Research Center Project

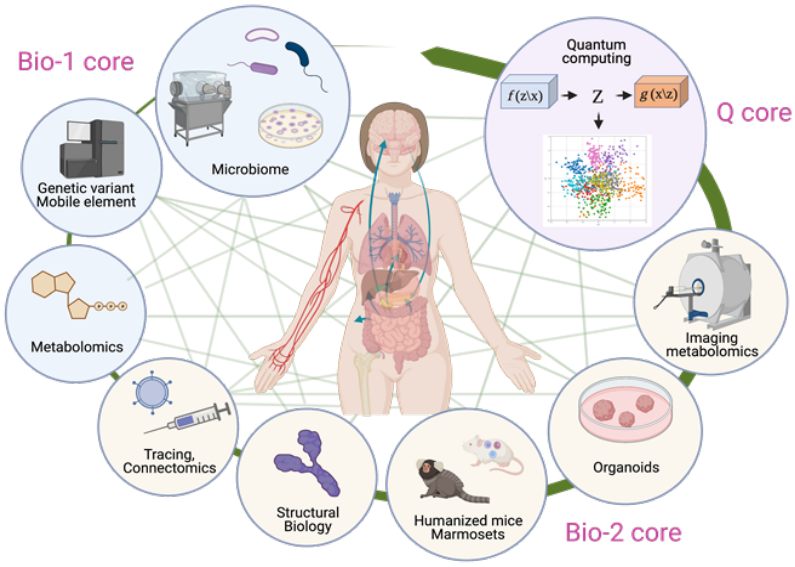
Center name: Human Biology-Microbiome-Quantum Research Center (Bio2Q)
Host institution: Keio University
Head of host institution: Kohei Itoh, President of Keio University
Prospective center director: Kenya Honda, Professor, Keio University School of Medicine
Appendix 1: "Biographical Sketch of Prospective 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 directors: Oltea Sampetrean (Assistant Professor) and Haruhiko Siomi (Professor) Keio University School of Medicine
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.

1. Mission Statement: We will establish a new life science research institution (Human **Bio**logy-Micro**bio**me-**Q**uantum, namely the "**Bio2Q"** Research Center) aimed at furthering our understanding of how humans process external environmental information and maintain homeostasis by dispersing and integrating signals among cells/organs, at resolutions higher than those achieved so far. We will address the question of how human homeostasis is regulated by the epithelial, immune, nervous, and metabolic systems, with an emphasis on microbiome analysis. We will conduct multimodal analyses of human specimens by leveraging microbiome, genomic, and metabolomic approaches. Further, we will develop a novel pipeline that implements quantum computing together with artificial intelligence (AI) to robustly analyze the collected multiomics data and uncover novel multiorgan interaction pathways. The causality of the associated pathways will be verified through state-of-the-art technologies in structural biology, connectomics, organoids, and humanized animal models. Our mission is to forge a new interdisciplinary research area that will lead to groundbreaking progress in elucidating the regulatory mechanisms of biological homeostasis in humans. In the long term, we will develop new prophylactic/therapeutic approaches to promote healthy longevity.

2. Identity: In humans, homeostasis is maintained through complex interactions between multiple organs. This interaction includes the microbiome, which exists on every external surface of the body, and the resulting information is converted, regulated, and utilized in a coordinated manner. Under the direction of a world leader in microbiome research, our center will draw from the experience of top experts in multiple life science disciplines in the Bio-1 (Multidimensional data analysis) and Bio-2 (Homeodynamics mechanistic analysis) core units. Furthermore, the center will implement a quantum computing (Q) core to support these Bio cores, reducing the time it takes to discover biological pathways and bring scientific breakthroughs from bench to bedside. The Q core is the only team in Japan that can perform both annealing and gate-based quantum computing and will be the first to address complex biology and multidimensional omics data. Thus, our center will function



as a unique and highly competitive research institution that will establish a new interdisciplinary research field by blending human biology, microbiome, and quantum computing research with the goal of decoding the human multiorgan homeostatic interactions.

3. Goals of the program: To accomplish our mission, the collaborative team will focus on six main goals: 1. Accumulate multiomics data from humans (including those from centenarians) and model organisms (animals/cells) and compile a multidimensional database. 2. Elucidate the structure and function of microbiome-derived metabolites. 3. Refine imaging metabolomics and structural biology to promote *in situ* functional analysis of metabolites in organs and cells. 4. Develop quantum computing-based algorithms and pipelines to analyze the complex interactions between multiple organs and microorganisms. 5. Establish research approaches that can model the interface between the environment and epithelial, immune, and nervous systems by advancing organoid technology and animal models and elucidate the mechanisms underlying the conversion of information from external environmental factors into internal signals. 6. Invent new technologies in connectomics and structural biology to understand the organized complexity and dynamic multiorgan interactions, including gut-brain communication.

By achieving these goals, we will generate a new entity of life science and decipher causal relationships in multiorgan and microbiome interactions in humans during health and disease, with a particular emphasis on understanding of microbiome-derived metabolites, microbiome-epithelial interactions, gut-brain communication, and healthy longevity in a way that cannot be accomplished by conventional approaches.

2) World-Leading Scientific Excellence and Recognition

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)

Title of Research Area: Human multiorgan-microbiome homeostatic interactions

The importance of the target research field: Homeostasis in humans is maintained by a complex circuitry of interactions between multiple organs connected by the vascular, nervous, immune, and metabolic systems. Accumulating evidence suggests that this complex network confers robustness against external perturbations. Biological functions (outputs) are appropriately regulated in response to external environmental changes (inputs), and the breakdown of multiorgan networks results in chronic diseases. However, fundamental gaps in knowledge and several technical bottlenecks remain regarding the complex interplay between organs. The human body is not merely a collection of different parts. Whenever the hierarchy changes from the genome to cell to tissue/organ/organ to individual, the higher organized levels show emergent properties not apparent in the sum of the properties of the lower levels. Information is dispersed, integrated, and transmitted in a feedback loop between the lower and upper layers. To understand such extremely complex interactions, conventional approaches that focus primarily on single organ/cell networks ultimately fall short.

A typical example of a multiorgan network is the direct projection of nerves from the intestine to the central nervous system ("gut-brain axis"). Recent research has shown that nutrient metabolism after digestion and absorption is regulated via the central nervous system. However, the pathways involved in the metabolic control of dietary nutrients are likely far more complex than currently understood. Within the defined space of a living organism, signals are likely distributed through

multiple pathways, thereby achieving optimization and robustness. In addition to metabolism, the autonomic nervous system controls immunity and inflammation by innervating various peripheral organs, such as the intestine, thymus, spleen, and bone marrow, and sends afferent signals from peripheral organs to the central nervous system. However, the synaptic structures between the autonomic nervous system and peripheral organs remain largely unknown.

Moreover, every external surface of individuals, such as skin and intestine, harbors trillions of microorganisms (collectively defined as the microbiome), whose function profoundly affects human homeostasis. Multi-million-dollar nationwide projects, such as the Human Microbiome Project (HMP), have revealed associations between the state of the microbiome and various human conditions and diseases that exceed previous predictions, including inflammatory bowel disease, cancer, diabetes, obesity, Parkinson's disease, cognitive impairment, and neuropsychiatric and developmental disorders. Furthermore, the efficacy of fecal microbiota transplantation therapy has been demonstrated in several diseases, making the human microbiome a new attractive therapeutic target. However, the mechanism of action of the microbiome remains largely unknown. In particular, the microbiome is thought to exert its function by producing tens of thousands of unique bioactive metabolites by converting host/diet-derived natural products; however, the vast majority of metabolites (>99%) have not been annotated structurally and functionally (thus remaining unidentified "dark matter"). In addition, unlike infectious diseases caused by a single pathogen, the physiological functions of the microbiome are mostly exerted by a community of multiple bacterial species. However, none of the currently existing systems can effectively and accurately decipher which members of the microbiota causally act as effector microbes and how the combinations of microbial metabolites are projected into the interorgan network and translate into phenotypes.

Therefore, to clarify the details of the complex multiorgan and microbiota networks, it is necessary to develop new research approaches using multiple modalities as well as a workflow that integrates a large amount of information from diverse interacting components and leads to a systems-level understanding.

Rationale to develop a WPI center: The conversion mechanism from external information to internal biological signaling, and the complex networks connecting the immune, neural, and metabolic systems cannot be fully addressed by conventional research approaches. In addition, it is difficult to decipher and verify the mechanisms that translate the functions of the microbiome into the host phenotypes. The most challenging aspect of current microbiome research is understanding the structure and function of microbial metabolites. We developed an unbiased metabolic pipeline that detected tens of thousands of metabolites. However, only a handful of their functions (i.e., their receptors and subsequent conversion mechanisms into host phenotypes) have been identified. Furthermore, effective computational analysis methods for integrating multiomics data from multiple organs and microbiomes are yet to be established. Despite AI-driven technologies such as deep learning being state-of-the-art, further development in the computational sciences is necessary to facilitate the analysis of multi-variable, small-sample size, multimodal, and multiorgan data.

The current situation, however, is gradually improving due to the development of cutting-edge technologies. For example, metabolomics, which captures metabolite diversity and dynamics through advanced mass spectrometry, and organoids, which facilitate semi-permanently culturing of human tissue stem cells, have led to significant progress in the field of microbiome and human biology. Likewise, epigenomics, which targets transposon-mediated modifications, and connectomics, which combines virus-mediated tracing of neural networks and *in situ* structural biology techniques, have revolutionized our understanding of the interactions between multiorgan systems. In addition, quantum computing coupled with AI has been attracting attention in biological research. Quantum computing employs quantum bits and quantum mechanical principles for processing information in a

superposition of 0s and 1s and is expected to answer a number of complex biology-related questions. In the case of comparing multidimensional data sets, for example, it may be useful to translate network structures into an ultra-high-dimensional quantum Hilbert space by quantum computing to understand the molecular and biological features ("quantum signatures") associated with the given phenotype. By applying AI and quantum computing in a biological space, we expect to discover potential causal relationships that have previously been difficult to determine.

