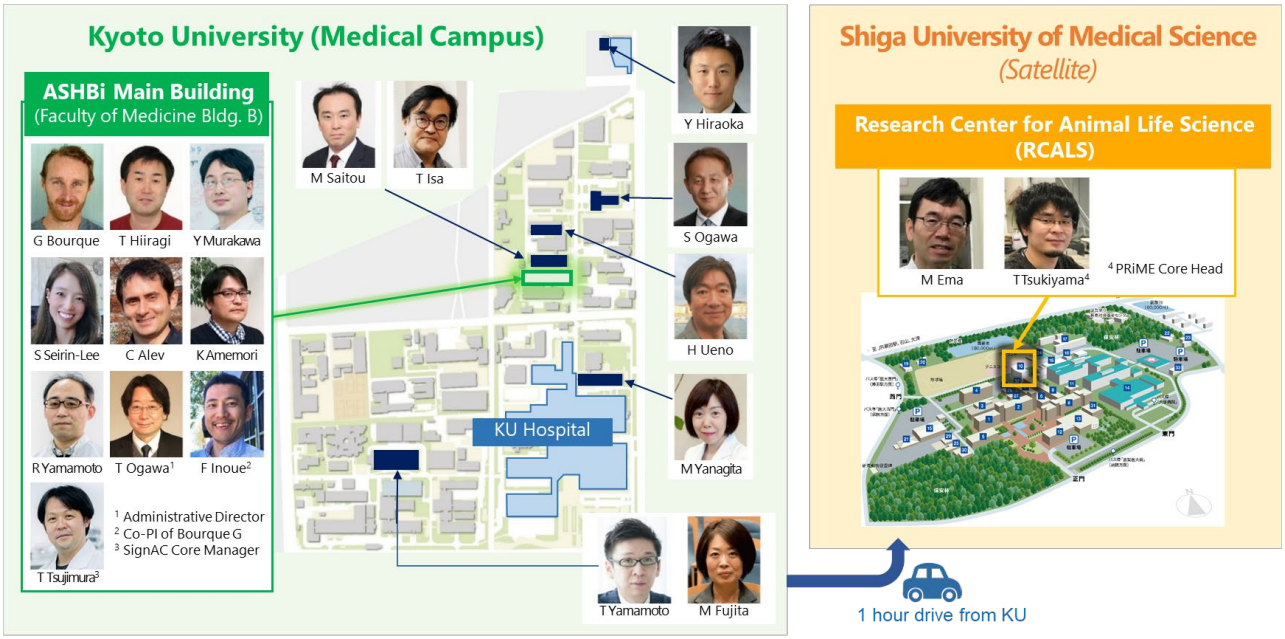
- **SINGLE-CELL GENOME INFORMATION ANALYSIS CORE (SignAC)** provides support for facilitating large-scale single-cell genomic analyses through convenient access to next-gen sequencers and development of key technologies. The operation of the Core is managed by **Takuya Yamamoto** (Core Head) and **Taro Tsujimura** (Core Manager), and 7 technical and administrative staff.

- **PRIMATE GENOME ENGINEERING CORE (PRiME)** is a domestic satellite of the Institute and is located in the Research Center for Animal Life Science (RCALS) of Shiga University of Medical Science, located within an hour's drive from the Institute. This core has been established to generate genome-edited monkeys and to retrieve oocytes/embryos for the research at the Institute. The operation of this core is managed by **Tomoyuki Tsukiyama** (Core Head) and 2 supporting staff.

- **NON-HUMAN PRIMATE PHENOTYPE ANALYSIS FACILITY (NPAF)** is located in the Faculty of Medicine Campus of KU. This facility has been established to analyze the phenotypic aspects of genome-edited macaque monkeys, including social interaction behavior, cognitive function, and emotional expressions. The operation of this facility is supervised by **Tadashi Isa** and one other researcher. Two staff are also employed for animal health care, feeding, and cage cleaning.

THE INSTITUTE'S ADMINISTRATIVE OFFICE

The Institute's Administrative Office provides effective research support to the Institute's researchers. The Office is managed by **Tadashi Ogawa** (Administrative Director) and consists of two units. The **Administrative Management Unit** consists of 7 staff members and is responsible for regular administrative operations, such as human resources and accounting. The **Research Acceleration Unit** consists of four experts with a unique function of providing support to resolve problems associated with



conducting research at the Institute.

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

* Paste onto table a) in Appendix: personnel_in_the_center.

	At beginning of project	At end of FY 2022	Final goal (Date: Mar, 2025)
Researches from within the host institution	8	14	13
Foreign researchers invited from abroad	4	2	2
Researchers invited from other Japanese institutions	1	2	1
Total principal investigators	13	18	16

b) Total number of members

* Paste onto table b) in Appendix: personnel_in_the_center.

			At beginning of project		At end of FY 2022		Final goal (Date: Mar, 2025)	
			Number of persons	%	Number of persons	%	Number of persons	%
Researchers			13		**66**		**70**	
	Overseas researchers		4	31	23	35	26	37
	Female researchers		3	23	16	24	21	30
	Principal investigators		13		**18**		**16**	
		Overseas PIs	4	31	4	22	4	25
		Female PIs	3	23	3	17	3	19
	Other researchers		0		**48**		**54**	
		Overseas researchers	0		19	40	22	41
		Female researchers	0		13	27	18	33
Research support staffs			2		22		22	
Administrative staffs			3		30		30	
Total number of people			18		118		122	

		At beginning of project		At end of FY 2022		Final goal (Date: Mar, 2025)	
		Number of persons	%	Number of persons	%	Number of persons	%
Doctoral students		—		83		90	
	Employed	—		12	14	20	22

※b) The number of doctoral students in the lower table can be duplicated in the upper table of overall composition.

2)-4 Securing research funding

Past record

* Give the total amount of research funding (e.g., competitive funding) secured by the principal investigators who will join the center project. Itemize by fiscal year (FY2018-2022).

Amount of External Funding (million yen)

Fiscal Year	FY2018	FY2019	FY2020	FY2021	FY2022
External Funding*	**709**	**792**	**940**	**1,179**	**1,237**

Funding prospects after the establishment of the center

* Based on the past record, describe your concrete prospects for securing resources that match or exceed the WPI grant (FY2023-2027).
* Calculate the total amount of research funding (e.g., competitive funding) based on the amount of funding that the researchers will allocate to the center project. Be sure that the funding prospects are realistically based on the past record.

Amount of External Funding (million yen)

Fiscal Year	FY2023	FY2024	FY2025	FY2026	FY2027
External Funding	**1,699**	**1,699**	**1,699**	**1,699**	**1,699**
Host Institution Support	277	277	277	277	277

The funding prospects will be the allocated sum of expected external funding of all researchers (including the PIs) in the Institute. Note that Kyoto University allocates all of the headquarters' portion in addition to the indirect cost of the Institute.

3) Interdisciplinary Research

* Describe the fused research domains, why interdisciplinary research is necessary and important in the target field(s), and what new field(s) can be expected to be created by way of this project. Describe your concrete strategy for fusing different research domains and creating new field(s) by the fusion.

