World Premier International Research Center Initiative (WPI)

Research Center Project

* Compile in English within 20 A4 pages.

Center name: Institute for the Advanced Study of Human Biology

Host institution: Kyoto University

Head of host institution: Juichi Yamagiwa, President

Prospective center director: Mitinori Saitou, Professor, Graduate School of Medicine

Appendix 1: "Biographical Sketch of Prospective Center Director" (to be attached)

Appendix 2: "Reference (recommendation) for prospective center director by world's distinguished researcher(s) in the center's target field" (to be attached)

Prospective administrative director: Tadashi Ogawa, Professor, Center for Enhancing Next-Generation Research

Appendix 3: "Biographical Sketch of Prospective Administrative Director" (to be attached)

1) Overall Framework of the Center Project

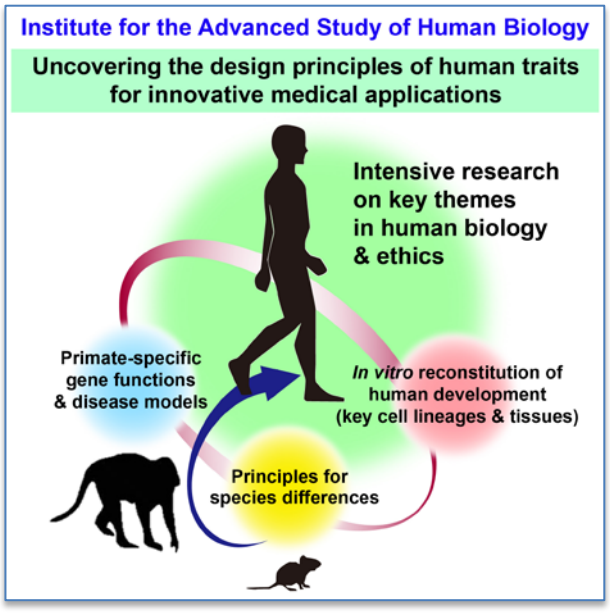
* Cleary and concisely describe your center's mission statement as a WPI center, its identity, and its goals toward achieving the objectives of the WPI program.

The mission of the **Institute for the Advanced Study of Human Biology** is to elucidate the design principles of human traits, 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 achieve outstanding research in key themes in human biology with an intense focus on genome regulation and disease modeling in the areas of reproduction, development, growth and aging as well as heredity and evolution.
2) to elucidate, with multi-disciplinary approaches, the principles for the emergence of species differences for appropriate extrapolation of the findings in model organisms to humans.
3) to generate primate models for intractable diseases and key gene functions.
4) to reconstitute and validate key human cell lineages and tissues based on integrative information.
5) to formalize an ethics for the appropriate use of human and non-human primate materials and create a philosophy to direct the values of the Institute's research outcomes.

In the realization of these goals, the Institute will create and promote advanced study of human biology" as a forefront 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. The advanced study of human biology will create such a strategy, providing a foundation for the development of innovative medical interventions.



Despite the obvious importance and urgent need,

due to technical/ethical difficulties, there is as yet no institute 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.
* Appendix 4: "Up to 10 English-written papers (review papers are also acceptable) closely related to the center's project and their list" (to be attached)

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 an 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 machine learning and topological data analysis (TDA)** and **between life sciences and humanities/social sciences (bioethics** and **philosophy on life)**, respectively, and will implement two research development cores for **multi-hierarchical genome information analysis at the single-cell level** and **cutting-edge genome editing in primates**, 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

The elucidation of the design principles of human traits, 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 well being 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 unsuccessful to translate 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 many outcomes of drug discovery research in model organisms such as mice have not been replicated in human clinical trials.** We would here like to point out two prominent examples:

First, during human evolution, remarkable changes have been accomplished 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 the 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 candidate drugs developed using rodent models proving ineffective in pre-clinical trials and many mega-pharmas withdrawing from drug development for such disorders.

Second, the kidney is a critical organ that maintains homeostasis of the body fluid. It is becoming clear that rodent models are insufficient for understanding the pathology of human kidney diseases. For example, diabetic nephropathy is a main cause of the 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. Acute kidney injury (AKI) refers to a condition in which kidney function declines rapidly. Various drugs have shown effectiveness in the pre-clinical trials using AKI mouse models, but 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 human models due to species differences, most likely in most tissues/organs. Accordingly, human biology necessitates the use of human materials. However, such materials, particularly those for human development, are technically and ethically difficult to obtain. We therefore need to create systematic and ethically appropriate opportunities for access to human materials, as well as 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), who are the closest to humans among the models amenable 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, and simultaneously, to clarify the principles of the emergence of species differences, allowing better extrapolation of the knowledge from model organisms to humans. Indeed, in a broader context, a major challenge for 21st century life science will be to understand the mechanistic basis of species differences—namely, 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 the research findings anticipated at this Institute (artificial human gametes, cerebral cortices, 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 highly 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

To realize the salient and ambitious goal of establishing 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 drawing 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 setting.

Currently, the access to human materials is more limited in Japan than other countries. On the other hand, Japan has a clear advantage over Europe and the USA in terms of the access to non-human primates. While creating systematic opportunities for the access to human materials, the Institute will simultaneously implement the **Core for Primate Genome Editing** 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 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 Center, both in Japan and around the world. Thus, it is highly timely and advantageous for the Institute to implement the **Core for Primate Genome Editing** and expand on research using non-human primates. Moreover, **the Core for Primate Genome Editing will be tightly linked and will 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 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 rapidly 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** is invited in 2018). **The Wellcome Trust is currently preparing a new initiative, the Human Developmental Biology Initiative (HDBI)** (in which **Takashi Hiiragi** is involved)**, at a cost of £10m**. These activities are primarily 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 yet no institute among the world's leading countries that is primarily focused on human biology. We consider that 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 overall very limited. **EMBL** has recently established a new outstation in **Barcelona** dedicated to tissue biology and disease modeling. However, their studies are so far limited to stem cell culture 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, their large size and high diversity would make it difficult to coordinate their efforts along a focused research line such as 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 could play a unique and world-leading role in the fundamental research of human biology.