A group of world-leading researchers across multiple disciplines have now gathered at Keio University. By fostering scientific excellence, we believe that we can synthesize a new life science field that integrates human biology, microbiome research, and computational science. We will collect multiorgan multiomics data (including microbiome data) associated with human pathological and health conditions and conduct data mining and evaluation using multimodal biological technologies combined with AI and quantum computing. Based on the insights obtained into the mechanisms underlying multiorgan interactions and the maintenance of homeostasis, we aim to develop new treatment strategies and biomarkers for promoting healthy longevity.

Other world-class research centers for microbiome and human biology research:

1) Stanford, ChEM-H: Stanford ChEM-H brings together chemists, biologists, engineers, and clinicians to understand life at the molecular level and apply this knowledge to improve human health. Similar to Bio2Q, ChEM-H collects and processes human samples and conducts in-depth analyses.

2) Cleveland Clinic Discovery Accelerator (a joint Cleveland Clinic-IBM Center): The Cleveland Clinic, a US-based clinic that provides medical care, research, and education, has formed a 10-year partnership with IBM to utilize AI and quantum computing technologies in medical/life science research.

3) The University of Chicago, Duchossois Family Institute (DFI): The DFI aims to investigate the microbiome to reduce susceptibility and/or enhance resistance to a range of human diseases and inflammatory conditions.

4) The Broad Institute: The Broad Institute is a biomedical and genomic research center where physicians, geneticists, and molecular, chemical, and computational biologists launch innovative projects, invent new technologies, build computational tools, and develop new therapeutics.

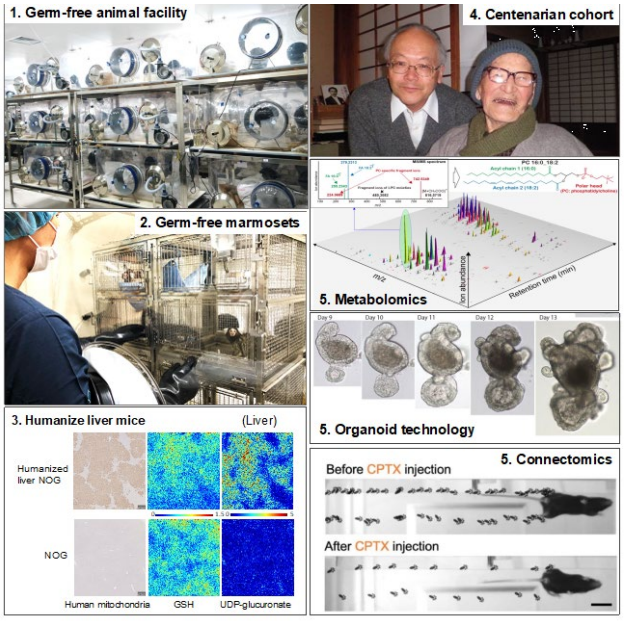
5) UCSF, The Benioff Center for Microbiome Medicine: The center's collaborative community leverages the unique potential of the human microbiome to predict health outcomes and to create microbiome-based therapeutics for a wide variety of gastrointestinal, skin, and neurological diseases, with the goal of bringing these treatments to patients in the shortest time possible.

The strength of Bio2Q is comparable to that of those world-renowned institutions because it possesses several cutting-edge technologies and unique resources, including:

1. Gnotobiotic pipeline: A particular strength of the Bio2Q is that we have developed an effective gnotobiotic screening system to track the causal effects of biologically-relevant microbiota molecules and strains with host-modulatory capabilities. Bio2Q is home to one of the world's largest germ-free animal facilities, with full-time technicians and embryo transfer specialists to maintain about 150 isolators capable of producing more than 1,500 gnotobiotic mice a month. An in vivo system is essential for testing microbes directly, as microbiota members generally act as a community to cooperatively produce metabolites that affect host physiology, a scenario that can be recapitulated and rigorously studied in gnotobiotic animals.

2. Germ-free common marmoset monkeys: Non-human primates are critical for translational research to bridge the gaps between rodents and humans. Common marmosets have several advantages, including human-like brain architecture and function with complex social and cognitive

behaviors. Moreover, the gut microbiota composition and metabolome in marmosets are similar to those in humans. Sasaki at CIEA, a satellite of Bio2Q, has succeeded in establishing an effective method to generate and maintain germ-free marmosets for the long term under sterile conditions. Germ-free marmosets are suitable for analyzing the effects of the microbiota on neurodegenerative and aging-associated diseases.



3. Humanized mouse models: In addition to NOG-based humanized immune mice, CIEA recently developed “humanized liver mice” in which a herpes simplex virus type 1 thymidine kinase transgene is expressed within the liver on the immunodeficient NOG background and human hepatocytes are stably transplanted. The humanized liver mice mimic the profiles of intestinal and plasma metabolites and the gut microbiota components, and can therefore a powerful tool for studying host-microbiome interactions.

4. Centenarian cohort: Centenarians, or individuals who have lived more than a century, represent the ultimate model of successful longevity associated with decreased susceptibility to aging-associated illness and chronic inflammation. The Center for Supercentenarian Medical Research at Keio University has been following and collecting clinical information and blood and fecal samples from a cohort of more than 1,000 centenarians, including those over 110 years old ("Supercentenarian") over 20 years.

5. Organoid, connectomics, metabolomics, computing expertise: Sato pioneered the development of organoid technology and established >1,000 lines of human organoids from healthy individuals and patients at Keio University. This organoid biobank confers key advantages to Bio2Q over the other centers. Augustine, who found the Center for Functional Connectomics in Korea, has been a leader in the field of connectomics. Yuzaki is one of the first to discover that the C1q complement family functions as a novel synapse organizer in the central nervous system. By using connectomics tools, Yuzaki has clarified where and how the C1q family proteins control synapse formation and maturation. Yuzaki and Aricescu have created a synthetic synaptic organizer (termed CPTX), by combining the structural elements of natural synaptic organizers. CPTX effectively treats symptoms of mice with Alzheimer's disease and spinal cord injury. Arita has developed a non-targeted mass spectrometry platform to elucidate the structural diversity of >8,000 lipid species (10 times less was defined previously) and is leading the Lipidome Atlas project. In addition, Keio University is one of the few institutions in the world capable of gated and annealing quantum computing. These cutting-edge technologies and resources will confer key advantages to Bio2Q over the other centers.

Collectively, Bio2Q is uniquely positioned to be a world-leading institute as it integrates cutting-edge technologies, including microbiomics, lipidomics, imaging metabolomics, connectomics, organoids, quantum computing, etc., which enable practical causality-driven basic sciences. As Honda has been exchanging information and collaborating internationally in microbiome research for many years with Michael Fischbach from ChEM-H, Ramnik Xavier from the Broad Institute, and Eric Pamer from DFI, Bio2Q can accelerate microbiome and human biology research in collaboration with these institutes (Fischbach and Xavier will participate in Bio2Q as international collaborators).

2) -2 Research objectives and plans

* Describe in a clear and easy-to-understand manner to 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, describe what world-level scientific and/or technological issues are you seeking to solve, and 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 research center will establish a new life science research area to discover and verify human homeostatic multiorgan and microbiome interaction mechanisms that have not yet been elucidated. By further refining microbiomics, metabolomics, organoid technology, *in situ* structural biology, and connectomics, we will establish a research platform that can model the interface between the environment and the human body. Further, we will elucidate the mechanisms underlying the conversion of external environmental changes (including the microbiome) into internal signals, and examine the associated multi-organ regulatory networks (the gut-brain axis in particular) at a greater resolution than currently prevalent. We will also innovate computational techniques to extract previously unexplored biological pathways from multidimensional multiomics data. The goals of the center are to explore new cross-disciplinary paradigms in multiorgan and microbiota interactions through integration of emerging technologies in biology and computational sciences. By doing so, we will establish a new field in the life sciences that is unreachable by conventional methodologies, and identify "causal" relationships in homeostatic multiorgan interactions, particularly in the context of the gut-brain axis and healthy longevity. In the long term, we will develop new therapeutic and preventive modalities based on rational design, such as microbiota manipulation, bacterial design, dietary intervention, and artificial synaptic connector therapy, to contribute to creating a society that supports healthy longevity across the life course.

Research plan: We will establish three core units designed to accelerate the discovery and validation workflow to identify multiorgan and microbiome interactions: **Bio-1, Multidimensional data analysis core** (Core Director: Makoto Arita); **Bio-2, Homeodynamics mechanistic analysis core** (Core Director: Toshiro Sato); and **Q, Quantum computing core** (Core Director: Shu Tanaka). These three cores will share technologies, expertise, and pipelines to streamline data generation, mining, and evaluation. The Bio-1 core will analyze human multiorgan samples and model organisms by integrating human microbiome, genomic, epigenomic, and metabolomic methods, and construct a multidimensional database. The collected multiomics data will be analyzed in the Q core by quantum computing combined with AI to identify "quantum signatures" associated with the given phenotypes. Subsequently, these signatures will be evaluated in the Bio-2 core in collaboration with the Bio-1 core, using connectomics, organoid, and structural biology techniques to validate the cause-effect relationships. An imaging metabolomics team will operate at the interface between Bio-1, 2, and Q to detect small metabolite-derived nuclear magnetic signals *in situ* at high sensitivity and spatial resolution, and identify the function of microbiome-derived metabolites in the multiorgan networks. By accelerating the reverse translation cycle, we will achieve and exploit novel discoveries in human biology to optimize the functioning of the host multiorgan system, reduce unfavorable or pathological conditions, and promote healthy longevity.