The Institute aims to investigate the core concepts of human biology and to uncover human-specific traits in various biological contexts. Toward this end, it will be highly valuable to develop novel methodologies based on appropriate mathematical underpinnings for analyzing multi-hierarchical large-scale omics data for gene expression, genome sequence and structure, and epigenetic profiles as well as high-content imaging data, and to perform comparative analyses of relevant biological contexts in humans and other key species, thereby elucidating the principles that define species differences and human traits. Indeed, understanding the mechanistic basis for species differences—i.e., the diversity of life created through evolution—will be one of the most fundamental challenges in 21st century life science. **Although it has been extremely difficult to address such themes, along with the recent advances in genome science, it has become timely to explore this key theme using multi-disciplinary approaches.**

Accordingly, the Institute will aim to develop such novel mathematical descriptors for multi-hierarchical large-scale omics and imaging data. Toward this end, the Institute have created two Mathematical Science Groups with complementary mathematical expertise. **Yasuaki Hiraoka**, an expert on mathematical data analysis, will develop novel methodologies for analyzing large-scale, multi-species/multi-cell type, and multi-hierarchical data using advanced mathematics such as TDA, optimal transport, dynamical system, high-dimensional statistics, and machine learning. **Sungrim Seirin-Lee**, an expert of mathematical modeling, will develop cutting-edge multi-disciplinary methodologies for modeling and analyzing multi-hierarchical scales of tissue patterning. Through tight collaborations with life science groups in the Institute, the groups aim to contribute to the investigation of the core concepts of human biology and to the understanding of the

traits specific to humans in various biological contexts.

The Institute will realize this interdisciplinary research through tight cooperation among the **Mathematical Science Groups**, the life science groups, and the **Single-Cell Genome Information Analysis Core**. Specifically, 1) scientists in life science groups will provide scientists in the **Mathematical Science Groups** with intensive lectures for genome science, species differences, and human biology and establish a system for mathematical scientists to truly understand the cutting-edge knowledge and issues in life science; and 2) scientists in mathematical science will train scientists in life science for mathematical analyses and establish a system for life scientists to gain the capacity to develop new analytical methods and perform in depth analysis of the data. **This system is critical to foster life scientists with capability for cutting-edge mathematical analysis.** The Institute will also create ample opportunities for specific problem-oriented discussions among postdocs and students, and for small-scale joint lab meetings to facilitate interdisciplinary science. With these systems, the Institute will create a truly fused domain between mathematics and life science.

At the outset, in order to robustly acquire biological data as well as to realize a real fusion between mathematics and life science, the Institute implemented one **PI (Yasuaki Hiraoka) for the Mathematical Science Group**, and **Guillaume Bourque** and **Takuya Yamamoto**, who are proficient in statistics-based informatics, to support the **Mathematical Science Group**. In October 2021, the Institute appointed one more **PI (Sungrim Seirin-Lee)** to realize more comprehensive math-biology fusion researches. Under the 2 PIs, **Mathematical Science Groups** set a flagship project to establish a new mathematics called "data representation theory" upon collaborations with life science groups.

See **"The Importance of the Target Research Fields**" for the importance of the fused domain between life science and humanities. **Misao Fujita**, an expert of bioethics using an empirical approach, will lead the **Bioethics and Philosophy Group**. In close collaboration with all life science groups, the Bioethics and Philosophy Group will consider the ethical use of human samples (fetal tissues and early postmortem tissues) and the values of research outcomes (in vitro gametogenesis and embryo models) by pursuing three research projects: 1) formulation of rules for fetal tissue research, 2) producing ethical guidelines for early postmortem tissue research in view of establishing a platform, and 3) establishing a research ethics consultation system. Based on their research and activities, the group will shed new light on the philosophy of life and set-up a framework the ethics of conducting advanced study of human biology.

More specifically, the group will summarize 1) **a report on the academic rationale for the fetal tissue research, with guidelines** that can be referred to by researchers, health professionals, and institutional ethics review committees when conducting fetal tissue research. The results of this project will be used as basic materials to anticipate future discussions when the government and related academic societies begin considering the formulation of rules for such research. The group will compile 2) **a report including institutional ethical guidelines for the use of early postmortem tissue in research** toward establishing a platform. The outcome of this project will contribute to Institute's mission, particularly with respect to the aging studies aimed to elucidating the mechanisms of aging and pathological conditions associated with aging in the human body, where healthy 'control' tissues for comparison purposes are deemed indispensable. 3) The group also aims to establish **a research ethics consultation system, helping**

bioscience researchers resolve ethical and social concerns that arise during the course of their research. In order to avoid ethical issues that may arise that could hinder the progress of research on *in vitro* gametogenesis, human embryos, and human embryo models, and to promote research in a timely manner, it is essential to have a system that can immediately address ethical questions and concerns that scientists in the Institute may have about ethical aspects of their research.

Furthermore, we will create regular opportunities for mutual discussion among scientists in the life science and the bioethics and philosophy groups. We will also make it a standard practice to have a bioethics session in all regular international scientific symposia of the Institute, to promote timely discussions in an international context. Through these efforts, **we will exemplify a world-standard for bioethics and the philosophy of life, paving the way at the forefront of the life sciences for the coming decades**.

Additionally, during the course of the Institute's research, **the director will play a leading role in facilitating continuous discussion among the PIs and the Institute's members on how to create truly interdisciplinary scientific domains and attain the goals of such new disciplines**.

4) International Research Environment

4)-1 System for advancing international research

* Describe your concrete plan for building an international research center including the makeup of its foreign researchers, establishment of oversea satellites, or similar functions. Include a time schedule for the plan.
* Describe concretely your strategy for staffing foreign researchers (e.g., postdoc positions) through open international solicitations. Describe the procedures you will use to do so.

INTERNATIONALIZATION OF PIS

As of April 2023, 4 out of 16 PIs are foreign PIs (**Alev**, **Bourque**, **Seirin-Lee**, and **Ueno**), bringing the ratio of foreign PIs to 25%, exceeding the WPI standard of 20%. In order to further increase the ratio of foreign PIs, the Institute will work closely with the KU's "**HAKUBI Project**", which recruits more than 20 promising young researchers from around the world per year, with the aim of fostering world-class researchers at the University. Under the collaboration with the HAKUBI project, some non-Japanese HAKUBI researchers will be invited to join the Institute as young PIs. They will be able to pursue research based on their own research plans. Furthermore, we are planning to establish a system whereby the selected HAKUBI researcher can be hired as a regular PI through a vacant tenure post at the Institute if his/her performance is evaluated as a promising PI.

INTERNATIONALIZATION OF RESEARCHERS

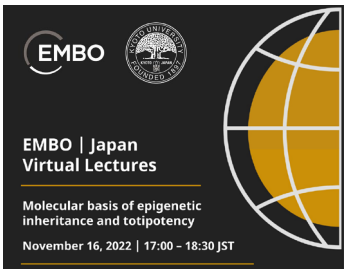
As of April 2023, the ratio of foreign researchers is 35%, but in order to further increase this ratio, we plan to utilize the "**ASHBi Foreign and Female Researcher Recruitment Support Program"** more effectively. We will continue to promote the recruitment of foreign researchers (especially female foreign researchers), so that the percentage of foreign researchers and female researchers exceed 30%.