Ten papers closely related to the center's project and their list

Appendix 4

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 10 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 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 ten year, the key research goals of the Institute will be the following:

1) to achieve outstanding research in human biology with an intense focus on genome regulation and disease modeling in the areas of reproduction, development, growth and aging as well as heredity and evolution.
2) to clarify the principles for the emergence of species differences in organismal traits among humans, non-human primates, and rodents, creating a strategy for better extrapolation of the knowledge from model organisms to humans.
3) to uncover the primate-specific functions of key genes and to create critical disease models by genome editing in cynomolgus monkeys.
4) to re-create in vitro the development and physiology of key cell lineages and tissues (e.g., early embryos, germ cells, neural tissues, lymphocytes, etc.).
5) to formalize an ethics for the appropriate use of human and non-human primate materials and create a philosophy to direct the values of the Institute's research outcomes.

Thus, 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

The Institute will inaugurate with 13 PIs. These will include 9 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)**, 2 PIs leading the interdisciplinary sciences and 2 research development cores (2 PIs). Together, these units will allow the Institute to achieve a coherent research program focused on its goal of advanced synthesis of human biology (Figure: page 7). The Institute will recruit 3 young PIs (Associate Professors) to accelerate its mission.

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

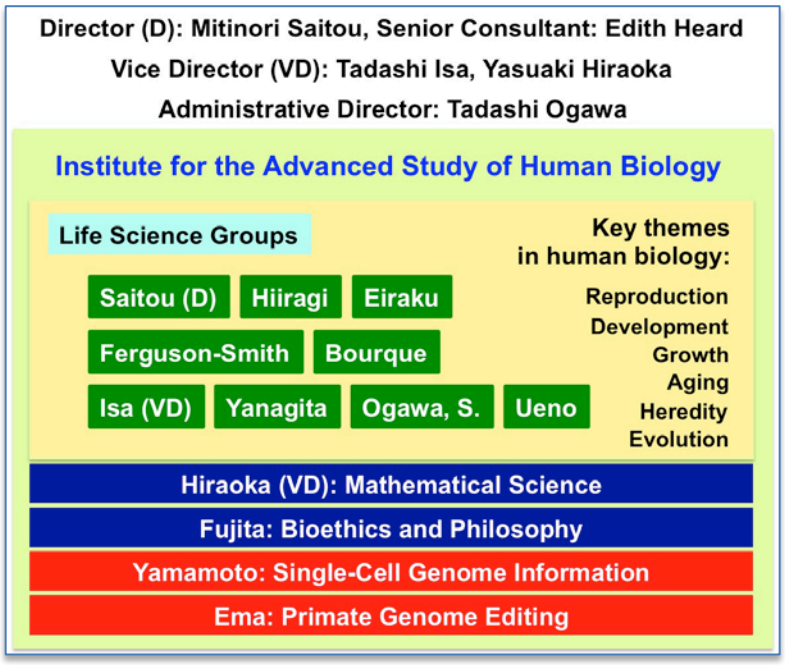
Yasuaki Hiraoka (Prospective Vice Director), a world-leading mathematician in topological data analysis (TDA) and applied mathematics, will lead the **Group for Mathematical Science**. This group will develop novel methodologies for analyzing multi-hierarchical, large-scale omics data based on mathematics such as TDA and machine learning to clarify the principles for the emergence of species differences of "homologous" cell types or on the scales of time and physical dimensions in development among humans, non-human primates and rodents, allowing appropriate extrapolation of the knowledge from model organisms to humans.

Misao Fujita, an expert in bioethics using an empirical approach, will lead the **Group for Bioethics and Philosophy**. This group will formalize an ethics for the appropriate use of human and

non-human primate materials and create a philosophy to direct the values of the Institute's research outcomes (e.g., artificial gametes, artificial cerebral cortexes, genome-edited monkeys). For details on their activities, see section 3) Interdisciplinary Research.

Takuya Yamamoto, an expert of genome information analysis, will lead the **core for single-cell genome information analysis**. The core will develop cutting-edge technologies for acquiring multi-hierarchical large-scale datasets for gene expression, genome sequence and structure, and epigenetic profiles at the single-cell level, supporting the research of all groups. In addition, **Yamamoto** will develop methodologies for measuring global post-transcriptional modifications and translational regulations to capture entire gene expression processes, contributing to exploration of the principles for the emergence of the species differences based on such comprehensive datasets.

Masatsugu Ema, who is an expert of developmental engineering based at the **Research Center for Animal Life Science, Shiga University of Medical Science (the domestic satellite of the Institute)**, will lead the **core for primate genome editing**. The core will ensure a stable supply of embryos/adult tissues of cynomolgus monkeys, and by developing cutting-edge genome-editing technologies, will generate **genome-edited cynomolgus monkeys** for exploring primate-specific gene functions and establishing relevant disease models, serving an integral function for the research performed by all the PIs. The target genes include those responsible for **brain functions in primates** and for **kidney development and growth, which are significantly divergent between primates and rodents, and for which rodent models have been largely unsuccessful in drug screening** (see "The Importance of the Target Research Fields"). Specifically, these include the core knockouts genes, such as *CHX10* (**Isa**: a candidate for instructing the development of primate-specific hand dexterity), *DYT1* (**Isa**: a gene responsible for dystonia), *DISC1* (**Isa**: a gene responsible for schizophrenia), *PKD1* (**Ema**: a gene responsible for polycystic kidney), *NPHS1* (**Yanagita**: a gene responsible for congenital nephrotic syndrome), 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. The Institute will establish a close link with the **Division of Marmoset Research at the Central Institute for Experimental Animals**, which is a key center for generating gene-edited marmosets, promoting the research for primate genome editing in Japan to the world top level. The Institute will also establish a link with the **Kyoto University Primate Research Institute**, promoting such research goals as the sampling of materials from aged macaques and the derivation of iPSCs from a variety of primates.



The life science groups will promote intensive investigations on key targets in human biology in the areas of reproduction, development, growth and aging as well as heredity

and evolution.

Mitinori Saitou (Prospective Director) is a world leader of 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) into oocytes and spermatogonia. Based on such systems, the group will develop in vitro systems to generate oocytes and spermatogonia from PGC-like cells (PGCLCs) derived from h/cy induced pluripotent stem cells (iPSCs)/embryonic stem cells (ESCs), realizing in vitro analyses of the mechanism for 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. In addition, **Saitou's** group will clarify the mechanism of the species difference in relation to the developmental time for germ cell development among these species.

Takashi Hiiragi is an expert in the developmental biology of mouse early embryos and of their live-imaging analysis. By using the cutting-edge technique of *in toto* live-imaging as well as by developing an in vitro culture system from zygotes to the blastocyst and gastrulation stages, **Hiiragi's** group will establish a primate early development atlas at single-cell resolution. **Hiiragi's** group will combine imaging data with cutting-edge lineage mapping and single-cell RNA-seq data to comprehensively elucidate the mechanism for early development of primates, uncovering the principles conserved across mammalian species and those newly evolved in primates.