Bio-1: Human multidimensional data analysis core: The Bio-1 core will collect human multiorgan samples associated with health, disease, and aging, and analyze them from multiple perspectives. The information will be shared in the center and satellites to enable breakthroughs.

Human disease analysis team (**Seki, Yoshino**)**:** The clinical picture of chronic diseases and conditions as observed in clinical practice is extremely diverse, and a comprehensive understanding derived from a large amount of patient information is essential to obtain a complete picture of the disease concept. Together with the center's collaborators, the team will obtain clinical samples and information on cancer, diabetes, obesity, neuropsychiatric disorders (Parkinson's disease, dementia, and depression), developmental disorders (autism spectrum disorder), allergic diseases,

inflammatory bowel disease, and aging. For example, Seki has created a multicenter database that includes more than 1,000 patients with Parkinson's disease (Seki, Parkinsonism Relat Disord 2013). Parkinson's disease is rapidly increasing in an aging society and has been considered a systemic disease. The gut microbiome has attracted attention for its influence on the pathogenesis of Parkinson's disease and drug metabolism. Optimization of treatment and provision of tailor-made medicine based on the evaluation of the microbiota is paramount for improving medical care for patients with Parkinson's disease. In addition to Parkinson's disease, Keio University Hospital has collected blood and clinical data from over 10,000 patients with inflammatory bowel disease and approximately 1,000 centenarians (including those over 110 years old). Centenarians aged 100 years and older are known to be less susceptible to age-related diseases, such as hypertension, diabetes, obesity, cancer, and infectious diseases. There are centenarian-specific members of the gut microbiota (Sato, Nature 2021), which might not be merely a consequence of adaptation to aging, rather actively contribute to maintaining homeostasis, resilience, and successful aging. Clinical information and specimens will be shared with the Bio-1, Bio-2, and Q cores, and analyzed from multiple perspectives.

Microbiome Team (**Honda, Huh, Tuganbaev, Atarashi**): The human body is colonized by microbes from all three domains of life, with the gastrointestinal tract exhibiting the greatest microbial density and diversity. Gut microbes outnumber the host by over 25-fold in terms of genetic composition. Unsurprisingly, this vast microbial ecosystem interacts intimately and, for the most part, mutualistically with its human host, performing essential metabolic functions. While sequence-based microbiome-wide association studies provide correlative support for the notion that the microbiota influences human health and disease, they address neither the causality nor the directionality of the host-microbiota relationship. Therefore, we have shifted toward causational studies to identify bacterial species that directly contribute to human homeostasis in specific ways (important examples are Atarashi, Science 2013; Atarashi, Cell 2015; Tanoue, Nature 2019; and Sato, Nature 2021). In particular, the combination of two complementary reductionist approaches, that is, gnotobiotic and metabolite-based, has enabled a detailed mechanistic understanding of the microbiota-mediated maintenance of homeostasis and multiorgan systems, in which specific bacterial species and their products play critical roles. In the WPI program, we will create a more effective feedback cycle between the gnotobiotc study and the rigorous mechanistic studies, ultimately enabling for the identification of causally effective and therapeutically applicable minimal microbes and microbial products. The "gut-brain communication" is a typical example of a multiorgan network. It has been reported that the intestinal information, particularly that from the gut microbiome, is delivered to the central nervous system, and CNS sends signals back to peripheral organs to control their functions. Recent evidence suggest that this Gut-brain axis affects the pathogenesis of several diseases, including Alzheimer's and Parkinson's diseases. We will interrogate the molecular and cellular basis of the gut-brain communication. We will particularly horn in on the intestinal enteroendocrine cells. Enteroendocrine cells are known to "chemosense" the intestinal contents via GPCRs. They also have a structure called neuropod, which forms synapse-like structure with the vagus nerve. We believe that elucidating this synapse-like structure will be the best first step in determining the basis of the gut-brain connection. We will 1) elucidate the signaling pathway from the intestinal tract (namely the gut microbiota) to the CNS by tracing anatomical pathways and 2) define their physiological functions. To do so, we will advance culture techniques along with high resolution mass spectrometry that will provide an additional lens for identifying small molecules correlated with diseases and specific conditions. Moreover, in collaboration with the Metabolomics Team, we will compile a metabolomics database specific to the microbiome. We will determine the bacterial enzymes that are responsible for the production of the given metabolites through a series of steps, including isolation of bacterial

strains, sequencing bacterial genomes, creating mutant strains, and analyzing the effects of the lack of specific genes in the microbiota on the host using the gnotobiotic pipeline. Moreover, in collaboration with other core members, we will elucidate the molecular and cellular mechanisms underlying gut-brain crosstalk, the interaction of the microbiota with genomic mobile elements, and the influence of the microbiota on the mucosal barrier (gut and skin) stem cells. We will also bridge circadian biology and microbiology to uncover how multiple organ systems of our body dynamically interact with the microbiome throughout a circadian cycle thus adding a dimension of time to the definitions of homeostasis and disease. Indeed, the quantity of bioactive small molecules that can cross the epithelial barrier at any given moment is not constant but: a) is diurnally fluctuating increasing up to three-fold at peak vs trough; b) is regulated by microbiome (Tuganbaev Cell 2020). Therefore, the temporal understanding of host-microbiome interactions will lead to the development of novel type of intervention strategies. Much like wave interference, diurnal rhythms of microbes and the host can be utilized in combinatorial ways to rationally maximize therapeutic or minimize side effects of microbiome-derived metabolites or orally administered drugs on the host.

In addition, in collaboration with the Q core, we will build a new pipeline to understand the community action of multiple bacterial species using AI and quantum computing. Honda, Atarashi, Sampetrean, and Tuganbaev have world-class strengths in the technologies required for microbiome analysis (e.g., culture techniques to propagate difficult-to-culture or previously unculturable organisms, gnotobiotic techniques, and commensal bacterial gene manipulation techniques). Huh is a world-leading scientists in the fields of immunology and gut-brain axis research. Combining the state-of-the-art gnotobiotic expertise from the Honda lab with the neuroimmunology strength of the Huh lab will lead to the identification of mechanisms of action by which the bacterial community interacts with host cells, including epithelial cells and immune cells, to affect health and disease in humans. In addition, **Mucida** (Rockefeller University), **Littman** (NYU), **Xavier** (Broad Institute), **Fischbach** (Stanford University), **Iwasaki** (Yale University), **Devlin** (Harvard University), and **Kajimura** (Harvard University), with whom Honda has collaborated for many years, have joined as international collaborators. The microbiome is a key component of the human biology, and decoding its impact on the immune system, metabolism (including drug metabolism), aging, and gut-brain interactions will be accelerated in this collaborative team.

Metabolomics Team (**Arita, Soga**)**:** Advances in non-targeted lipidomics technology developed by Arita and colleagues have revealed the existence of a far greater variety of lipid molecules in living systems than previously thought (Tsugawa, Nat. Biotechnol. 2020). The diversity of molecular species and modifications of lipids has the potential to generate a wide variety of biological information as functional elements. Indeed, the identification of new functional lipids often leads to a new understanding of biology and pathophysiology. In this project, by combining non-targeted mass spectrometry and molecular spectrum networking technology (which supports structural estimates of unknown molecules), we will identify new lipid molecular species that are uniquely produced by the microbiota. To verify the structure-activity relationship of functional lipids and their causal relationship with the given phenotypes, we will chemically synthesize lipids, including structural isomers, and evaluate their biological activities by conducting a wide range of bioassays. Moreover, we will develop a computational mass spectrometry platform that facilitates the annotation of metabolites by integrating the collision cross-section and MS/MS spectra. We will advance MS imaging technology to visualize the localizations of more than 1,000 molecular species of lipids. This spatial lipidomics platform will enable the visualization of functional lipid distribution in cells and organs *in vivo*.

Most molecules from central carbon and nitrogen metabolism are hydrophilic (e.g., phosphorylated sugars, phosphorylated carboxylic acids, carboxylic acids, amines, amino acids, nucleic acids, nucleosides and nucleotides). Despite their importance, no analytical method has been

developed to cover all these metabolites because of their high polarity, non-volatility, and difficulty in identification. Furthermore, the coexistence of over 1,000 metabolites with similar physical and chemical characteristics in the cell complicates their analysis. Focusing on these characteristics, Soga developed a metabolomic profiling method based on capillary electrophoresis mass spectrometry (CE-MS) of polar and charged metabolites (Soga, Proteome Res. 2003). CE provides fast and effective analysis, whereas MS provides high sensitivity and selectivity. The CE-MS method has several advantages, such as its low sample consumption and the ability to easily detect charged compounds. The utility of this method has been exemplified by the discovery of low-molecular-weight biomarkers for several diseases (Yoneshiro Nature 2019). Building on these methods, we will develop a highly sensitive and high-throughput metabolomic profiling method and single-cell metabolomics method. Our goal is to discover new biological regulation mediated by bacterial metabolites (both hydrophobic and hydrophilic metabolites) and to comprehensively understand host-microbe interactions in multiorgan systems.

Genome Dynamics Team (**Siomi, Ishigaki**): An extraordinary abundance of transposable elements (TEs) is one of the most striking aspects of mammalian genomes. Their ability to mobilize and insert anywhere in the genome can cause mutations that are generally detrimental to the host. TEs may also play a major role in mammalian biology by forming gene regulatory networks as part of the 'self.' Barbara McClintock, who discovered TEs in the late 1940s, realized that TEs are not only mobile genetic elements but are "controlling elements" because of their regulatory influences on neighboring gene expression and function. The activation of TEs in response to environmental stresses induces mutations and/or epimutations (epigenetic modifications) that initiate a highly programmed sequence of events within the cell to cushion the effects of the stress and could help the organism adapt to new environmental conditions. Recent studies support the idea that the host immune system uses TEs to communicate with microbiota, which controls tissue homeostasis and inflammation. With the resources available within the WPI program including tissue organoids and microbiome cultures, Siomi will address how TEs sense the microbiome to initiate the host immune response using state-of-the-art (epi)genomics tools and bioinformatics.