INTERNATIONALIZATION OF STUDENTS

The Institute's PIs host and supervise 16 master's students and 83 doctoral students (99 total) in their laboratories. To further increase the number of international students, we will effectively utilize the "**ASHBi Financial Support Program for International Graduate Students**", which supports living expenses necessary for international students to stay in Japan. In addition, we will also utilize the aforementioned "**McGill-Kyoto International Joint Program in Genomic Medicine (Joint Ph.D. Program)**" to recruit international students who are interested in studying in Japan.

RESEARCHER EXCHANGES THROUGH ORGANIZATIONAL COLLABORATION

The Institute has received invitations for research exchanges from some of the world's leading research communities. One example being the relationship with **EMBO** (the **European Molecular Biology Organization**), which has more than 1800 researchers and is active in the life sciences in Europe and more globally. The Institute and EMBO has and will continue to co-organize "EMBO-Japan Virtual Lectures", with particular emphasis on exchanges between senior researchers and young researchers and students. To date, two lectures have already been held. We will continue to co-host these lectures in 2023 and further future.



Furthermore, the Institute, together with KU School of Medicine, has signed an agreement with the **Max Delbrück Center for Molecular Medicine** (Berlin, Germany) to initiate an organized research collaboration started in 2022. This collaboration will promote, among others, the following activities: 1) exchange of scientific materials, publications, and information; 2) exchange of faculty and researchers; 3) exchange of students; and 4) joint research and meetings for research.

RESEARCHER EXCHANGES THROUGH INTERNATIONAL MEETINGS

We have actively organized large-scale international symposia and international summer schools. To date, we have held four international symposia and two summer schools in an onsite/online format. We will continue to hold international meetings and create opportunities for exchanges with overseas researchers.

In addition, in order to provide opportunities for exchanges with overseas researchers, the Institute's PIs frequently organize meetings inviting overseas researchers (**ASHBi Seminars**). Each PI is required to host at least one seminar per year. For on-site seminars, the Institute has and will continue to provide financial support for overseas researchers to travel to Japan. We will continue to maintain this seminar series in the future and to actively create opportunities for exchange and collaborations.

4) -2 Establishment of international research environment

* Describe your concrete strategy for establishing an international research environment, administration system, and support system (e.g., appointment of staff and provision of startup funding) to accommodate researchers from overseas.
* Concretely describe how the center will provide an environment in which researchers can work comfortably on their research by being exempted from duties other than research and related educational activities, and how they will be provided adequate staff support to

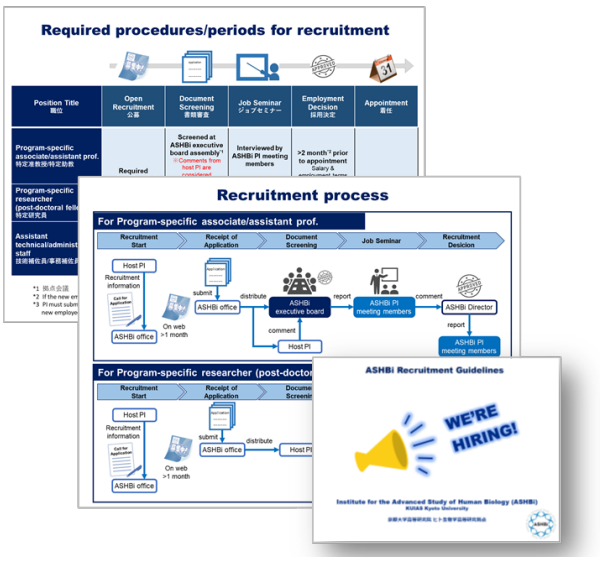
handle paperwork and other administrative functions. Include your procedure and time schedule.

* Describe your strategy, procedure and timing for periodically holding international research conferences or symposiums (at least once a year).

PROBLEM SOLVING-TYPE SUPPORT FOR OVERSEAS RESEARCHERS

The Institute's Administrative Office comprises of bilingual employees to support non-Japanese researchers. At the Institute, paperwork, e-mail exchanges, and other internal communications are provided in both English and Japanese. More importantly, when overseas PIs/researchers encounter any problems in conducting their research, we provide organizational support to solve them. For example, problems regarding the setup of a new laboratory, purchasing research equipment, hiring post-docs and technicians, and creating a website for his/her laboratory, in addition to other support. For the non-Japanese PIs/researchers, many of these administrative procedures in Japanese universities are unfamiliar and typically complicated, thus becoming a serious obstacle in conducting their research.

To solve this problem, the **Research Acceleration Unit** of the Administrative Office offers two types of practical support. First, the Unit provides English-language manuals that help visualize basic administrative procedures in an easy-to-understand manner. Second, the Unit has established a consultation platform operated by a pair of the Unit's experts and English-speaking secretary. When a non-Japanese PI/researcher faces a problem, the Unit's expert discusses it with the non-Japanese PI/researcher and consults with the relevant departments to find a solution. The expert then shares the solution with the secretary so from next time onwards, the secretary can handle the problem by themselves.



SUPPORT FOR ENTERING JAPAN AND LIVING IN JAPAN

We provide support for non-Japanese researchers and their families in obtaining visas and entering Japan, in close cooperation with the KUIAS staff who is in charge of immigration support. The Institute's English-speaking secretary for the non-Japanese PIs/researchers also provides assistance in finding housing, opening bank accounts, applying for tax credits, and among other types of support.

SUPPORT FOR ORGANIZING INTERNATIONAL MEETINGS

We invite world-class researchers and hold at least one large-scale international symposium or workshop per year. Two professional staff members are assigned from the **ASHBi Administrative Office** to assist in organizing these conferences. One of them has more than 10 years of experience in an international travel

agency. The staff are responsible for most of the preparations required in organizing international meetings, including preparing posters, disseminating conference information and the registration for the conference, online meeting operation, payment of speaker honorarium, and arrangements for flights and accommodations. This support greatly reduces the burden of the Institute's researchers who host international meetings.

FINANCIAL SUPPORT FOR OVERSEAS/YOUNG PIS TO SET UP THEIR LABORATORIES

Overseas PIs and young PIs are typically provided with start-up support (overseas PIs: 30 million yen, young PIs: 10 million yen) for the first two years after starting their positions at the Institute.

5) Center Management and System Reform

5) -1 Project management

* Describe the role of the center director and the administrative director.
* Concretely describe your concept for establishing an administrative organization, the center's decision-making system and how authority is allocated between the center director and the host institution.
* Concretely describe how the center will adopt a rigorous system for evaluating research and will introduce a system for merit-based compensation (e.g., annual salary scheme). Describe your procedures and timing for operationalizing these systems.

The Institute's decision-making system

THE ROLE OF THE DIRECTOR

The **Director** of the Institute has the authority to make the final decision on important institutional matters, such as the institutional research vision, screening/selection of PI candidates, and the budget execution plan. This high-degree of independence for the Director is guaranteed by the special structure of the **KUIAS** (**Kyoto University Institute for Advanced Study**), which was created as a hub to house the centers/institutes under its umbrella while maintaining a high degree of autonomy for each.

THE EXECUTIVE BOARD AND THE PI BOARD

The **Executive Board**, consisting of the Director, the Vice Director, the Core Head of the SignAC, and the Administrative Director, convenes Executive Board meetings twice a month to discuss important matters under the leadership of the director. These institutional decisions are shared with the **PI Board**, which consists of the 16 PIs, the co-PI, and the Administrative Director which hold PI Board meetings once a month, to further discuss and decide on implementing those institutional decisions into concrete action plans (if necessary, individual committees/working groups of PIs are also created). In addition, the PI Board meeting consistently gathers opinions of all PIs and Co-PI for the important issues prior to the decision-making at the Executive Board meeting. Thus, this system allows transparency and active involvement of all PIs and co-PI to enable the coherence of the Institute.