Mototsugu Eiraku is a pioneer of the induction of neural tissues, such as optic cup structures with well-stratified retina, from mouse and human PSCs, and has demonstrated that the in vitro development of neural tissues recapitulates the differences in developmental time between mice and humans, e.g., the induction of optic neurons from mouse PSCs requires ~20 days of culture, whereas that from human PSCs requires more than 150 days. Using cutting-edge imaging technologies and multi-hierarchical omics analysis, **Eiraku's** group will investigate cellular, molecular and genomic dynamics during the induction of neural tissues from mouse, monkey and human PSCs, clarifying the principles that create the species differences of neurons and their developmental time.

Anne Ferguson-Smith is a world leader of the investigation into the mechanism of epigenetic inheritance. **Ferguson-Smith's** group will test the hypothesis that certain repetitive elements in primates have the potential to influence the behaviour of endogenous genes via their epigenetic properties, that these elements are more sensitive to the environment and that these elements can either propagate or reconstruct an epigenetic memory of the previous generation with an influence on phenotype. The group will also utilise an in utero compromise model in Cynomolgus to decipher the extent and mechanisms of non-genetic inheritance of such compromise with implications for human health and well-being.

Guillaume Bourque is an expert of comparative genome information analyses and has been studying the impacts of repetitive elements on the acquisition of species-specific regulatory circuitry during evolution. The specific objectives of the **Bourque's** group will be to: 1) Build detailed epigenomics maps in different human individuals and non-human primate species; 2) Develop computational methods to predict the impact of non-coding variants; 3) Apply these new predictive tools to study various disease cohorts; 4) Facilitate the distribution of software to study genomics and epigenomics datasets. These works will be a better characterization of non-coding DNA and its impact on health and disease.

Tadashi Isa (Prospective Vice Director) is a world leader of studies of neural networks in primates. **Isa's** group will explore three key aspects of brain functions specific to higher primates: 1) highly skilled hand movements; 2) motor systems highly dependent on the cortico-subcortical loop circuits; and 3) highly developed cognitive functions. For 1), using single-cell RNA-seq analysis, the group will explore genes and their networks specific to cortico-spinal neurons in macaques. The group will first analyze knockout monkeys for *CHX10* or *SPP1*, which are specifically expressed in spinal interneurons mediating the cortical command or cortico-spinal neurons in primates, respectively. For 2), the group will generate knockouts for *DYT1*, a gene responsible for dystonia, a basal ganglia disorder, and analyze the neural basis of their behavioral phenotypes, which are expected to be specific to primates. For 3), the group will generate knockouts for *DISC1*, one of the candidate genes responsible for schizophrenia, which is considered to be caused by dysfunction of the neural network involving the dorsolateral prefrontal cortex highly developed in primates, and analyze their phenotypes. Thus, **Isa's** group will create a foundation for the study of gene functions in primate brain functions and generate critical disease models.

Motoko Yanagita is an expert of kidney biology and has made key contributions to understanding of the pathogenesis of many kidney diseases. **Yanagita's** group will perform three lines of research using cynomolgus monkeys: 1) verification of kidney disease models; 2) generation of gene-knockout monkeys; and 3) verification of "fetal programming" in the kidney. For 1) the group will generate an ischemia reperfusion model as an acute kidney injury model, and compare its pathologies with those of mice and humans. For 2), the group will generate knockouts for *NPHS1*, a gene responsible for congenital nephrotic syndrome and encoding NEPHRIN, a slit-membrane protein of podocytes. The group will also generate knockouts for *NPHP1*, a gene causative for nephronophthisis type 1 and encoding nephrocystin-1. Nephronophthisis type 1 is characterized by cyst formation and inflammation in the kidney, and leads to end-stage renal disease at around age 13-14 in humans. For 3), using the maternal nutrition restriction model, the group will verify whether the decrease in the number of nephrons can be reproduced in monkeys, and analyze the gene expression over time to explore the mechanism of nephron number determination by maternal nutrition.

Seishi Ogawa is an expert of 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. Targeting tissues including the mammary epithelium, esophagus, large intestine and hematopoietic system, **Ogawa's** group 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, **Ogawa's** group, together with the **Core for Single-Cell Genome Information Analysis**, 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 informatics for population genetics.

Hideki Ueno is an expert of human immunology and a world leader of the investigation into human T follicular helper cells (Tfh). **Ueno's** group will define the genetic and epigenetic basis regulating the differentiation of naïve CD4+ T cells of different origins. Specifically, the group will define the commonalities and differences among species, i.e., mice, macaques, and humans; among anatomical sites in human organs, i.e., peripheral blood, tonsils, spleen, and gut; and among peripheral blood naïve CD4+ T cells obtained from subjects of different ages. In this way, the group will establish

the principles for the emergence of species/environmental/age differences of the immune responses.

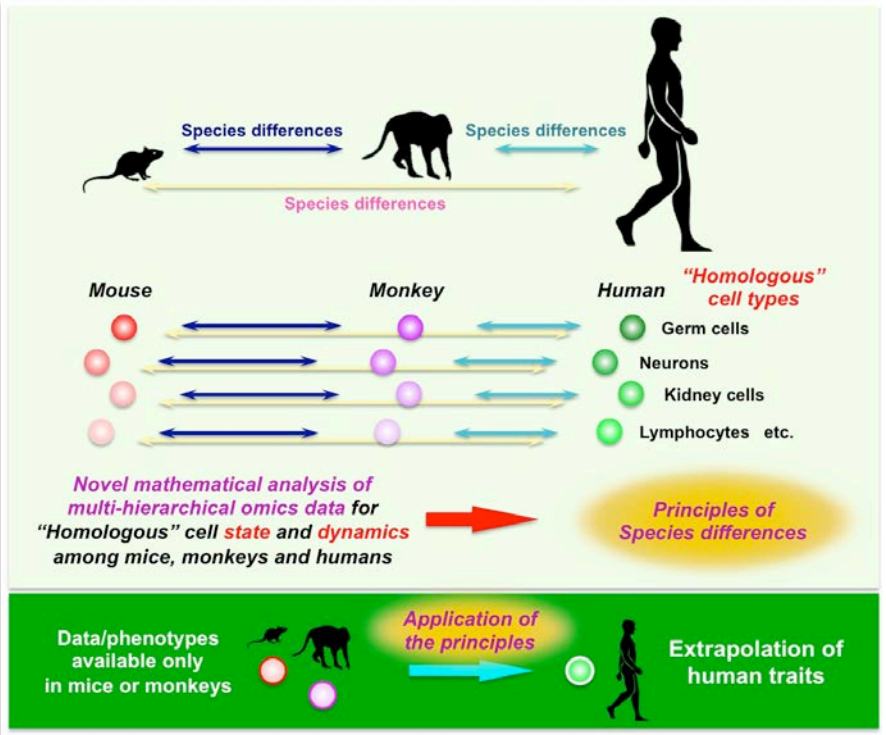
All the PIs are committed to creating a new chapter in the study of human biology, on the basis of their research focusing on key targets in human biology.