Millions of genetic variants define the phenotype of each individual. Variants in cell type-specific enhancers influence the transcriptome, proteome, metabolome, and, eventually, more complex phenotypes (e.g., immune cell functions and host-microbiome interactions). Therefore, a precise understanding of the functional readouts of genetic variants can help elucidate the molecular basis of human biology. Ishigaki will investigate how genetic variants influence cell type and tissue specific molecular phenotypes using state-of-the-art technologies such as organoids, single-cell multiomics platforms, and CRISPR single base-editing.

Bio-2: Homeodynamics mechanistic analysis core

Reverse translation studies will be performed on human multiorgan samples using organoids and animal models along with Bio-1, and causal relationships will be tested based on inferences obtained with the Q-cores.

Organoid Team (**Sato**): The intestinal epithelium plays a pivotal role in maintaining homeostasis through nutrient absorption and anti-bacterial protection. Deregulation of these epithelial functions leads to an imbalance in gut microbiota associated with systemic disorders, such as chronic inflammation, obesity, and cancers. However, owing to the paucity of experimental systems, the biological mechanism by which epithelium regulates gut microbiota and host homeostasis remains unclear. Sato and **Clevers** (Hubrecht, now Roche) developed organoid technology that enables ex vivo analysis of the human intestinal epithelium and host-microbe interactions, which provides a critical functional platform for the causality assessment. The expertise in technical development and

rich insights into the stem cell biology of the Sato group will create a robust competitive edge.

The intestinal epithelium consists of various cell types, and each cell type expresses a diverse array of receptors corresponding to gut microbes and their metabolites. This many-to-many relationship is further complicated by potential epigenetic alterations by gut microbes. To tease out such chaotic configurations, the Sato group, in collaboration with the Genome dynamics team and Q core, will identify pathways by which external inputs induce specific biological phenotypes at the single-cell level. Enteroendocrine cells in the intestinal epithelium are known to sense various metabolites derived from gut microbes and exhibit unique neuroendocrine and metabolic responses. Using co-culture of organoids with non-epithelial cells such as immune cells and neurons, the Sato group will explore how the environmental cues modulate organ functions via epithelial interactions with neural, endocrine, and metabolic systems, in coordination with the Metabolome and Microbiome teams and the Neuroregulation team. The group will also collaborate with the Structural biology team to analyze the interactions between epithelial receptors and gut microbiota-derived metabolites at the structure level.

The Sato group will procure tissue samples from patients and establish disease organoid models with the Human disease analysis team to facilitate an understanding of disease pathobiology and the development of therapeutic strategies. In collaboration with the Humanized animal model team, the Sato group will streamline an in vivo experimental platform and provide its access to all team members. The group will further work with the Imaging metabolomics team to survey clinical human or patient data and analyze their consistency with organoid and humanized animal model data.

Neuroregulation Team (Yuzaki, Minagawa, Augusine): In recent years, attempts have been made to elucidate all functional and structural connections between neurons in the brain via a “connectomics” approach in international frameworks such as the Brain Initiative. The Augustine Group will apply functional connectomics approach, by which neuronal activities are stimulated or inhibited by illumination while monitoring Ca^{2+} changes in target tissues, for mapping projection neurons in lymphoid tissues. The Yuzaki group aims to apply existing and newly developed connectomics tools to elucidate brain-gut junctions. For example, various metabolites produced by the microbiome, as well as nutrients and bile acids, are sensed by receptors expressed by enteroendocrine cells (EECs) scattered in the intestinal epithelium. EEC signals are transmitted to the nucleus tractus solitarii (NTS) in the medulla oblongata via the sensory vagal nerve and further integrated with various kinds of information in the higher-order centers in the brain to control visceral, cognitive, and emotional functions, which are relevant to certain psychiatric and neurological disorders. To fully understand the relationship between the microbiome and the nervous system, it is essential to elucidate each of the following steps: 1) how metabolites produced by the microbiome are sensed by EECs, 2) how EECs communicate with sensory vagal nerves, and 3) how signals from the NTS are integrated in the higher-order centers. To achieve these goals, the team will first develop a viral vector toolkit to specifically manipulate gene expression in different subpopulations of EECs and vagal nerves. In addition, in collaboration with the Q core, the team will establish a pipeline for computational analysis of multidimensional data obtained using microbiome, genomics, and metabolomics approaches, as well as functional imaging of the vagal nerve and higher-order centers. Cognitive and motor functional abnormalities in animal models of psychiatric and neurological disorders, such as Alzheimer’s disease and autism spectrum disorders, will also be quantified and integrated into the database. The team will also collaborate with the Humanized Animal Model Team and the Organoid Team to establish a platform for visualizing the activity of EECs and the vagal nerve using genetically encoded Ca^{2+} sensors in response to the administration of metabolites derived from the microbiota. The Augustine group will perform *in vivo* imaging of immune cell trafficking in the CNS to elucidate the effect of microbiome and its metabolites on immune cells in the brain. The effects of the microbiome and its

metabolites on animal behavior will be further examined by inhibiting or activating specific subpopulations of EECs, lymphoid tissues and the vagal nerve with chemogenetic tools *in vivo*. The Augustine and Yuzaki groups have previously developed a technique for tracing neuronal networks in the CNS using viral vectors. Both groups have ample experience using optogenetic and chemogenetic tools to alter the function of specific neuronal circuits to establish a link between synaptic functions and animal behavior. Thus, the team will establish a causal relationship between the microbiome and neurological and neuropsychiatric disorders by integrating data on the nervous system, animal behavior, and multiomics.

The Yuzaki group has developed CPTX, an artificial synaptic connector based on the structure of molecules identified at CNS synapses in collaboration with the Structural Biology Team (Aricescu and Suzuki). CPTX administration induces rapid synapse formation *in vivo* and effectively reduces the symptoms in Alzheimer's disease and spinal cord injury mouse models (Suzuki, Science 2020). The group also developed a technique called the split-TurboID method to identify molecules associated with cell-cell adhesions using contact-dependent proximity labeling followed by high-resolution LC-MS (Takano, Nature 2021). Autonomic nerves in the intestinal epithelium are not distributed randomly as previously thought, but form synapse-like adhesion structures with specific EECs. However, the molecules involved in the formation and maintenance of such synapse-like structures remain unclear. By applying the split-TurboID method, the group will identify structures between the autonomic nerves and EECs and their molecular components. Similar to CPTX, which can induce CNS synapses, the group will develop new therapeutic tools to artificially modify the brain-gut connection. The integrated brain-gut correlation database will be used to enable predictive simulations of the effects of such tools.

Over the years, Minagawa has collected cortical brain activity data from infants using optical topography. Furthermore, the group intends to analyze microbiome data in conjunction with cortical activity in children with autism spectrum disorders. International collaborator **Choi** (MIT) will investigate the relationship between inflammation and autism spectrum disorders. The Neuroregulation Team will also obtain microbiome and metabolome data in various age groups in conjunction with brain activity data, which will be provided to the Q and Bio-1 cores.

Structural Analysis Team (Aricescu, Suzuki): Enteroendocrine cells express several orphan G protein-coupled receptors (GPCRs) with unknown ligands. GPCRs are among the best candidates receptors for functionally undefined metabolites produced by the microbiota. The Aricescu group has solved the crystal structures of a variety of membrane proteins including the heteromeric GABA receptor (Sente, Nature 2022). Aricescu and Suzuki will collaborate with the Microbiome Team and the Neuroregulation Team to elucidate the microbiome-host interface, bacterial membrane structure, and the structure of GPCRs responsible for interaction with bacterial metabolites.

X-ray crystallographic analysis of highly purified proteins has enabled single-particle analysis under non-crystallizing conditions. However, it has become clear that membrane proteins such as GPCRs and synapse-forming molecules, which function stably in the presence of lipids and other proteins, undergo conformational changes when isolated as single particles. Thus, *in situ* structural analysis of molecules in an intact lipid environment is essential. At the WPI center, *in situ* structural analysis technologies will be developed in collaboration with the Organoid Team and the Humanized Animal Model Team of the Bio-2 core.

Humanized Animal Model Team (**Sasaki**): The gut microbiome compositions in humans and mice are quite different, and certain members of the human microbiota cannot colonize the mouse intestine upon transplantation, which might be due in part to the differential liver-derived metabolites. Indeed, mice and humans have differential profiles of liver cytochrome P450s as well as intestinal bile acid compositions and other liver-derived metabolites. To overcome such a species specificity, we have developed “humanized liver mice” in which a herpes simplex virus type 1 thymidine kinase transgene

is expressed within the liver on the highly immunodeficient NOG background and human hepatocytes are stably transplanted (Hasegawa, BBRC 2011 and Uehara, Drug Metab Pharmacokinet 2022). The humanized liver mice exhibit significantly different profiles of intestinal and plasma metabolites and the gut microbiota. By generation of germ-free and gnotobiotic humanized liver mice, we can investigate mechanisms of homeostasis regulated by microbiota and enterohepatic circulation.

The common marmoset is a nonhuman primate experimental animal closely related to humans and a useful model animal that is genetically manipulatable (Sasaki, Nature 2009, Sato, Cell Stem Cell 2016). We have recently succeeded in generation of genetically modified Alzheimer's disease models (Sato, bioRxiv) and germ-free marmosets (Inoue, Research Square 2021). We also developed an automated behavioral monitoring system (Yurimoto, bioRxiv). Moreover, by using embryo splitting technics, genetically identical twins of the Alzheimer's model can be created to analyze the interaction between intestinal microbiome and neurodegeneration and behavioral changes under germ-free and conventional conditions, which provides a molecular and cellular basis underlying gut-brain communication in nonhuman primates, independent of genetic background. We will collect multimodal data using whole-brain imaging, fMRI, mass spectrometry imaging, behavioral tests, and metabolomics from marmosets in health, disease, and aging.