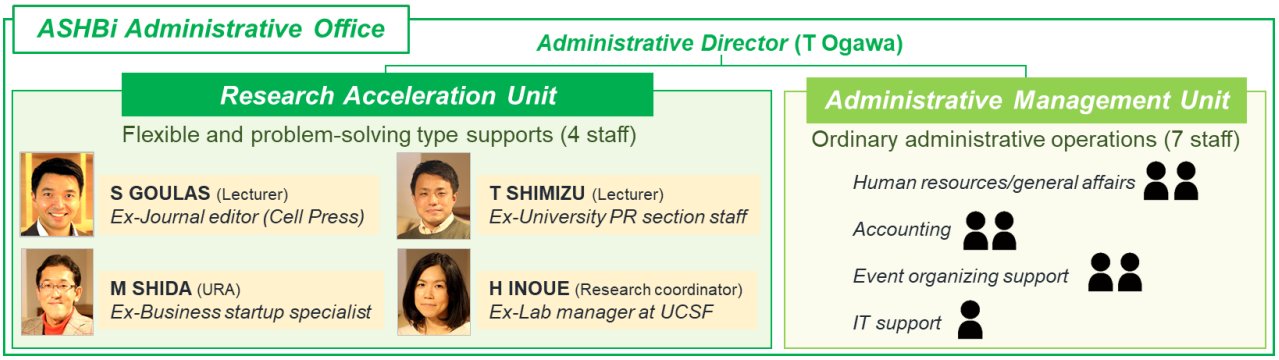
Administrative organization

THE ROLE OF THE ADMINISTRATIVE DIRECTOR AND THE ADMINISTRATIVE ORGANIZATION

The main role of the **Administrative Director** is to build and maintain the administrative organization (the ASHBi Administrative Office) and to direct the administrative staff. The Office consists of the "**Administrative Management Unit**" and the "**Research Acceleration Unit**". While the former is responsible for regular operation (e.g. general affairs, human resources, and accounting services), the latter is unique and responsible for its 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 support programs to implement an institute-wide issue (e.g. internationalization of the Institute's researchers),

and promoting non-Japanese researcher activities. In addition, this unit organizes seminars to foster young researchers.

To fulfill the above roles, four experts have been hired for the Research Acceleration Unit. **Spyros Goulas** is a former scientific editor at Cell Press (Journal: *Developmental Cell*) and is supporting the Institute members (especially young researchers) in developing and improving their abilities to write their research papers as well as providing strategic advice on publications. **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 researchers' ability to obtain grants. **Hiromi Inoue** is a former lab manager at UCSF specializing in life sciences and she utilizes her experience to support the Institute's management. She also provides data visualization support to improve how researchers can display their research results.



SEMINARS FOR FOSTERING EARLY-CAREER RESEARCHERS AND GRADUATE STUDENTS

The Research Acceleration Unit will continue to organize seminars to promote the research activities of foreign and early-career researchers, such as seminars on scientific paper writing designed to help early-career researchers in developing the ability to convey their research story and its significance to journal editors and reviewers. Additionally, the Unit organizes seminars on writing grants, international news releases, and scientific illustrations. Thus, the Research Acceleration Unit not only provides direct support to researchers but it also supports early-career researchers in establishing a stronger foundation, enabling them to accelerate their scientific career development. These seminars are open to academic researchers outside the Institute and contribute to fostering early-career researchers within Japan.

Evaluation system and incentives

ASSESSMENT OF THE INSTITUTE'S PIS

We have introduced a system for allocating allowances to the Institute's PIs based on their scientific contributions to the Institute and research output. In addition, before the start of the second half of the WPI program in April 2023, an Interim Evaluation for the Institute PIs, who have been with the Institute since its inception, will be conducted. The performance of these PIs will be evaluated through a self-evaluation report describing the results of the first five years of the WPI program, together with the research plans for the second five years written by each PI (that has already been submitted), which will then be evaluated by the Director (by March 2023). The allocation of research funds and amount of allowance will be determined based on the results of this evaluation.

ASSESSMENT OF RESEARCHERS

Salaries of the Institute's researchers are paid on an annual basis, and their annual salary can be flexibly changed as seen necessary. Therefore, the researchers' research performance will be reflected on their salary under the discretion of their host PIs.

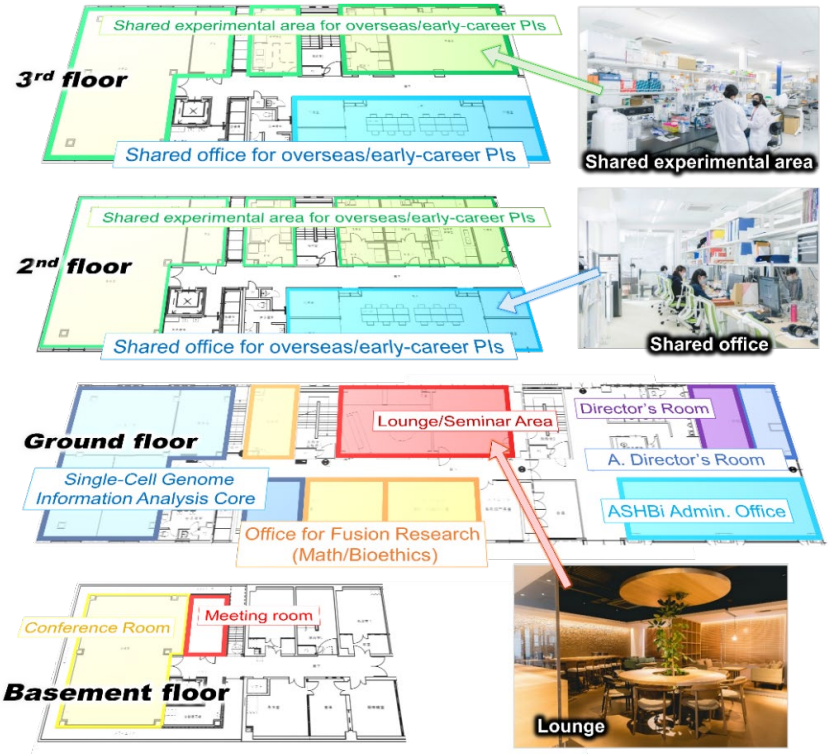
5) -2 Research environment

* Concretely describe how equipment and facilities, including laboratory space, will be provided in a manner appropriate for a "world premier international center." Include your procedure and timing.
* Concretely describe how the center will consider to arrange for its researchers to participate in the education of graduate students.
* Describe your measures other than the above to ensure that world's top researchers from around the world can comfortably devote themselves to their research within an international and competitive environment at the center.

Research space and facilities

ASHBI MAIN BUILDING

After the launch of the Institute in October 2018, we have continuously renovated our 2,010 m^2 main building to improve its functionality as an interaction hub. The first-floor houses facilities that play a central role for the interaction of researchers within/outside of the Institute, with the SignAC core facility, offices of mathematics and bioethics for interdisciplinary studies, a lounge, seminar room, and the administrative office. 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 interactions between the different PI groups.