Moreover, under the leadership of the director, **all the life science groups** will acquire multi-hierarchical omics data for gene expression, genome sequences and structures, and epigenetic profiles of relevant "homologous" cell types and their differentiation processes among mice, monkeys and humans, which they will then use to **actively contribute to the clarification of the principles explaining the emergence of species differences**.

Thus, with the assistance of **Yamamoto** in the single-cell genome information core, **Saitou** and **Ferguson-Smith** will acquire such data for germ cells, **Hiiragi** for early embryonic cells, **Isa** and **Eiraku** for neurons, **Yanagita** for kidney cells, and **Ogawa** and **Ueno** for hematopoietic lineages, and all such data will be subject to meticulous analyses by novel mathematical methodologies being developed by **Hiraoka** in close collaboration with **Bourque**. The principles for the emergence of species differences uncovered as a synthesis of these endeavors will serve as a strong basis to overcome the gaps between humans and model organisms (Figure: page 10).

All the PIs will therefore be tightly linked with the theme of how the human genome is regulated and how it has diverged from that of model organisms, creating ample opportunities for mutual discussion and synergistic research development toward **the single theme of addressing "how it is to be human as a biological entity"**. We envision that this initiative will lead to the elucidation of the design principle of human beings, a key goal and breakthrough of the Institute with direct relevance to medical innovation.

To date there have been no studies making careful comparison of human disease phenotypes with those of non-human primate models. As a major and unique initiative of the Institute, with the assistance of **Ema** in the primate genome editing core, we will conduct such studies using cynomolgus monkeys one-by-one with a major focus on brain and kidney diseases. Combined with the theoretical strategy as described above (see also 3)



Interdisciplinary research for details), which will realize a better extrapolation of the knowledge from model animals to humans, **defining a strategy to create an original benchmark for exploring human gene functions** (Figure: page 10).

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 5: "List of Principal Investigators" (If there are changes from the PI list in the first screening application documents, describe the points changed and reasons.) (to be attached)
* Appendix 6: "Biographical sketch of principal investigator" (to be attached)
* Appendix 7: "Composition of personnel in center" (to be attached)
* Appendix 8: "Letters from researchers invited from abroad or other Japanese institutions expressing their intent to participate in the center project" (to be attached)

The Center's Research Organization

The Institute will inaugurate with 13 PIs. These will include 9 PIs investigating key themes in human biology, 2 PIs working on leading interdisciplinary sciences and 2 PIs for the research development cores. The Institute will also recruit 3 young PIs (Associate Professors), who will join the Institute in FY2019, to accelerate the Institute's mission. Each PI will recruit 3 research staff (Assistant Professors or Postdocs). The PIs from overseas will recruit 1 co-PI (Associate Professor) and 2 research staff (Assistant Professors or Postdocs). Each PI will recruit at least 1 non-Japanese staff/postdoc. Young PIs will recruit 1 research staff (Assistant Professor or Postdoc). All PIs can recruit research support staff and research associates (RA) at their discretion. In addition, the **Core for Single-Cell Genome Information Analysis** will recruit 2 technical experts and the **Core for Primate Genome Editing will recruit** 5 support staff to efficiently run the cores. The Institute will reach a fully staffed state by the end of FY2019.

The Institute will begin with an Administrative Director and 2 university research administrators (URA) allocated from Kyoto University, and by the end of FY2018 will run its administration with 14 administrative staff in total. See a) Principal Investigators and b) Total Members below.

The Center's Satellite

The Institute will create a key satellite at the **Research Center for Animal Life Science, Shiga University of Medical Science**, where **Masatsugu Ema** (Professor, Shiga University of Medical Science) will lead the **Core for Primate Genome Editing, which bears one of the largest cynomolgus monkey colonies and the most advanced capacities in reproductive technologies in Japan and in the world (~700 cages and isolation of ~40 oocytes per week)**. The core is located within an easy commute (~1 hr) from the Institute.

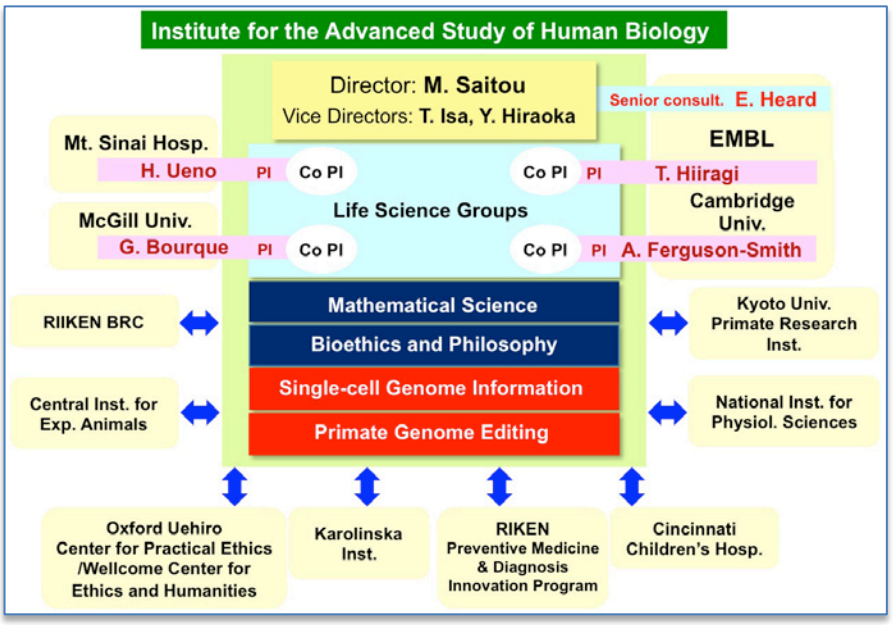
The core will ensure the Institute's research by establishing two units: the **Reproduction Unit** will consist of 4 personnel and will supply embryos/adult tissues of wild-type and genome-edited cynomolgus monkeys through reproductive technologies: ovarian stimulation, oocyte collection, sperm injection, egg transfer to recipients and recovery of embryos. This unit will develop a novel strategy to improve the efficiency of the egg recovery, leading to the promotion of animal welfare. The **Genome Editing Unit** will consist of 5 personnel, and will develop cutting-edge strategies to create transgenic and knock-out/knock-in monkeys for disease models.