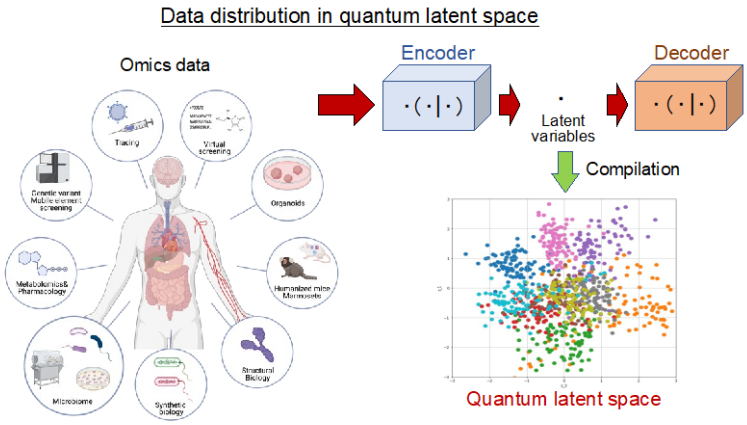
Imaging metabolomics Team (**Suematsu, Hishiki**): The Team aims to refine and advance multidisciplinary imaging metabolomics using three different modalities: imaging mass spectrometry (IMS), high-power and wide-open (11.7 Tesla/22 cm bore) functional MRI, and surface-enhanced Raman imaging (SERS). For two decades, Suematsu and Hishiki devoted their efforts to developing IMS technology to visualize metabolites and hormones responsible for the maintenance of organ homeostasis and immunological responses. By using ^{13}C- or ^{15}N-labeled substrates, IMS can reveal the spatial and temporal biotransformation of glucose, glutamate, etc. The 11.7-Tesla fMRI will define the anatomical distribution of metabolites through diffusion-tensor tractography. Theoretically, the fMRI can map metabolite distribution at 100 μm spatial resolution. Water constitutes almost 70% of the body and serves as a major source of proton signals. We will utilize fMRI with a water suppression device to visualize NMR signals derived from metabolites. By combining these technologies together with germ-free mice, germ-free marmosets, and humanized liver mice, we will visualize the distribution of bioactive metabolites and explore how the microbiota affects the host physiology. Gold nanoparticle-based large-area SERS, which was establish by Suematsu group, can be used to visualize the spatial distribution of several metabolites including reactive sulfur species, volatile fatty acids, and small molecular gaseous compounds such as CO, CO_2, NOx, and hydride/hydrogen (H-/H_2) (Suematsu, JCI 1995; Shiota, Nat Commun 2018). *In vitro* studies have revealed that these compounds are actively utilized as nutrients and signaling molecules by anaerobic microbes, and possibly as host macromolecules (Kabe, Nat Commun 2016). In addition to these infrastructures, the IM Team will provide key technologies including high-performance affinity nanobeads for chemical biology, which can be used to mine candidate metabolites that can interact with the intestinal epithelial cells and/or immune cells. Chemical biology can further reveal the identity of receptors of individual metabolites. Collectively, using multidisciplinary imaging metabolomics and chemical biology, we will decipher metabolite-mediated multiorgan regulatory networks in health and disease.

Q: Quantum computing core

The Q core will play a fundamental role in integrating data obtained from the Bio-1/2 cores and perform high-precision analysis using both gate- and annealing-model quantum computing techniques.

Quantum computing has attracted considerable attention owing to its calculation efficiency and representational power. However, issues in finding the efficient solution to various problems remain.

Although various techniques have been implemented, calculation errors owing to environmental noise are inevitable. Moreover, because practical applications in biological and medical biology have not been explored rigorously, the immediate challenge is to find tasks in various fields of biological sciences in which quantum computing can be applied. In the first five years, we will develop new research methods utilizing quantum computers that apply to human biology. We will develop black-box optimization using quantum annealing, which is the result of Tanaka's research described below, into a method applicable to human biology. In addition, we will identify bottlenecks in applying quantum algorithms for gate-model quantum computing to human biology and propose improvements for the application of quantum algorithms for gate-model quantum computing to human biology. In the next five years, we will apply the developed methods to the data obtained from the Bio-1 core and achieve discovery results that will contribute to multi-organ circle research, which will be connected to the research in the Bio-2 core.



Using variational Autoencoder (VAE) and quantum computing, the omics data obtained from clinical or basic research can be plotted in a quantum latent space. This may facilitate visualization of differences between data ("Quantum signature"), such as physiological vs. pathological conditions, or before and after taking medications.

Quantum AI, which combines gate-model quantum computing with conventional AI, is expected to lead to more accurate heuristic methods by combining the advantages of both. This will establish a method for extracting “quantum signatures” that lie behind the circuitry of multi-organ molecular and cellular interactions associated with a given phenotype, potentially with high speed and accuracy (see above figure). The number of qubits in gate-model quantum computers has been increasing rapidly in recent years, and the dimension of the variables that can be handled in the problem is increasing exponentially. Substantial improvements in error correction systems will be made, and the number of algorithms will be increased in a gate-model quantum computer, with a corresponding increase in the capability of handling complex quantum circuits and the potential for its application in biomedical sciences. Keio University Quantum Computing Center has put forth a significant effort to advance gate-model quantum computing and has made several research findings on quantum AI (Nakaji, Sci Rep. 2021; Kishi, IEEE J. Emerg. Sel. 2022). In the WPI, Sakakibara will analyze multidimensional human multiorgan multiomics data obtained from Bio-1 using non-negative matrix factorization on a “quantum space” defined by qubits, extract quantum signatures, and feed them back to Bio-2. The data from the microbiome, metabolome, and genomic analysis of human multiorgans are sparse and have tens of thousands of dimensional matrices. Matrix factorization in quantum space can rapidly decompose them into low-dimensional factor matrices, that is, “quantum signatures”. Kawaguchi and Yamamoto will develop exploratory algorithms that can deal with data structures obtained from the Bio-1 core (i.e., small number but multivariate structures) by taking advantage of the high representational capability in the feature space. For example, by extending a method utilizing quantum kernels to capture the relationships among variables (Kawaguchi, arXiv, 2021), algorithms that can estimate causal structures more accurately than conventional methods will be developed to provide accurate hypotheses, which will then be linked to Bio-2.

Annealing-model quantum computing called “quantum annealing” is a promising method for efficiently solving “combinatorial optimization problems’’. However, most of the current research on quantum annealing is limited to investigating basic problems in mathematical optimization. Tanaka has been working on a proof-of-concept in several applications, mainly in industry-academia collaborative research, such as web advertisement serving optimization (Tanahashi, J. Phys. Soc.

Jpn. 2019), network analysis (Yoshimura, IEICE Trans. Inf. Sys. 2021), and stable structure searches for multiple polymers. Tanaka has also developed a black-box optimization method that drastically expands the range of applications using quantum annealing (Kitai, Phys. Rev. Research 2020). Building on these research findings, Tanaka and Kawaguchi will establish a fast and accurate method to solve many-to-many combinatorial optimization problems behind multiorgan algebras by quantum annealing. For example, in collaboration with Bio-1, we plan to extend our network analysis method using quantum annealing to discover functionally similar metabolites with distinct structures. In addition, we propose black-box optimization methods and stable structure search methods to predict potential pathways for a given metabolite with high efficiency. In collaboration with Bio-2, we will discover and test potential mechanisms in multiorgan networks.

Through these studies, we will establish critical application methods for quantum computing in the biomedical sciences. Because medical biology deals with a complex system that has a nonlinear, non-equilibrium, and multi-hierarchical nature, providing examples of applications of quantum computing will have an immeasurable impact on the quantum computing field.

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. Regarding the composition of the center's personnel, describe measures to obtain diversity such as gender balance.
* 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: Bio2Q will build a research structure with the 7 core values described below, having at least 5 international PIs or Jr PIs who reside on site. In parallel, we consider the long-term vision of the center. We will endeavor to build a system that can attract and train promising early career researchers from around the world. Our educational system will include mentoring by center PIs and the establishment of a joint program between the Graduate School of Medicine, Graduate School of Pharmaceutical Sciences, and the Graduate School of Science and Technology, which will expand the scope of study for students and foster the development of future WPI researchers. We underscore the importance of providing ample support through our administrative and research support organizations so that researchers can fully dedicate themselves to their research. The responsibilities of these support organizations include preparing to accept international researchers, organizing events, and handling administrative procedures, such as research fund management that researchers otherwise have to handle themselves.

We will ensure diversity among the researchers at the WPI center by having a variety of nationalities, genders, and ages represented, with the goal of having at least 30% international researchers and 50% female researchers. The center is expected to comprise approximately 120 members in total, including 30 PIs and junior PIs (including 5 international PIs or Jr PIs who reside on site), 10 international collaborators, 50 postdocs and graduate students, and 30 research support and administrative staff. English will be used as the official language of the center.