CORE FACILITIES

The Institute has implemented three cores to facilitate its capacity for research development. First, the Institute has established **Single-cell Genome Information Analysis Core (SignAC)** within the Institute's main building. SignAC has continuously introduced state-of-the-art instruments for genome information analysis, such as high-throughput DNA sequencers and long-read single-molecule sequencers. Combined with the expertise developed by the highly-skilled staff scientists and technical staffs, the core facility has developed to serve as one of the key hubs for life science research at Kyoto University. By further extending its development, SignAC aims to strengthen its presence and competitiveness around the world. Second, **Primate Genome Engineering Core (PRiME)** has been established at the Research Center for Animal Life Science (RCALS) of the Shiga University of Medical Science, which has one of the largest colonies of cynomolgus monkeys in Japan. PRiME develops basic technologies for the genetic engineering of cynomolgus monkeys. Third, the Institute has established **Non-human Primate Phenotype Analysis Facility (NPAF)**, which is used for analyses of the phenotypic aspects of genome-edited macaque monkeys, including social

interaction behavior, cognitive function, and emotional expressions.

Participation to the graduate student education

COLLABORATION WITH THE KU GRADUATE SCHOOL OF MEDICINE

The KU Graduate School of Medicine offers research training courses on 12 different themes. The Institute will jointly organize the "Developmental Biology/Cell Biology/Systems Biology" course. This course provides discussion beyond specialized fields and will be organized as a monthly seminar that includes two talks in English. Every year, 2-3 PIs from the Institute are invited to teach this course, and the Institute PIs have the opportunity to interact closely with graduate students in the Graduate School of Medicine.

JOINT PHD PROGRAM BETWEEN KU AND MCGILL UNIVERSITY

To further enable Institute PIs to participate in the education of international graduate students, we have been and will continue to utilize the joint PhD program, "**Kyoto-McGill International Collaborative Program in Genomic Medicine**" established in October 2018 between KU and McGill U. Students accepted into this program spend their time between the two universities. The Institute PI, **Guillaume Bourque**, is one of the main organizers at McGill U.

FUNDING SUPPORT FOR RECRUITING INTERNATIONAL STUDENTS

To further promote the recruitment of international graduate students, we will effectively utilize the "**ASHBi Financial Support Program for International Graduate Students**" established in 2020. This program supports the living expenses of international students studying at the Institute. Graduate students selected for this funding support program receive a monthly stipend of 150,000 yen for the duration of their enrollment in the doctoral (or master) degree program.

5) -3 Establishing an independent research center in sync with reorganizing the host institution

* Concretely describe how your proposal seeks to establish a new center that will achieve independence within 10 years and how the project will advance synchronization between WPI center support and reform of the host institution's existing organization?
* With prior consent from the host institution, describe concretely the host institution's mid-to-long-term plan and schedule for achieving the center's independent operation within the host institution, including adjustments to the existing organization and/or acquisition of external funding.

In order to carry out the Institute's operation and research activities after the WPI program, KU will provide various supports as described below.

i) CORE FACILITY MAINTENANCE

KU will make the Institute's core facility (SignAC) a university-wide shared facility and take responsibility of its personnel, operating costs and further developments.

ii) PARTICIPATION IN THE UNIVERSITY-WIDE CORE FACILITY PLATFORM

KU has invited the Institute's core facility (SignAC) to join the "Innovative Support Alliance for Life Science (iSAL)", a university-wide platform of core facilities from various life science-related departments. This platform provides open access to both internal and external researchers of KU, allowing SignAC to increase its revenue. Furthermore, researchers, as well as technicians, have been assigned to the Core to further develop its technologies. This has enabled SignAC to obtain external grants on their own (e.g., AMED BINDS). These measures will allow SignAC to maintain its cutting-edge, as well as to support its

self-sustainability.

iii) PERSONNEL SUPPORT

KU will provide 5 professorship tenure positions to the Institute. Two of these tenure positions were already offered to the Institute at the end of 2021. KU will further provide three tenure positions by April 2024 and actively seek possibilities to assign additional posts. Furthermore, the newly tenured professors will be assigned as collaborative faculty members to graduate schools allowing them to take graduate students in their labs.

iv) FINANCIAL SUPPORT

For indirect funding acquired by the Institute's researchers, the portion that is typically allocated to the university headquarters' will be allocated to the Institute as university support [#1]. The following support will be maintained by covering its costs with indirect funds from KU.

- The Institute's PIs will continue to receive allowance and post-doctoral employment expenses (at least one) to keep the integrity of the Institute's PIs even after the end of the WPI funding.

- The Institute's main building will be maintained by covering its rental costs/utility expenses with financial support from KU.

- The Administrative Office's functions will be maintained by covering its personnel/operating costs with financial support from KU.

[#1]A special budget for WPI centers secured by the university headquarters.

v) SYSTEM REFORM

- KU allows the Institute to incorporate a flexible multiple-year budget for its funds. This enables the Institute to carry over a portion of its budget over two fiscal years to ensure flexibility in its budget operations.

- KU allows KUIAS to retain its excellent researchers to be employed even after the retirement age of 65.

- KU allows KUIAS to introduce a flexible allowance payment system so that the annual salary of tenured researchers, which is determined by the academic regulations, can be increased in accordance with their research achievements.

vi) COLLABORATIVE SUPPORT WITH THE HAKUBI PROJECT

In order to increase the number of foreign PIs at the Institute in the long-term, KU will establish a system to assign researchers from the HAKUBI Project as young PIs at the Institute. This KU project, with the aim of fostering world-leading researchers, recruits more than 20 promising young researchers from around the world each year. Through close collaborations with the HAKUBI Project, we will effectively promote the internationalization of the Institute's PIs.

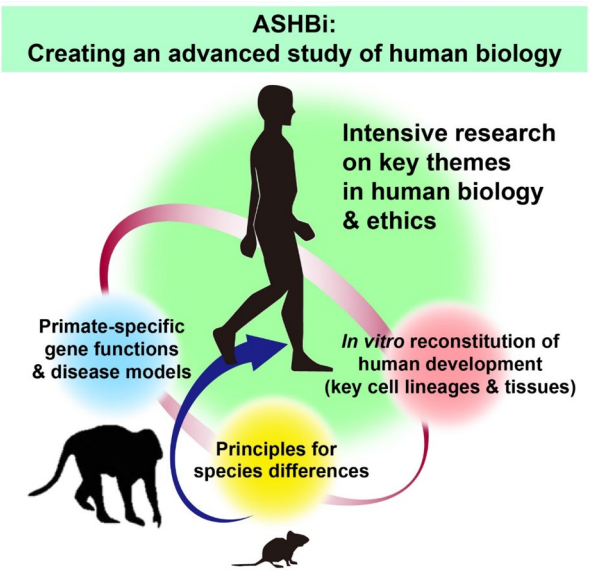
Center Director's Vision

We have established the **Institute for Advanced Study of Human Biology (ASHBi)**, with the mission of investigating the core concepts of human biology, including disease states. ASHBi investigates key aspects of human biology using multi-disciplinary integrative strategies in order to clarify what makes us 'human'. **The knowledge gained will not only provide insights into human evolution but also create the basis for delineating disease etiologies and allow the development of innovative therapies, thereby promoting health from birth to senescence (Figure).**