The core will support the analysis and characterization of the animals by utilizing CT, MRI and other equipment. The isolated samples (embryos or adult tissues) can be directly analyzed in the core or transferred to the Institute for various analyses. Under appropriate regulations, some of the adult animals, including genome-edited monkeys, can be transferred to the **Institute of Laboratory Animals, Graduate School of Medicine, Kyoto University** for various analyses.

Linkage with Other Institutions **(Figure: page 12)**

The Institute will appoint **Prof. Edith Heard, who is incoming Director of the European Molecular Biology Laboratory (EMBL), as senior consultant**, seeking her advice on the Institute's research direction and management, and establishing an intimate link with EMBL, e.g., having periodical joint meetings and exchanging ideas and expertise. The linkage with EMBL, the leading institute for life science in Europe, will help the Institute attain international standards both in science and management. **Mitinori Saitou** will collaborate with **Edith Heard** on the regulatory mechanisms of X chromosome activities during primate embryogenesis and stem-cell differentiation, corroborating the linkage. **Takashi Hiiragi** (current PI in EMBL) will play a key role in establishing the linkage.

The Institute will also form a linkage with **RIKEN**, particularly with the RIKEN Preventive Medicine & Diagnosis Innovation Program (Program Director, **Yoshihide Hayashizaki**), and will perform high-resolution enhancer mapping, thereby promoting exploration of the principles for species difference emergence among humans, non-human primates and rodents. The Institute will also form a link with the **Karolinska Institute**, where **Seishi Ogawa** is Visiting Professor, and will collaborate with the **Karolinska Institute's** core facility for **Eukaryotic Single Cell Genomics** (Facility Director, **Rickard Sandberg**) to develop cutting-edge methodologies for single-cell genomics.



The Institute will form close linkages with the **Division**

of Marmoset Research at the Central Institute for Experimental Animals (Principal Investigator, **Erika Sasaki**) and the **Bioresource Engineering Division at RIKEN Bioresource Center** (Principal Investigator, **Atsuo Ogura**), developing cutting-edge genome editing technologies in primates. The Institute will form a link with **Kyoto University Primate Research Institute**, promoting such research as the sampling of materials from aged macaques and the derivation of iPSCs from a variety of primates.

The Institute will form a link with the **Oxford Uehiro Centre for Practical Ethics/Wellcome Centre for Ethics and Humanities** (Director, **Julian Savulescu**), and make a cooperative effort to create a novel system of bioethical values for human research.

The Institute will form linkages with the **Cincinnati Children's Hospital Medical Center (Yutaka Yoshida)**, **Kyoto University Primate Research Center (Masahiko Takada)** and **National Institute for Physiological Sciences (Atsushi Nambu)**, with which **Tadashi Isa** will perform intense collaboration. The Institute will also form links with the **University of Cambridge** [**Anne Ferguson-Smith** and **Takashi Hiiragi** (as of October 2018)], **Icahn School of Medicine at Mount Sinai** (**Hideki Ueno**), and **McGill University** (**Guillaume Bourque**) to promote the Institute's research activity.

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

* Paste onto table a) in Appendix 7.

(persons)

	At the start of the project	At the end of FY 2018	Final goal (Date: 4, 2020)
Researchers from within the host institution	8	8	11
Foreign researchers invited from abroad	4	4	4
Researchers invited from other Japanese institutions	1	1	1
Total principal investigators	13	13	16

b) Total number of members

* Paste onto table b) in Appendix 7.

	At the start of the project		At the end of FY2018		Final goal (Date: 4, 2020)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	13		26		58	
Overseas researchers	4	31%	8	31%	18	31%
Female researchers	3	23%	6	23%	17	29%
Principal investigators	13		13		16	
Overseas PIs	4	31%	4	31%	5	31%
Female PIs	3	23%	3	23%	4	25%
Other researchers	0		13		42	
Overseas researchers	0	-	4	31%	13	31%
Female researchers	0	-	3	23%	13	31%
Research support staffs	2		15		20	
Administrative staffs	3		14		14	

Total number of people	18		55		92	

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 (FY2013-2017).

Amount of External Funding (million yen)

Fiscal Year	2013	2014	2015	2016	2017	Total
Domestic PIs	487	540	528	616	547	2,718
Overseas PIs	201	229	240	292	507	1,469

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 (FY2018-2022).
* 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	2018	2019	2020	2021	2022	Total
Total	600	630	662	695	730	3,317

The funding prospects are calculated as the sum of expected competitive funding of each PI (both domestic and overseas), which is the multiplication of the expected funding of each PI (the average of the past record) with the effort of each PI to the Institute's research, with an expectation that the secured funding will increase by 5% each year until YF2022. Note that Kyoto University will allocate all the indirect cost (30% of the competitive funding) to 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 uncover the design principles of human traits. To achieve this goal, the Institute will clarify the principles for the emergence of species differences, allowing appropriate extrapolation of the knowledge from model animals to humans. 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 highly timely to explore this key theme using multi-disciplinary approaches.**