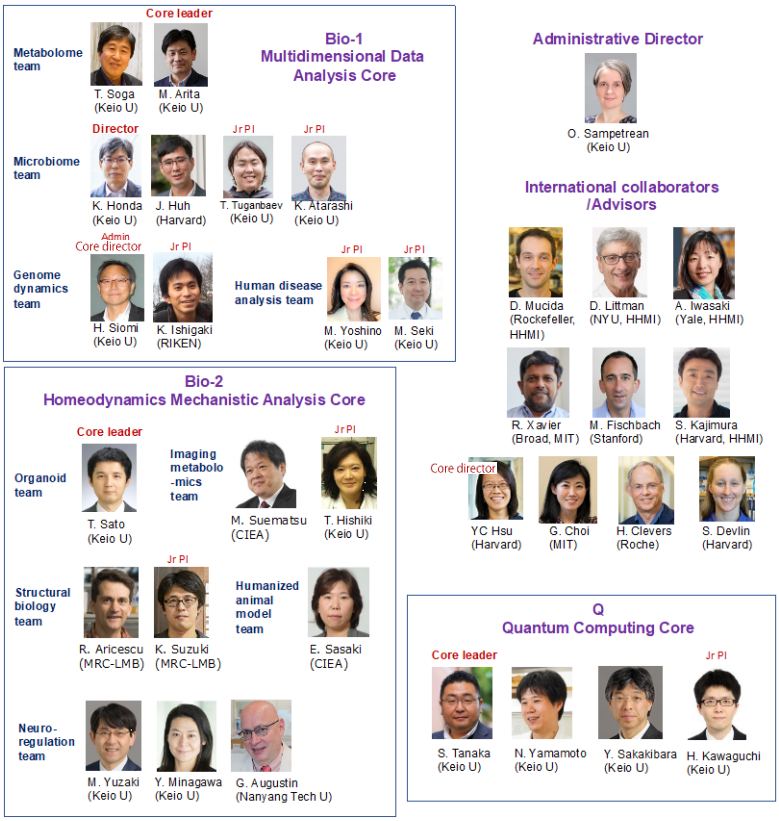
Core values of the center:

Bio2Q will build a research structure with the following 7 core values.

1. Excellence and professionalism: Bio2Q delivers work of the highest quality and professional

standards.
2. Collaboration and sharing of knowledge: The three Cores share technologies, expertise, and pipelines to streamline data generation, mining, and evaluation.
3. Transparency and integrity: Bio2Q encourages transparency, openness and reproducibility in science, as well as transparency in decision-making processes, except where confidentiality is strictly required.
4. Innovation and sustainability: Bio2Q is committed to discovering new talent and new ideas, attracting and learning from them, and stimulating new approaches and new ways of thinking.
5. Social implementation: Bio2Q values and accelerates research activities toward social implementation.
6. Diversity and globalization: Bio2Q strives to recruit in a focused manner to attract top talent while ensuring gender and cultural diversity. These are essential ingredients for a creative, exciting and successful work environment, and will help ensure our competitiveness on the international stage.
7. Education and fostering the next generation: Bio2Q creates an environment where graduate students and early career researchers are encouraged to learn and collaborate freely across disciplines.

Researchers and Satellites:



In collaboration with the Director (Honda) and Deputy Directors/Core directors (Arita, Sato, and Tanaka), 11 Principal Investigators (PIs) (15 PIs in total, including 3 international PIs and 2 female PIs) and 8 Jr PIs will work together at the three research cores. In addition, 10 international collaborative researchers /advisors will participate in the team to promote research collaboration. The home research institutes of PIs who participate in Bio2Q from institutions other than Bio2Q are called “satellites.” The Central Institute for Experimental Animals (CIEA) and RIKEN, with which an agreement for research collaboration has already been reached, will function as domestic satellite institutes, not only for research collaboration but also as human resource development institutions for graduate students and postdocs. The Medical Research Council Laboratory of Molecular Biology (MRC-LMB) in UK and Harvard Medical School in the USA will function as overseas bases for Bio2Q. It is worth noting that Augustin has extensive experience with developing and operating international research center and programs, such as the Center for Functional Connectomics in Korea as part of the World Class Institute program and international research programs at the Duke-NUS Medical School and Lee Kong Chian School of Medicine.

Sampetrean and Siomi will work together as Administrative Directors and provide a wide range of supports to the Director as well as other PIs. This two-person system will enable rapid coordination between the three departments and the satellites, and provide comprehensive support and agile management. Sampetrean is a neurosurgeon and basic scientist involved in brain tumor and microbiota research. She is a rare multilingual researcher who is fluent not only in Japanese and

English but also in 6 other languages. She will head up external operations, whereas Siomi will be in charge of internal affairs and provide continued support to Sampetrean.

Bio-1: Multidimensional data analysis core (Core director: Arita)

Human Disease Analysis Team: Morinobu Seki (Keio Med, Jr PI) and Mihoko Yoshino (Keio Med, Jr PI). Two clinical coordinators will be hired to facilitate clinical sample collection and ethical applications.

Microbiome Team: Kenya Honda (Keio Med.), Jun Huh (Harvard), Timur Tuganbaev (Keio Med.), Koji Atarashi (Keio Med., Jr PI), International Collaborators [Dan Littman (NYU), Daniel Mucida (Rockefeller), Ramnik Xavier (Broad Inst.), Michael Fischbach (Stanford), Akiko Iwasaki (Yale), Shingo Kajimura (Harvard), Sloan Devlin (Harvard), and Ya-Chieh Hsu (Harvard)].

Metabolome Team: Makoto Arita (Keio Pharma. Sci.) and Tomoyoshi Soga (Keio IAB).

Genome Dynamics Analysis Team: Haruhiko Siomi (Keio Med.), Kazuyoshi Ishigaki (RIKEN, Jr PI).

Bio-2: Homeodynamics mechanistic analysis core (Core director: Sato)

Organoid Team: Toshiro Sato (Keio Med.), International collaborator [Hans Clevers (Roche)].

Neuroregulation Team: Michisuke Yuzaki (Keio Med.), Yasuyo Minagawa (Keio Literature), George Augustine (Nanyang Technological University), International collaborator [Gloria Choi (MIT)].

Structural Analysis Team: Radu Aricescu (MRC-LMB), Kunimichi Suzuki (MRC-LMB, Jr PI).

Humanized Animal Model Team: Erika Sasaki (CIEA).

Imaging metabolomics team: Makoto Suematsu (CIEA), Takako Hishiki (Keio Med, Jr PI).

Q: Quantum computing core (Core director: Tanaka)

Shu Tanaka (Keio Sci. Tech.), Naoki Yamamoto (Keio Sci. Tech.), Yasufumi Sakakibara (Keio Sci. Tech.), Hideaki Kawaguchi (Keio Sci. Tech., Jr PI).

General management of the center:

The Planning and Administration Office is responsible for the overall management of the center, including the development of the center's rules and regulations, management of facilities, and reporting to relevant ministries and agencies. In addition, in cooperation with the digital transformation (DX) promotion coordinator, the office will be in charge of online research meetings and other events to ensure that our activities are not confined to the center.

The Finance Office will manage the annual budget of the center and implement measures to make the center self-sustaining, support the acquisition of external funds, solicit donations, etc.

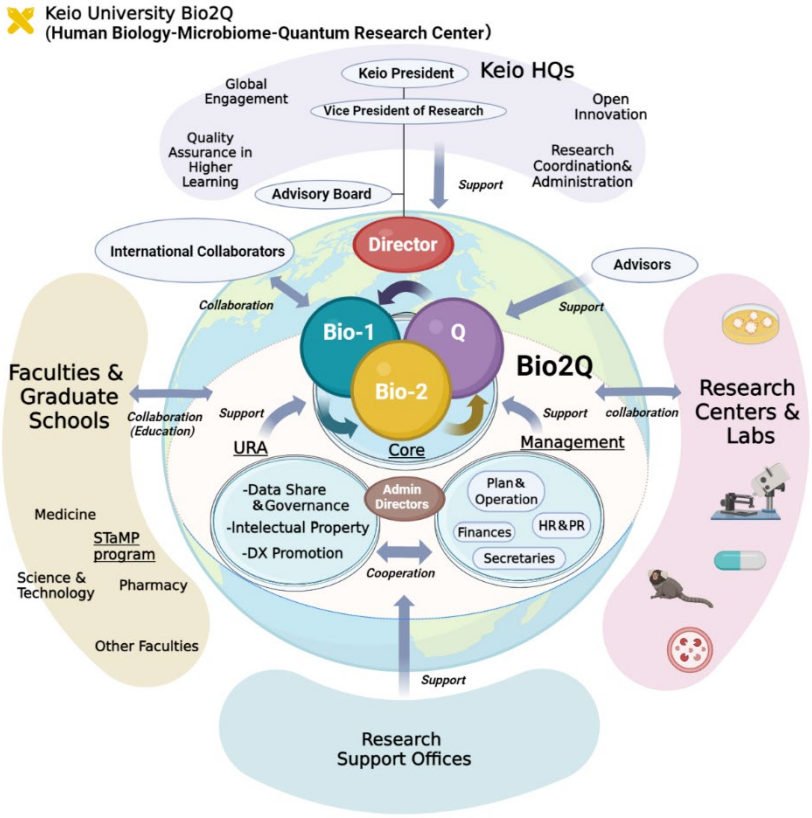
The Personnel and Public Relations Office will primarily be responsible for recruiting early career researchers. The office will be responsible for consistency in the center's PR activities so that it can inform international recruitment, contract negotiations, and hiring. We also consider outsourcing professional services to support international researchers in traveling to and from Japan, as well as helping them settle after arriving.

The Coordination Office will be responsible for providing general support for PIs' activities, including international PIs, to ensure that their research goes smoothly.

The Data Sharing and Governance Office will present an approach to sharing data in ways that will enable smooth collaboration between researchers, including those outside of Japan, and will establish an appropriate data management system in compliance with the laws and regulations for research using clinical data obtained from Keio University Hospital and other institutions.

The Intellectual Property Office will verify legal regulations, evaluate the appropriate intellectual property, and assess and negotiate licensing when concluding joint research agreements with companies to make the center self-sustaining. The intellectual property field is expected to include research related to drug discovery, IT (e.g., life science apps), and medical devices.