Understanding the basic biology of human beings is a fundamental challenge in the field of life sciences. In the 20th century, the life sciences elucidated the physical/chemical basis of life, demonstrating that basic processes for life have largely been conserved during evolution. On the other hand, the knowledge gleaned from model organisms has often been difficult or impossible to translate to human biology due to species differences in the regulations of key basic pathways. Accordingly, **many outcomes of drug discovery research in model organisms such as mice have not been replicated in human clinical trials**. This is not entirely surprising, considering that humans and mice have evolved independently over ~80 million years. The two species have diverged in crucial ways, with humans securing a much longer time span for individual development and growth, acquiring unique metabolic regulations, and achieving a remarkable development of their brain functions. **Although the genome and transcriptome in many organisms have now been sequenced, the exploration of species-specific gene functions, particularly in humans and other primates, is only in its incipient stage, and the methodologies for integrative analysis of multi-omics information across species remain to be developed.**

Thus, the study of human biology requires the use of human materials. However, such materials, in particular those related to human development, are technically and ethically difficult to obtain, and consequently, the mechanism for the origin of human life, i.e., human development, has been elusive. It is worth noting that access to human materials is more restricted in Japan than in other countries. To circumvent this difficulty, it is critical to create a systematic opportunity for access to human materials, as well as for the use of non-human primates as a human model. With this respect, however, it should be noted that even the macaque monkeys (e.g., rhesus and cynomolgus monkeys), who are the closest to humans among the models amenable for experimentation, have evolved independently from humans over ~25 million years. **Hence, to promote human biology significantly beyond the current practices, it is imperative to perform parallel investigations into humans and non-human primates and, simultaneously, to clarify the principles for the emergence of species differences in order to extrapolate the knowledge from model organisms to humans. Indeed, in a broader context, a major challenge for the 21st century life sciences is to understand the underlying mechanistic basis of species differences—i.e., the diversity of life forms driven by evolution.**

Accordingly, ASHBi will target humans and non-human primates as major research subjects in an effort to uncover the core concepts of human biology and disease states, through a multi-disciplinary scientific approach that we call **Advanced Study of Human Biology**. **By 'Advanced Study' this means the meticulous analysis of target processes, systems-level understanding of the collated information, reconstitution of key lineages, tissues and disease states based on such information, and further analysis of the reconstituted systems, which will ultimately lead to the "synthesis" of a comprehensive understanding of target processes.**



Towards this goal, **ASHBi will perform intensive investigations on key aspects of human reproduction, development, growth and aging as well as heredity and evolution**. Moreover, ASHBi will establish two lines of interdisciplinary science and three core facilities for cutting-edge technologies to deliver a highly coherent research program.

First, **by creating a fusion between the life sciences and mathematics, using machine learning and topological data analysis to extract the geometry of large-scale data, we will uncover the human traits and the principles defining species differences based on multi-species/multi-cell type/multi-**

hierarchical omics/imaging information, to allow for the better elucidation of human traits. We will extend this analysis to identify principles for the species differences on the scales of time and space during development and growth. Second, **by integrating the humanities and social sciences**, we will formalize the ethical grounds for the appropriate use of human and non-human primate materials and create a philosophy regarding the values of research outcomes of the Institute.

With respect to the three core facilities, we have first established **the single-cell genome information analysis core (SignAC), which will further expand and become accessible throughout Japan via Kyoto University,** to facilitate the acquisition of high-quality, multi-hierarchical, large-scale omics data for gene expression, genome sequence and structure, and epigenetic profiles at the single-cell resolution. Second, we have implemented **the primate genome engineering core (PRiME)**, which will provide a stable supply of embryos/adult tissues of macaques and create macaques lacking key genes for primate-specific traits for disease modeling and biological analysis. **In particular, this core will generate disease models for the nervous system and the kidney, two examples for which rodent models have been largely unsuccessful in drug screening.** Third, we have created **the non-human primate phenotype analysis core (NPAF)**.

Moreover, to strengthen the interactions among PIs and the identity of ASHBi, we will establish five flagship projects: **1. Deconstructing and reconstructing early 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 a new mathematics "data representation theory"; 5. Bioethics at the periphery of birth and death.**

Thus, ASHBi will elucidate the human traits and the principles defining species differences, reconstitute key lineages and tissues, and generate primate models for specific gene functions and intractable diseases. Together, these efforts will realize **advanced study of human biology as a forefront of life science in the coming decades and as a foundation for transformative therapeutic interventions.**

To accomplish this goal, ASHBi has built a critical mass of scientific expertise by drawing scientists with outstanding potential from Kyoto University and relevant institutions in Japan and overseas, creating an intellectually interactive and highly collaborative setting. To achieve such an international research effort, the Institute has provided principal investigators (PIs) from overseas with adequate budget support for building teams of professional research staff and postdoctoral researchers. The Institute will continue to actively recruit excellent researchers and postdocs through open international recruitments and it will support each PI team with at least one non-Japanese staff/postdoc. Further, the Institute will continue to maintain links with international institutions such as European Molecular Biology Laboratory (EMBL), McGill University, and Karolinska Institute, **creating a stratified organization for research promotion and strengthening the Institute's international profile and competitiveness**.

The center director, Mitinori Saitou, has been a world leader in germ cell biology and *in vitro* reconstitution of germ cell development (for review, see *Cell Stem Cell*, 2016). To extend the findings from mice to humans, Saitou has promoted research using cynomolgus monkeys and created a basis for defining the species differences among humans, monkeys and mice. This includes elucidation of a developmental coordinate of the spectrum of pluripotency among mice, monkeys and humans (*Nature*, 2016); the finding that the germ cell lineage in primates originates in the nascent amnion (*Dev. Cell*, 2016); and a robust induction of germ cell fate from human iPSCs and the identification of an underlying transcriptional architecture unique to primates (*Cell Stem Cell*, 2015; 2017). In addition, Saitou established a procedure for single-cell transcriptome analysis more than a decade ago (*NAR*, 2006; *Genes Dev.*, 2008). Thus, **Saitou's research not only represents a benchmark of the synthesis of scientific approaches, but together with his vision it will help promote the advanced study of human biology**.

Finally, the missions of ASHBi is distinct from those of the Institute for Integrated Cell-Material Science (iCeMS). iCeMS has accomplished outstanding research on the regulation of biological processes using materials such as porous coordination polymers, and has recently become a member of the WPI academy. Kyoto University founded the Institute for Advanced Studies (KUIAS), to which it assigned iCeMS as a constituent institute, thereby establishing a system for the continued development of iCeMS. **As a new WPI at KUIAS, ASHBi will adopt and further develop well-established and successful administrative systems for its effective management, so that it can continue to play a central role in the revitalization of the University.**

Host Institution's Commitment

13/02/2023

To MEXT

Kyoto University

Nagahiro Minato, President

I confirm that the measures listed below will be carried out faithfully and concretely as follows regarding "Institute for the Advanced Study of Human Biology".

Concrete Measures

・Describe the concrete measures that the host institution will take to satisfy the following requirements.

1) For the center to become a truly "world premier international research center" and independent by the time WPI support ends, the host institution must clearly define the center's role within its own mid-to-long-term strategy and provide its comprehensive support from the time that the funded project starts.