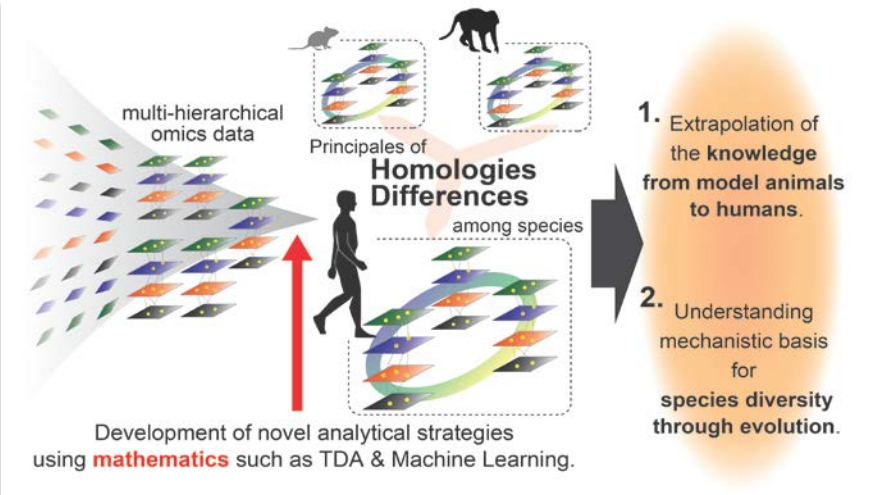
Accordingly, the Institute will clarify the principles underlying the emergence of species differences in the properties of "homologous" cell types and in their responses to key biological stimuli in humans, non-human primates, and rodents using an interdisciplinary approach of life science and mathematics. Specifically, using these species, the life science groups and the **Core for Single-Cell Genome Information Analysis** will acquire multi-hierarchical large-scale omics data for gene expression, genome sequence and structure, and epigenetic profiles of: 1) "homologous" cell types that appear with homologous timing during development, growth and aging (e.g., epiblast, primordial germ cells, naïve T cells, and hematopoietic cells types); 2) cell differentiation processes of specific lineages (e.g., differentiation of the epiblast from the inner cell mass) or of specific cell types by cytokines in vitro (e.g., differentiation of naïve T cells); and 3) induction processes of specific lineages from pluripotent stem cells (e.g., the germ cell lineage, neural tissues).

As discussed in 2)-2 Research Objectives and Plans, under the leadership of the director, **all the life science groups** will acquire necessary data and **actively contribute to the clarification of the principles explaining the emergence of species differences**. Thus, **Saitou** and **Ferguson-Smith** will acquire such data for germ cells, **Hiiragi** for early embryonic cells, **Isa** and **Eiraku** for neurons, **Yanagita** for kidney cells, and **Ogawa** and **Ueno** for hematopoietic/lymphopoietic lineages.

Yasuaki Hiraoka, a world-leading mathematician in topological data analysis (TDA), leads the **Group for Mathematical Science**. By combining mathematical theories such as those related to topology, representation, and probability, **Hiraoka** has succeeded in making TDA highly powerful and general for resolving practical problems such as structural clarification in materials science. Based on these experiences, **Hiraoka** and the **Group for Mathematical Science** will develop novel methodologies for analyzing large-scale, multi-species/multi-cell type/multi-hierarchical data using methodologies such as TDA (analyses based on theories such as persistent homology and quiver representation theory) and machine learning (analyses based on theories such as neural network or sparse model), identifying the principles for the emergence of species differences generated by divergent genome sequences in the properties of "homologous" cell types and in their responses to biological stimuli in humans, non-human primates and rodents (Figure: page 15).

Furthermore, **Takashi Hiiragi** will develop novel experimental and image-processing pipelines for the integration of multi-hierarchical single-cell omics data into a 4D morphogenetic map of primate and human embryonic development. The same strategy will be potentially widely applicable to the dataset obtained by all other PI groups. Accordingly, the Institute will ultimately combine these interdisciplinary strategies to identify principles for the species differences in the scales of time and physical dimensions of development and growth. **A systematic interdisciplinary science based on multi-species/multi-cell type/multi-hierarchical large-scale data can only be achieved through the establishment of this Institute.**

The Institute will realize this interdisciplinary research through tight cooperation among the **Group for Mathematical Science**, life science groups, and the **Core for Single-Cell Genome Information Analysis**. Specifically, 1) scientists in life science groups will provide scientists in the **Group for Mathematical Science** with intensive lectures for genome science and species differences, 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 will implement one **Group for Mathematical Science** (three staff scientists: **Yasuaki Hiraoka**, and an associate and assistance professor), and **Guillaume Bourque** and **Takuya Yamamoto**, who are proficient in statistics-based informatics, will support the **Group for Mathematical Science**. The Institute will expand the **Group for Mathematical Science** along with the progression of the Institute's research activities.

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 **Group for Bioethics and Philosophy**. In close collaboration with all life science groups, the Group for Bioethics and Philosophy will consider the appropriate use of experimental subjects (human and non-human primate materials) and the values of research outcomes (e.g., artificial gametes, artificial cerebral cortexes, genome-edited monkeys) by performing four lines of research: 1) theory-driven study, 2) empirical study, 3) outreach activities, and 4) policy proposals. Based on their findings, the group will formalize an ethics for the advanced study of human biology.

More specifically, the Institute will, 1) have regular meetings with key international centers for ethics such as the **Oxford Uehiro Centre for Practical Ethics/Wellcome Centre for Ethics and Humanities (Director, Julian Savulescu)** and the **Institute for Practical Ethics at UCSD (Co-Directors, Craig Callender and John Evans)** to investigate and discuss key bioethics and philosophy issues including the creation of artificial human embryos, human embryo cultures beyond 14 days, etc (theory-driven study), 2) create questionnaires and surveys to investigate perceptions of scientists in relevant fields and of the general public regarding such key issues (empirical study), 3) hold public symposia to disseminate the outcomes of these empirical studies and thereby create opportunities for more open and public discussion (outreach activities), and 4) publish papers asserting the Institute's position and lead active discussions in relevant areas such as at the Cabinet Office, the International Society for Stem Cell Research (ISSCR) and UNESCO, in all three of which **Fujita** has been serving as a member of the committee on bioethics, in order to spur the generation of new regulations (policy proposals).

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 rule 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 contribute to the creation of a world-standard for bioethics, leading 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.

To realize an international research effort, the Institute will provide the PIs from overseas with adequate budget support to build teams of professional research staff and postdoctoral researchers (one associate professor as co-PI, two postdoctoral fellows, 200 m^2 research space, 30 million JPY of start-up funding). The PIs from overseas will first recruit a co-PI/associate professor, who will establish close communications with the overseas PIs and work full time at the Institute to efficiently run the overseas PI group, particularly when the overseas PIs are absent from the Institute. The overseas PIs and their co-PIs will then recruit two postdoctoral fellows and research support staff to fully initiate their research.