The DX Promotion Office will promote virtual research environments and focus on sharing the center's findings, recruiting international early career researchers, overseeing public outreach, and transitioning the center to a paperless environment in coordination with other offices.



Advisory council: An Advisory Council consisting of about five international scientists will be independently established to evaluate the scientific progress of the center and provide advice regularly. In addition, the Center Director shall appoint Advisors who evaluate scientific progress and provide suggestion to the center. International collaborators can also serve as advisors. We plan to appoint Eisuke Yoshida of the Keio Faculty of Business and Commerce to oversee organizational management, and Takehiro Ohya of the Faculty of Law to oversee ethical, legal, and social issues (ELSI). We also plan to hire other staff, such as editors of well-known journals, to assist with research planning and publishing.

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

* Paste onto table a) in Appendix 7.

(persons)

	At beginning of project	At end of FY 2022	Final goal (Date: March, 2025)
Researches from within the host institution	10	10	10
Foreign researchers invited from abroad	3	3	4
Researchers invited from other Japanese institutions	2	2	2
Total principal investigators	15	15	16

b) Total number of members * Paste onto table b) in Appendix 7.

		At beginning of project		At end of FY 2022		Final goal (Date: March, 2025)	
		Number of persons	%	Number of persons	%	Number of persons	%
Researchers		32		32		90	
Overseas researchers		13	40.6	13	40.6	28	31.1
Female researchers		8	25.0	8	25.0	45	50.0
Principal investigators		15		15		16	
	Overseas PIs	3	20.0	3	20.0	4	25.0
	Female PIs	2	13.3	2	13.3	2	12.5
Other researchers		17		17		74	
	Overseas researchers	10	58.8	10	58.8	24	32.4
	Female researchers	6	35.3	6	35.3	43	58.1
Research support staffs		13		13		17	
Administrative staffs		6		6		11	
Total number of people		51		51		118	

		At beginning of project		At end of FY 2022		Final goal (Date: March, 2025)	
		Number of persons	%	Number of persons	%	Number of persons	%
Doctoral students		0		0		40	
	Expected employment	0	-	0	-	40	100.0

The number of doctoral students indicated in the lower table can also include those in the upper table of b) Total numbers.

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 (FY2017-2021).

	H29(2017)	H30(2018)	R1(2019)	R2(2020)	R3(2021)	Total	Average
Japanese PIs	990	2,823	1,302	1,481	1,813	8,409	1,682
Overseas PIs	780	2,959	829	334	540	5,442	1,088
Total	1,770	5,782	2,131	1,815	2,353	13,851	2,770

(Million yen)

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 (FY2022-2026).
* 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.

Year	R4 (2022)	R5 (2023)	R6 (2024)	R7 (2025)	R8 (2026)	R9 (2027)	R10 (2028)	R11 (2029)	R12 (2030)	R13 (2031)	total amount
WPI Grant	650	700	700	700	700	679	658	637	616	595	6,635
Funding from the host institution	256	534	536	538	512	531	551	570	589	608	5,225
Research Expenses from Competitive Funds & Other Sources	498	1,047	1,110	1,127	1,157	1,187	1,267	1,297	1,326	1,406	11,422

(Million yen)

WPI Grant

1. Personnel expenses: PIs, Jr PIs, international collaborators, University Research Administrators (URAs), administrative staff, postdocs, graduate students.
2. Project promotion expenses: Research environment maintenance (for the renovation of open labs, center support offices, community spaces, germ-free mouse facilities, germ-free marmoset facilities, and cryo-electron microscopy (cryo-EM)-related facilities), travel and living support, contractor expenses, and center website expenses.
3. Travel expenses: Travel expenses for international collaborators and newly hired postdocs.
4. Equipment expenses: Cryo-electron microscopy (cryo-EM)-related equipment.

Funding from the host institution

1. Personnel expenses: Center director, PIs, Jr PIs, administrative directors, full-time technicians, URAs, and administrative staff.
2. Project promotion expenses: Renting space for the center, utility expenses for spaces used for the center initiative.

Research expenses from competitive funds & other sources

1. Personnel expenses: Researchers and research assistants hired for competitively funded projects associated with the center.
2. Project promotion expenses: Expenses related to promotion necessary for competitively funded projects associated with the center.
3. Travel expenses: Domestic and international travel expenses for competitively funded projects associated with the center.

2) -5 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.

We expect that the technologies and results generated by the fusion of Biology, Microbiome, and Computing will affect other fields in multiple ways. Applications with a wide impact will include establishing new therapies, preventive modalities, and biomarkers. We believe that our efforts will also help forge the entire research field of biology and Q-computing and produce several innovative technologies. Establishing workflows of how to identify multiorgan and microbiome interactions and how to use quantum computing to advance biological knowledge can be applied to other fields and will set a precedent in creating new examples of interdisciplinary fusion.

In recent years, it has become clear that the microbiome has a significant impact on human health and organ systems. Microbiota exerts such effects primarily by producing tens of thousands of unique chemicals (metabolites). However, the vast majority of metabolites (>99%) have not been annotated structurally and functionally (thus remaining unidentified “dark matter”). In addition, the difficulty in accurate and high-throughput analysis of the community action of microbiota and their metabolites has hindered efforts to define the mechanistic connections between the microbiota and host phenotypes. Moreover, a comprehensive understanding of complex human biology requires an integrative analysis of multiple levels of data from the genome, transcriptome, metabolome, together with microbiome. However, it has been extremely challenging to infer causal molecular networks using multiomics data, underscoring the importance of continuing to develop new approaches. Quantum computing represents an exciting frontier with significant potential for discovery in the field of biological sciences, yet several challenges remain, such as improving accuracy, fault tolerance, and lack of practical applications in life sciences. Therefore, the Bio2Q WPI will harness quantum computing to shed light on the black box separating the complex system involving multiple organs and the microbiome, and determine scientific causal relationships. Establishing an algorithm/pipeline that fully utilizes the power of quantum computing will pave the way for significantly improving the discovery process in biological sciences. Such interdisciplinary research

requires the training of young scientists capable of collaborating across disciplines. To foster such scientists, graduate students and postdoctoral fellows in the fields of biology (Bio-1, Bio-2) and computing (Q) will be mentored by multiple PIs across cores and laboratories.

3) Global Research Environment and System Reform

3) -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.
* Describe measures to help foreign researchers sustain and strengthen their activities under conditions when international exchange is limited.

Plan for building an international research center: We will ensure diversity among Bio2Q researchers by including a variety of nationalities, genders, and ages, with the goal of having at least 30% international researchers and 50% female researchers. We will provide sufficient support for international researchers and their families to ensure a smooth start to their lives in Japan. Startup funding will be provided for international PIs so that they can promptly start their research at the center. Compensation will be determined in line with a global standard (those implemented the National Institutes of Health, USA), and not bound by university conventions. Through these measures, we will keep the center attractive for up-and-coming young scientists. The center structure will be developed within three fiscal years following the start of the project. We will increase opportunities to obtain research grants, such as by joint application for overseas foundation grants, thereby enhancing the international nature of the center's activities.

Strategy for recruiting international researchers: The Personnel and Public Relations offices will conduct public relations activities and create a system to recruit motivated postdoctoral and other young scientists from around the world throughout the year. Starting in the first year of the project, we will develop international recruitment programs and establish a system for reviewing and accepting applicants in accordance with the recruitment agreements and regulations of the center. In particular, we plan to strategically recruit 4-5 international Jr PIs within the first two years of the project.

Measures to help foreign researchers: We assume that there will be situations in which international PIs cannot physically come to Japan because of restrictions arising due to the COVID-19 pandemic. In such cases, state-of-the-art DX technologies such as virtual conferencing and cloud data storage system will be used to enable the PIs to engage in research activities from remote locations. We plan to create a virtual institute environment (the so-called “cyber one-roof”) to enable frequent, in-depth communication between researchers who would otherwise have trouble physically working at the center. We will also utilize a range of media, including social media, to share the latest findings at the center, create a network, and attract global interest from around the world.

3) -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 who can facilitate the use of English in the work process 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 (e.g., allocation of adequate staff support to handle paperwork and other administrative functions) including your procedure and time schedule.
* Describe your strategy, procedure and timing for periodically holding international research conferences or symposiums.

To promote globalization, we will secure and train personnel in English language proficiency and research administration skills. We will also promote DX to streamline working processes to support the globalization of the center and other research activities. The support office will take care of administrative procedures such as research grant management, preparation for events, and procedures for accepting international researchers. In the first and second years, the center will develop its facilities, establish rules within the center, and formulate a structure for research support

and administrative offices.

The center will regularly hold an international symposium gathering PIs and top researchers annually. To attract more participants and save costs with lower burden of preparation, web conferencing will be actively utilized for various meetings and discussions. Along with the research meetings, workshops will be organized for undergraduates and graduate students to facilitate interaction between them and top-level researchers.

3) -3 Center management and system reform

* Describe the role of the center director and the administrative director.
* Concretely describe your concept for establishing the center's administrative organization, the center's decision-making system and how authority will be allocated between the center director and the host institution. (Describe concretely the mechanism for decision making when the person in charge of management and the person in charge of research and education in the center are different, and describe the responsibility relationship between the two.)
* 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.

Role of the center director and administrative directors: The center will be an independent research institute under the administrative jurisdiction of Keio University. The Center Director will be appointed and dismissed by the President of Keio University, who acts as both Keio's chief executive officer and chairman of the board of trustees. The decision-making authority for the overall management of the center is left to the discretion of the Center Director to achieve highly flexible and agile management at the center. In day-to-day operations, the authority of the PIs, research cores, and divisions appointed by the Center Director will be clearly defined, and free and vigorous research activities will be prioritized. The Deputy Directors will support the Director and work with the PIs and other researchers to achieve research goals and create new research fields. Administrative Directors will strengthen collaboration with internal and external stakeholders and work with host institutions and external organizations to develop strategies and plans for stable management of the center.