※Describe the center's role within host institution's own mid-to-long-term strategy.

Kyoto University clearly defines the role of the Institute for the Advanced Study of Human Biology in its mid-to-long term strategy and provides its comprehensive support to the Institute.

<Positioning of the Institute in the University's mid-to-long-term strategy>

The roles of the KUIAS which include WPI center are clearly specified in the University's mid-to-long-term concepts/plans, namely, "Kyoto University's Vision for the Future (the WINDOW concept)," "Third Medium-Term Goals and Plans," and "Designated National University Proposal."

The "Kyoto University Institute for Advanced Study (KUIAS)" was set up as a foundational organization for the purpose of gathering superior researchers from Japan and around the world, creating an international research center with flexible organization, achieving an organizational structure able to respond to globalization, and providing research support functions.

In the Fourth Medium-Term Goals and Plans, Kyoto University clearly states that "KUIAS will be expanded with further development of the WPI institutes. In addition, Kyoto University will establish a system to support young researchers in challenging new academic fields, as well as to create new research fields with the support and close collaboration with the existing graduate schools and research institutes."

Kyoto University also aims to strengthen its shared facility functions by implementing a university-wide management system to strategically develop its facilities and equipment.

We will continue to support the further development of ASHBi and use it as a role model for globalization and interdisciplinary research at Kyoto University.

<Comprehensive support from the host institution>

・ Balancing intra-university interests by the Kyoto University provost

The "Kyoto University Provost" and the "University Strategy Council" will balance the interests of other departments to provide quick and flexible support for the Institute.

・ Organizational support by **Kyoto University Research Administration Center (KURA)**

The Institute could receive organizational and comprehensive support from KURA, which is one of the largest URA organization in Japan (~ 40 URAs) and received the highest possible score "S-rank" on MEXT's interim evaluation. Further, Kyoto University employs four experts at the Institute, and they operate as a hub maintaining close cooperation with KURA.

・ Collaborative support by the Kyoto University **HAKUBI project**

The HAKUBI project aims to foster and support young researchers who will pioneer new paths in their fields. This project plans to recruit 20 excellent young researchers each year from around the world. In order to increase the number of foreign PIs at the Institute in the long term, Kyoto University will establish a system to assign HAKUBI researchers to ASHBi as young PIs. This will provide an excellent research environment for HAKUBI researchers and excellent potential young PIs for ASHBi.

2) Providing a mid-to-long-term policy for amending the plan on the direction of the host institution's organization and operation, one that includes the reform of the institution's existing organization in ways that will achieve the center's independence and create a permanent place for it within the organization. A concrete plan and schedule must be set and carried out for restructuring the host institution's organization.

※Describe both a mid-to-long-term policy for amending the plan on the direction of the host institution's organization and operation and provide a concrete plan and schedule.

<Establishing and maintaining a globally competitive core research facility>

In order to become a truly world-leading research center, the center needs to possess globally competitive research facilities shared by researchers across Japan (core facility). The Institute has established a highly competitive core facility: the Single-cell Genome Information Analysis Core (SignAC), which has state-of-art instruments and robust analytic technologies for genome analyses at the single-cell level. Several highly-skilled scientists and technical staffs are assigned to this facility to maintain and improve the performance of its instruments and analytic technologies.

The efforts of the Institute to establish and maintain the core facility will serve as a basis to make a generalized model, which are applicable to other departments, to set up a globally competitive core facility. The University will take the initiative to spread this model to other departments.

<Basic plan/schedule>

- Improve and renew the instruments of SignAC to maintain its competitiveness (FY2023/FY2024).
- Increasing staff and expanding space at SignAC to strengthen its core facility function (FY 2025/FY2026).
- Make SignAC a university-wide shared facility independent of the Institute. (FY2027).

3) Provide sufficient support for carrying out the center's operation and research activities, including necessary personnel, financial, and system support.

In order to carry out the Institute's operation and research activities, Kyoto University provides various supports as described below.

<Core facility maintenance support>

Kyoto University will make the Institute's core facility (SignAC) a university-wide shared facility and take responsibility of its personnel, operating costs and further developments.

<Personnel support>

Kyoto University provides 5 tenure professor positions to ASHBi. Two of these tenure positions were already provided to ASHBi by the end of 2021. Kyoto University will provide three tenure

positions by April 2024 and actively seek possibilities to assign additional posts when necessary. The newly tenured professors will be assigned as the collaborative faculty members to graduate schools allowing them to take graduate students in their labs.

<Financial support>

For indirect funding acquired by ASHBi researchers, the portion allocated to the university headquarters' (half of the total indirect funding) will be allocated to ASHBi as university support[#1].

Furthermore, Kyoto University will cover the personnel costs for maintaining the Institute's administrative functions including the Research Acceleration Unit. In addition, Each ASHBi PI in Kyoto University will be provided the employment cost of at least one postdoc researcher as well as their PI allowances as an incentive after the WPI funding period. Kyoto University will actively seek possibilities for additional personnel and funding supports to ASHBi.

[#1] 世界トップレベル活動支援経費: A special budget for WPI centers allocated by the university headquarters.

<System support>

In order to promote the constant influx of promising young overseas researchers to ASHBi, Kyoto University will establish a system to assign HAKUBI researchers as young PIs/researchers at ASHBi.

Kyoto University allows ASHBi to incorporate a flexible multiple-year budget for its funds. This enables the Institute to carry over a portion of its budget over two fiscal years to ensure flexibility in its budget operations.

In addition, KUIAS is allowed to retain its excellent researchers to be employed even after the retirement age of 65.

KUIAS also introduces a flexible allowance payment system so that the annual salary of tenured researchers, which is determined by the academic regulations, can be increased in accordance with their research achievements.

4) Provide necessary support to achieve the independence of the center and sustain its research at a top world level after the WPI grant period ends.

Kyoto University will continue to supply the Institute with the support stated in (1)–(3) and (5)–(9) after the end of the WPI grant.

5) Provide a system that will in practice allow the center director to make decisions in implementing the center project, including personnel and budgets, and that will secure the autonomy of its operation.

Under the umbrella of KUIAS, which is a special research district at Kyoto University, the Institute's director has the authority to make the final decision on important matters, such as choice of research direction, personnel affairs, and budgetary concerns.

6) Provide support to the center director by coordinating with other departments regarding the assigning of researchers to the center and the creating of an effective environment for the center within the host institution. Needed adjustments to do so should be made proactively while giving consideration to their effect on the educational and research activities of those departments.

In the WINDOW concept (Strategic Priority 5-3), Kyoto University declares the following:

In order to break new ground in uncharted domains of academic endeavor, Kyoto University implements flexible and effective reorganization that removes the boundaries of existing academic departments through the ***Faculty Consort/Platform System***[#2] *of academic staff organization.*
And also "Key Presidential Policies" published in March 2021 clearly state that the university will promote reforms on introducing a more flexible and functional educational and research organizational system while fully pursuing the objective of the ***Faculty Consort/Platform System***.

Based on this conceptual direction, Kyoto University provides all-out support for the Institute's director by proactively adjusting the interests of other academic departments whose essential researchers for promoting interdisciplinary research at WPI center are dispatched to the Institute.