We fully understand that the actual presence of overseas PIs on site is crucial for the ongoing activities of their groups, and therefore, during the course of the development of the Institute's research, **the director will discuss with each overseas PI the ways in which to increase opportunities to be present on site, so that these PIs' work on site will have a strong presence in the Institute.**

Furthermore, among the three young PIs to be recruited, at least one will be non-Japanese and will stay in Kyoto at an effort level approaching 100%. Active international recruitment will take place for postdoc and other positions, with an aim to have well over one-third of the research staff be non-Japanese, according to WPI program standards. And the hiring of administrators with English language ability and overseas experience will be given a top priority, to provide a world-class working and living environment for all the Institute's personnel (see also 4)-2 Establishment of international research environment).

And finally, regular meetings, events, and retreats, both for core members as well as for all staff, will be held to increase inter-group communication and mutual understanding, all of which we expect will contribute solidly to the internationalization of the Institute (see also 4)-2 Establishment of international research environment).

The Institute will appoint Professor **Edith Heard, who is the incoming Director General of European Molecular Biology Laboratory (EMBL), as senior consultant to advise the Institute's research direction and management, establishing a tight link with EMBL**. Further, the Institute will establish a link with international institutions such as the University of

Cambridge and Karolinska Institute (see 2)-3 Linkage with Other Institutions for details), **creating a stratified organization for research promotion and strengthening the Institute's international profile and competitiveness**.

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).

Internationalization of Administrative Supports in the Institute

In the Institute, the administrative staffing will comprise bilingual employees. Paperwork, e-mail exchanges, and other internal communications will be performed in both English and Japanese. Additionally, the Institute will provide a wide range of support to foreign researchers and their families for the duration of research activity and their daily lives in Japan, in cooperation with **the International Service Office** of Kyoto University. If necessary, the Institute administrative staff will accompany the foreign researchers to municipal government offices to complete registration procedures.

Support for Research Activity	Laboratory start-up support Management of research funds Seminars on research ethics, information security, and other topics Introduction to the foreign researcher community
Support in Daily Life	Provision of visa and certificate of eligibility before arrival Residential registration at municipal government offices Housing information (orientation concerning deposits/key money) Application for university accommodation Medical care and national health insurance Japanese language education

International Research Meetings at the Institute

The Institute plans to hold international symposia, workshops, and seminars, by inviting world-leading researchers. Such gatherings would greatly stimulate the intellectual curiosity and motivation of the institute researchers, particularly the younger researchers and graduate students.

International Symposium	The institute will hold an annual international symposium, to which world-class investigators in the Institute's specialty research fields and related fields are invited.
PI Seminars	Individual PIs at the Institute will each hold a seminar at least once every two years (or six times a year for the Institute as a whole), inviting researchers whose recent work has been highly distinguished.
Meetings Based on Younger Researchers' Initiative	Younger researchers are highly encouraged to hold interdisciplinary meetings together with investigators in other fields.

Supports for Overseas PIs and Independent Young Researchers

Overseas PIs and younger, independent researchers will be provided with a start-up fund, research

space, and employment expenses.

Overseas PIs (four professors)	**One associate professor (as co-PI)** **Two postdoctoral fellows** 200 m^2 research space Start-up fund (JPY 30 million)
Independent Young Researchers (three associate professors)	**One assistant professor** 200 m^2 research space Start-up fund (JPY 10 million)
Domestic PIs (nine professors)	**Three postdoctoral fellows**

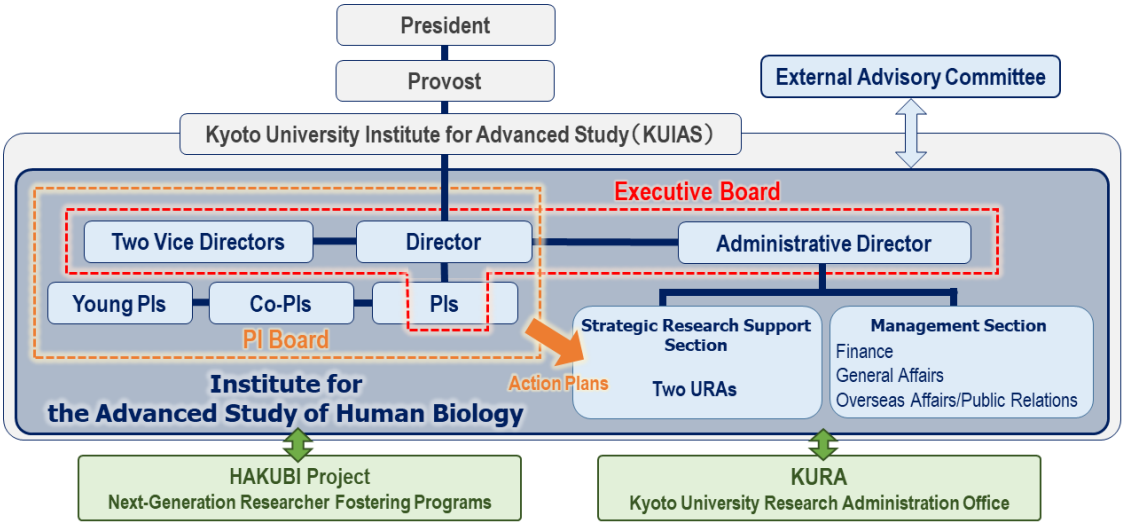
5) Center Management and System Reform

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 Independence within its Host Institution

The WINDOW concept was formulated in August 2015 by Kyoto University as a vision for its future. WPI is an important aspect of this concept (Strategic Priority 2-2). To realize this conceptual plan, in April 2016, Kyoto University created a new organizational structure called Kyoto University Institute for Advanced Study (KUIAS) to house WPI as a permanent entity. The KUIAS is designated a special district having a high degree of autonomy. Under the KUIAS umbrella, the Institute's director can exercise strong leadership, implementing top-down management.



Decision-Making System within the Institute

The director of the Institute will have the authority to make the final decision on important matters, such as the choice of research direction, personnel affairs, and budgetary concerns. **The executive board**, consisting of the director, two vice directors, two PIs, and the administrative director, will convene once a month to discuss important matters under the leadership of the director. A **PI board** comprising 13 PIs, 4 co-PIs[#1], and 3 independent associate professors will discuss the matters decided by the executive board and make concrete decisions and action plans concerning the Institute. **The external**

advisory committee comprising five internationally recognized researchers including Professor **Edith Heard** will evaluate the activities of the Institute periodically (e.g., once a year) and provide advice on the implementation of programs.

Administrative Office Supporting the Institute research

#1Co-PI System
A co-PI system will allow overseas researchers to participate in the Institute's research activities. Four overseas PIs will respectively employ younger researchers (associate professors) as co-PIs. These co-PIs will study full-time at the Institute, maintaining close contact with overseas PIs.

