

Prospective Center Director's Vision

We propose to establish the **Institute for the Advanced Study of Human Biology**, with the mission of elucidating the design principles of human traits, including disease states. The Institute will investigate key targets in human biology using multi-disciplinary integrative strategies and clarify the grand design of human attributes. **The knowledge gained should provide insights into human evolution, while also creating a basis for delineating disease etiologies and developing innovative therapies, thereby promoting health from birth to senescence (Figure).**

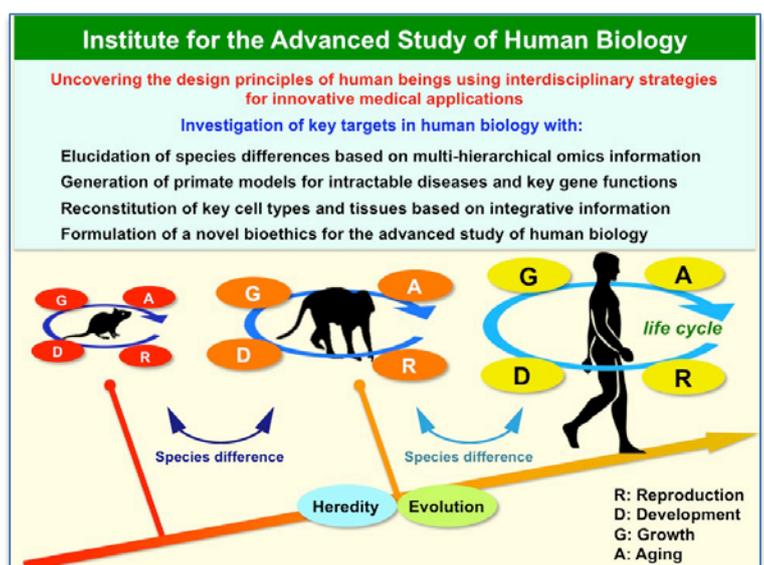
Understanding the basic biology of human beings is a fundamental challenge in the field of life sciences. In the 20th century, the life sciences have elucidated the physical/chemical basis of life, demonstrating that basic processes for life have largely been conserved during evolution. On the other 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.**

The exploration of human biology thus necessitates the use of human materials. However, such materials, in particular those for 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. Note that the access to human materials is more restricted in Japan than 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. In this context, 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 practice, 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, allowing an extrapolation of 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 mechanistic basis of species differences—i.e., the diversity of life forms driven by evolution.**

Accordingly, the Institute will target humans and non-human primates as major research subjects in an effort to uncover the design principles of human beings and disease states, through a multi-disciplinary science approach. This approach **consists of 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, leading to “synthesis” of a comprehensive understanding of target processes.**

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

First, **by creating a fusion between the life sciences and mathematics, such as machine learning and topological data analysis to extract the geometry of large-scale data, we**



will define the principles of the emergence of species differences in phenotypes of homologous cells based on multi-species/multi-cell type/multi-hierarchical omics information, allowing better extrapolation of the knowledge from model organisms to humans. We will extend this analysis to identify principles for the species differences on the scales of time and physical dimensions in development and growth. Second, **by integrating the humanities and social sciences,** we will formalize an ethics for an 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 two core facilities, we will first establish **a core for single-cell genome information analysis** 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 will implement **a core for primate genome editing,** 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 key examples for which rodent models have been largely unsuccessful in drug screening. Note that Kyoto University will expand on these core-facilities for utilization throughout Japan.**

Thus, on the basis of individual research focusing on key targets in human biology, the Institute will elucidate the principles underlying the emergence of 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 life science in the coming decades and as a foundation for transformative therapeutic interventions.**

The prospective center director, Professor 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 in mice to humans, Professor 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, Professor Saitou established a procedure for single-cell transcriptome analysis more than a decade ago (*NAR*, 2006; *Genes Dev.*, 2008). **Professor Saitou's research thus represents a benchmark of the synthesis approach, which will be further broadened in his vision of the advanced study of human biology.** The Institute for the Advanced Study of Human Biology will build 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 realize an international research effort, the Institute will provide principal investigators (PIs) from overseas with adequate budget support for building teams of professional research staff and postdoctoral researchers. It will call all the staff and postdoc positions by open international recruitments. In addition, the budget from the Institute supports the recruitment to each PI team of at least one non-Japanese staff/postdoc. **The Institute will appoint Professor Edith Heard, who is the incoming Director General of European Molecular Biology Laboratory (EMBL), as senior consultant for advising 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, **creating a stratified organization for research promotion and strengthening the Institute's international profile and competitiveness.**

Finally, we should note that the missions of this Institute will be clearly 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 become a member of the WPI academy. Kyoto University founded the Institute for Advanced Study (KUIAS), to which it assigned iCeMS as a constituent institute, thereby realizing a system for the continued development of iCeMS. **As a new WPI at KUIAS, the Institute shares an administrative department with iCeMS, and adopts and further advances well-established and successful administrative systems for its effective management, playing a leading role in the revitalization of the University.**