[#2] 京都大学 学域・学系制: A system introduced in April 2016 to ensure effective coordination of educational and research activities by separating researchers' personnel affairs from departments (educational and research organizations).

7) Offer cooperation in flexibly applying, revising, or supplementing the host institution's internal systems as needed for the center to effectively implement new management methods unfettered by conventional modes of operation (e.g. English-language environment, merit-based pay, top-down decision making, linkage to graduate school education).

Under the umbrella of KUIAS, which is a special research district at Kyoto University, it is possible to flexibly revise and improve the Institution's systems, such as abolishing mandatory retirement, establishing an incentive system based on performance, assigning bilingual administrative staff, and determining personnel affairs based on top-down management by the Institute's director.

8) Secure, provide and deliver the necessary infrastructure for the center to carry out its activities (e.g. research space, facilities, land).

<Research space>
Kyoto University provides ASHBi to use Faculty of Medicine Building B as its main building in addition to the spaces provided to the PIs residing in Kyoto University. The ASHBi Main Building serves as a home ground to the laboratories of overseas PIs and young PIs, the SignAC core facility, open space for researcher interactions, and the ASHBi administrative office. Kyoto University will flexibly seek opportunities to provide additional spaces to ASHBi in the future.

A director's room and an administrative director's room are located in the ASHBi main building, in order to facilitate regular interactions between the Institute's executives, researchers, and administrative staff. Another director's room is also secured in the KUIAS building, enabling regular exchanges with KUIAS's executives and the utilization of KUIAS's expertise and knowledge.

<Use of animal research facilities>
ASHBi researchers are given permission to use the Institute of Laboratory Animals in the Graduate School of Medicine Kyoto University, which is one minute walk away from the main research building.

<Online platform infrastructure of core facilities >
Kyoto University invites SignAC to join the **"Innovative Support Alliance for Life Science (iSAL)"**, a unified platform of core facilities from various departments related to life science studies. Using the online management system of the iSAL for equipment reservation and payment, SignAC can provide smooth access to its facilities for researchers in/out of ASHBi.

9) Provide other types of assistance to give the center maximum support in achieving its concepts and objectives and in becoming a world premier international research center in both name and deed.

Kyoto University commits itself to provide maximum support for the establishment of the Institute as a leading international research center under the University's mid-to-long-term vision. Furthermore, Kyoto University will strongly pursue for additional supporting possibilities and options to ASHBi in maintaining its role after the WPI funding period.

10) The host institution is to self-evaluate the results of the system reforms achieved by the center and distribute the results that it evaluates highly to all of its departments.

The **University Strategy Council** members and the University executives evaluate the Institute's system reform outcomes and the proposed reform models. If positively evaluated, the **Kyoto University Provost** will take the initiative to spread the good system reforms to other departments throughout the University.

11) (For host institutions that already have an existing WPI center) Fully support and sustain the existing center and advance its development as a top world-level research institute while being concurrently capable of fully supporting the new center.

The existing WPI center, iCeMS, is now located as a core and the research institute of KUIAS as a permanent entity. Separate to the support for ASHBi, Kyoto University will provide personnel support for iCeMS (11 tenure posts and 1 early career researcher) as well as financial support providing headquarters' allocation of indirect expenses to iCeMS from competitive grants acquired by the institutions' researchers. Kyoto University will support both research institutions continuously in the future.

12) (For host institutions that already have an existing WPI center) Take the initiative to spread the existing center's good system reform results to other departments throughout the institution and thus applied them to its own reform.

Kyoto University has extended the good system reform results from iCeMS throughout the university. Three representative examples are shown below.

1) System reforms newly provided by iCeMS such as the cross-appointment system, annual salary system, and exceptions to mandatory retirement have been introduced in other departments (**Graduate School of Advanced Integrated Studies in Human Survivability**, the **Institute for Liberal Arts and Sciences**, and **KUIAS** including ASHBi).

2) Various forms of support for foreign researchers from the **Overseas Researchers Support Office** in iCeMS have led to the establishment of the **International Service Office** in the University. This has been expanded to many other departments in the University, including ASHBi.

3) Based on knowledge gained at iCeMS concerning international public relations, a new **Office of Global Communications** was established in the University in October 2015. ASHBi receives strong support from this office for its international public relations efforts.

Appendix

List of Principal Investigators

・If the number of principal investigators exceeds 10, add columns as appropriate.
・Place an asterisk(*) by the name of the investigators who are considered to be ranked among the world's top researchers.
・Give age as of 1 April 2023.
・For investigators who cannot participate in the center project from its beginning 1 April of 2023, indicate the time that their participation will start in the "Notes" column.
・Include principal investigators affiliated with satellite institutions. Give the name of their satellite institutions in the "Notes" column.

	Name	Current affiliation (Department/ School/Institution)・Title	Specialization	Effort * (%)	Notes
1	Mitinori Saitou *	Professor, Kyoto University Institute for Advanced Study, Kyoto University	Cell Biology, Developmental Biology	90%	
2	Tadashi Isa *	Professor, Graduate School of Medicine, Kyoto University	Neuroscience	80%	
3	Yasuaki Hiraoka *	Professor, Kyoto University Institute for Advanced Study, Kyoto University	Applied Mathematics	70%	
4	Guillaume Bourque *	Professor, Human Genetics, McGill University	Bioinformatics, Genomics, Epigenomics	25%	
5	Seishi Ogawa *	Professor, Graduate School of Medicine, Kyoto University	Molecular Oncology	90%	
6	Hideki Ueno *	Professor, Graduate School of Medicine, Kyoto University	Immunology	95%	
7	Takashi Hiiragi *	Hubrecht Institute–Group Leader/ Professor, Graduate School of Medicine, Kyoto University	Developmental Biology	20%	
8	Motoko Yanagita *	Professor, Graduate School of Medicine, Kyoto University	Nephrology	70%	
9	Takuya Yamamoto	Associate Professor, Center for iPS Cell Research and Application, Kyoto University	Molecular Biology, Bioinformatics	80%	
10	Masatsugu Ema	Professor, Research Center for Animal Life Science, Shiga University of Medical Science	Developmental Biology, Developmental Engineering	70%	Satellite institution: Shiga University of Medical Science
11	Misao Fujita *	Professor, Center for iPS Cell Research and Application, Kyoto University	Bioethics	70%	
12	Cantas Alev *	Associate Professor, Institute for the Advanced Study of Human Biology (ASHBi), Kyoto University	Developmental Biology	100%	
13	Ken-ichi AMEMORI	Associate Professor, Institute for the Advanced Study of Human Biology (ASHBi), Kyoto University	Neuroscience	100%	
14	Yasuhiro MURAKAWA *	Professor, Kyoto University Institute for Advanced Study, Kyoto University	HumanGenomics,Medical Science,Systems Biology	100%	
15	Ryo YAMAMOTO	Associate Professor, Institute for the Advanced Study of Human Biology (ASHBi), Kyoto University	Hematology	100%	
16	Sungrim SEIRIN-LEE	Professor, Kyoto University Institute for Advanced Study, Kyoto University	Mathematical Biology and Medicine, Mathematical modeling, Applied Mathematics	100%	

* Percentage of time that the principal investigator will devote to working for the center vis-à-vis his/her total working hours. (Activities carried out using competitive funding can be included as effort as long as they correspond to the purpose of the WPI center and are conducted for the center.)