The administrative office will consist of the administrative director, **the strategical research support section,** and the management section (general affairs, finance, overseas/public relations). **Tadashi Ogawa**, the prospective administrative director, is currently the program manager at both the HAKUBI and K-CONNXE researcher development programs**#2** (where he has served for more than 3 years). Under the leadership of the director, the administrative director will lead and manage these two sections. The strategic research support section will employ two URAs (PhD holders in biology or life science).

#2Kyoto University HAKUBI and K-CONNEX projects
Both the HAKUBI and K-CONNEX projects aim at fostering young researchers and currently employ ~60 associate and assistant professors. Their research activities are highly evaluated and have major influence worldwide (an article from HAKUBI published in *Nature* was selected as one of the 2017 top-10 papers in physics). The HAKUBI project is managed by the university's own fund, and K-CONNEX is managed by the fund from MEXT.

#3Kyoto University Research Administration Office: KURA
KURA is the largest URA organization in Japan, and its work is highly respected. KURA received the highest possible score of an S-rank in the MEXT's interim (mid-term) evaluation. KURA currently consists of more than 40 URAs whose role is to strategically support university functions, intra-university synergies, and international commitment, and enhance the research environment, by promoting university reform, research enhancement, and global engagement.

The URAs will play a key role in planning and implementing programs to foster younger researchers, international training courses, academic–industry cooperation, and other programs. To effectively fulfill such missions, the administrative director and the two URAs of the Institute will operate as a hub, maintaining close cooperation with **KURA#3** and the **HAKUBI/K-CONNEX projects**.

Evaluation System and Incentives

The Institute will introduce an additional-compensation program as an incentive founded on the performance of the director, vice directors, PIs, and administrative director. The performance of these individuals (except that of the director) will be evaluated in a formal manner, with the amount of compensation being determined by the director. The director's incentive will be determined by a committee including some executive directors (vice-presidents) of Kyoto University, with consideration for the achievements of the Institute.

Fostering Young Researchers and Supporting Research Activities of Female Researchers

To foster young researchers, the strategical research support section will hold various seminars and workshops. For example, younger researchers will learn the art of scientific writing directly from the editors of *Nature* (*Nature* masterclasses) and will learn how to find and obtain overseas research positions (the *Nature* job interview). In order to promote gender equality, the Institute will provide the essential support for female researchers to balance work with personal responsibilities such as childbirth and childcare, in cooperation with the Kyoto University Gender Equality Promotion Center.

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 Spaces and Facilities

Kyoto University provides 4,600 m^2 of space for research activity at its Faculty of Medicine Campus: 1,700 m^2 of new space, in addition to the existing 2,900 m^2 of space designated for the 9 PIs of Kyoto University. Most research spaces related to the Institute will be located closely. The new space will be used for the four overseas PIs, the three young PIs, the core for single-cell genome analyses, meeting rooms, the director's office, and the administrative division office. Moreover, another space (the total floor space: 19,000 m^2) in the same area will be secured for a new building, providing the opportunity for all researchers in the Institute to be gathered within the same building.

The Specialization and Uniqueness of the Institute Cores Will Enhance Visibility and Competitiveness

The Institute will implement two cores to facilitate its capacity for research development. First, the Institute will establish **the core for single-cell genome information analysis** within the Institute building at Kyoto University. To greatly strengthen its international competitiveness, the Institute will strategically introduce a set of ultra-fast, high-performance, and/or large-scale analysis instruments and

improve their performance by assigning two technical staffs, in addition to several highly-skilled staff scientist, to the core. Second, **the core for primate genome editing** will be established at the Research Center for Animal Life Science of the Shiga University of Medical Science, which has one of the **largest colonies of cynomolgus monkeys in Japan**. The Institute will also set up high-performance instruments in this core. The specialization and uniqueness of the two cores will enhance the visibility and competitiveness of the Institute.

Opportunities for Teaching Graduate and Undergraduate Students

The Institute is a core institution of KUIAS, whose faculty members are able to participate in the education of graduate students, within the confines of the agreement between KUIAS and the graduate school. Additionally, Kyoto University hosts teaching courses called ILAS seminars, in which faculty members educate small numbers of undergraduates face-to-face. This will provide the chance to perform outreach to young students and to draw their attention to the basic sciences in order to secure

the next generation of researchers.

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.

The Institute as a Permanent Research Institution in KUIAS

As previously noted, Kyoto University has created a new organizational structure called KUIAS to house WPI on a permanent basis. Because KUIAS is designed as a special district, having a high degree of autonomy, the Institute's director will have the freedom to implement strong leadership, making decisions on the most important matters concerning the Institute.

Exceptional and Unique Core Facilities Will Contribute to the Independence of the Institute

As described above, the Institute will strategically establish two cores to provide specialized functions in Japan. The specialization and uniqueness of these **core facilities** (including the technical know-how to use them) will enable them to grow as central research hubs, effectively realizing core facilities for the whole of Japan (FY2018, FY2019). The Institute plans to hold open-use programs and international training courses, in which other university researchers and company investigators will be able to utilize the core facilities, further increasing the visibility of the Institute (beginning FY2021). In addition, the improvements of the facility performance and the accumulation of technical know-how will enhance the competitiveness of the Institute. Based on this strong visibility and competitiveness, the Institute faculty members will attempt to acquire major external funding, in cooperation with those researches who are not the Institute members but heavy/power users of the core facilities, in order to maintain and renew the core facilities after the end of the WPI support period (after FY2023).

Systematic Support by KURA for the Acquisition of Large-scale External Funding

Although the PIs of the Institute will have significant ability to obtain external funding, this may not be sufficient to sustain the Institute following the grant period. So that the Institute can achieve independence, KURA will support it to increase the amount of its overall budget. KURA will be able to provide crucial support for the acquisition of overseas, large-scale external funds. Additionally, KURA will provide crucial support for foreign researchers seeking KAKEN grants, revealing any barriers to entry for foreign researchers and assisting them to overcome those barriers.

Securing Indirect Costs of Appropriate Scale for the Institute's Independence

To ensure the Institute's independence after the end of the WPI support, the Institute must fund its indirect costs, such as management personnel expenses, facility depreciation, cost of lighting, and heating. However, it is difficult to directly calculate indispensable indirect costs. The University will make a prototype model that can appropriately evaluate the amount of the indirect costs required for the Institute's management (FY2019, FY2020). This model will be actually applied at the Institute as a test bed (from FY2021).