On the other hand, compliance measures, such as research ethics and biosafety, as well as accounting procedures, are supported by the administrative office of the School of Medicine. For issues that may arise at the center that cannot be resolved within the center, the Office for Interdisciplinary Research Initiatives at the Headquarters for Research Coordination and Administration (RCA) will consider the issue and solve it as a university-wide problem. RCA will also provide support to take successful examples within the center and apply them across the departments. In this way, the Center Director will be given a great deal of discretionary authority to carry out center activities with confidence and a feeling of security. RCA also regularly reviews center activities and provides feedback as necessary. The host institution will be involved in preventing the abuse of power on the part of the Center Director, and if there is a situation that is not expected to improve, replacement will be considered at the discretion of the President of Keio University.

System for evaluating research and merit-based compensation: The center will hierarchically evaluate researchers and research results once a year: The Center Director will evaluate the Deputy Directors, and subsequently, the Deputy Directors will evaluate the PIs, Jr PIs, and postdocs. The evaluation will be based on the overall achievements in terms of publications, research presentations, acquisition of research funds, fostering young researchers, and contribution to society. The center can determine the salary amount according to the performance evaluation within the scope of various labor laws, without being bound by internal conventions. In terms of institutional support, we plan to offer a competitive employment package by exempting researchers from compulsory retirement regulations and by introducing an incentive reward system for individuals out of the funding that they have obtained.

3) -4 Research environment

* Concretely describe how equipment and facilities, including laboratory space, will be provided in a manner appropriate for a "world premier international research center." Include your procedure and timing.

* Describe measures taken with regard to the research environment to sustain and strengthen research activities under conditions when international exchange is limited.
* Concretely describe how the center will consider arranging for its researchers to participate in the education of graduate students.
* Describe new measures to improve or abolish existing systems and practices in the host institution toward optimizing the center's research environment.
* Describe your measures other than those described above for ensuring 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.

Equipment and facilities, including laboratory space: From the outset of the WPI project, more than 3,000 m^2 will be set aside for the center on Shinanomachi Campus, including open labs, PI offices, center support offices, and a community space. In particular, 1,300 m^2 in the Center for Integrated Medical Research Building and 540 m^2 in core facility of Keio Medical School will be used as a "globally visible" research center. In addition, a core facility (540 m^2) of Keio Medical School, outfitted with the latest research equipment, will be made freely available to all WPI researchers. In the first year of the project, we will start by installing cryo-electron microscopy-related equipment, which will be the core of the center's activities, to accelerate the implementation of structural analysis. Germ-free animal facilities (for mice and marmosets) will also be prepared to facilitate microbiome studies.

Simultaneously, we will focus on developing a best-in-class computing environment for analyzing and processing vast amounts of human biological data. In 2018, Keio University established the IBM Q Network Hub, becoming the only organization in Asia that has access to IBM's best quantum computer. Together with seven industrial partners, Keio has been recognized as the world's most impactful quantum computer software and algorithm development center, with an unprecedented mastery of IBM's latest quantum chips, which are evolving rapidly. Because of active collaborations with universities and research institutes in Europe and the U.S., we will be able to accelerate the analysis of the vast amount of multiomics data acquired at the center using quantum computing in addition to state-of-the-art AI. Although IBM is developing a gated-based quantum computer, we will also have access to a cloud-based quantum annealing technique, which excels in combinatorial optimization problems.

After the center opens, existing spaces will be reallocated as research develops, and facilities will be expanded and further developed as needed. As part of the Keio University Mid-Term Plan 2022-2026, Shinanomachi Campus, where the center will be established, will be developed as a "globally visible" research center and will continue to drive innovation at Keio University in the future, even after the WPI grant period ends. As the WPI program develops, we will consider the ideal facilities required for researchers to work under one roof and assess the transformation of the center's research environment, including the construction of new research buildings on Shinanomachi Campus as part of campus development in line with university-wide plans for construction.

Sustaining research activities in conditions where international exchange is limited: If a researcher is unable to physically stay at the center because of the COVID-19 pandemic or other reasons, they will be able to maintain and advance their research through regularly scheduled meetings. Methods for sharing research information will be designed early in the first year of the project, and a system will be established to manage and share raw research data on the cloud, leveraging online collaboration tools such as Dropbox and Box to establish a virtual laboratory space that will enable regular communication and sharing of research progress.

For researchers belonging to other campuses, a room will be set up in the center to facilitate smooth collaboration with other researchers belonging to the Bio2Q. For overseas PIs, a secretary in charge will be appointed, and researchers residing in Japan at the same research core will provide support for their research activities, thereby creating a mechanism to promote WPI research activities, both remotely and when visiting Japan, without delay. When overseas researchers visit Japan, the WPI office will provide support for their arrival in Japan and their daily life.

Researchers' participation in graduate education: By establishing a joint cross-disciplinary graduate English program tentatively called **STaMP** (**S**cience and **T**echnology, **a**nd **M**edicine, **P**harmacy) between the Graduate School of Medicine, Graduate School of Pharmaceutical Sciences, and Graduate School of Science and Technology, the WPI center will create a "place of resonance" where faculty, researchers, and students from the three graduate schools can directly interact with one another. PIs affiliated with the center will be qualified to supervise graduate students at any of the graduate schools for medicine, pharmaceutical sciences, or science and technology. This will enable each graduate student to work with multiple mentors and receive guidance that transcends graduate school boundaries. We expect that these measures will create a virtuous cycle that will lead to more findings in core research units, which will, in turn, lead to more students and early career researchers coming to the center. In addition, Jr PIs and postdocs at the center will be able to gain educational and teaching experience by regularly working together with graduate students on their research projects. Since graduate education is conducted across graduate schools, PIs and early career researchers are expected to expand their knowledge of other academic fields and forge new collaborations through their participation in graduate education at the center.

Improvement of existing systems and elimination of customs: The university will position the center as a place where it can implement new initiatives to optimize its research environment. The center will be designated as a special zone to enable the employment of excellent researchers from Japan and abroad (including individuals who are beyond the retirement age). WPI faculty member salaries will be determined flexibly based on performance. Project researcher salaries will be determined by the Center Director based on PI evaluations. This arrangement will allow us to employ world-class researchers regardless of age. The headquarters of RCA, a university-wide organization, will be responsible for promoting and expanding research collaboration at the center and will create a system for connecting undergraduate faculties and graduate schools using the center as a platform. Keio University is committed to creating a comprehensive research environment befitting a premier international research center.

4) Values for the future

4) -1 Generating and disseminating the societal value of basic research

* Describe concretely and quantitatively the center's policy for widely disseminating the societal significance and value stemming from the results of its basic research to the general public.

Innovation through intellectual property: The center will establish new life science methodologies for discovering and verifying uncharted multiorgan homeodynamics. The basic research performed will generate knowledge that will contribute to preemptive medicine and healthy longevity care in a society where people are healthy throughout their lives and contribute to a sustainably growing society. The process of intellectual property creation and licensing of basic research results will be strengthened. We will promote industry-academia collaboration to translate research findings to the clinic with the help of the Clinical and Translational Research Center at the Keio University Hospital. We will also promote researcher entrepreneurship to promote the social implementation of intellectual property. This initiative will also be supported by the center's URAs and Keio's Office for Open Innovation and Office of Research Development and Sponsored Projects. The WPI program will be connected with the COI-NEXT program "A Health Commons Center to Empowering Social Well-being" (Host Organization: Keio University) to create a cycle that emphasizes the importance of basic research in a new light and generates funding for human resource development.

Outreach: Sharing the details of our research, findings, and their value, is of paramount importance. We plan to build a dedicated outreach team led by URAs with research experience and specialized knowledge, hire professionals with backgrounds in content management, and create an attractive

website with engaging content. Information will be published and shared publicly across different media, including social media, to disseminate our contribution to the realization of a bioeconomy society that aims to solve environmental and medical problems. As the center aims to seek a way to connect biotechnology with quantum computing, sharing the outcome from this unprecedented collaboration with other organizations and the public will provide valuable insights and contribute to the development of new applications for quantum computing technology. In addition, we will develop ways to attract interest in research from the younger generation through open campus days targeting junior and senior high school students via events that will combine lectures and workshops.

4) -2 Fostering next-generation human resources linked with higher education

* The center should be a platform for establishing a research system in which new interdisciplinary domains can be created within a rich international environment. Describe concretely and quantitatively the initiatives to be taken to foster young researchers, including doctoral students, through participation in such a research system within the center.

As academic fields become increasingly diversified and specialized, it is essential to promote interdisciplinary research by creating positive feedback loops that transcend academic disciplines to pursue disruptive innovations. As such, in conjunction with higher education, we plan to establish a joint cross-disciplinary graduate program tentatively called **STaMP** in FY2023 (the official language is English). Because each of the Keio graduate schools exists on separate campuses, the physical distance has made it a challenge to implement collaborative programs. However, the center will create a virtuous cycle in which faculty, researchers, and students from the three graduate schools can interact directly with one another. The Keio University Center for Quality Assurance in Higher Learning will provide comprehensive support for the planning and operation of STaMP. It is important that we foster these positive feedback loops in an open environment, where graduate students and early career researchers are encouraged to collaborate freely across disciplines. Keio University has entered into a basic research and education agreement with RIKEN in 2008, followed by a comprehensive cooperation agreement with the Central Institute for Experimental Animals (CIEA) in 2016. The center will leverage these agreements to build stronger feedback loops to foster talent and expand joint research opportunities. Furthermore, as detailed below, STaMP will, in the future, be integrated into the **Institute for Advanced Studies** (tentative), which will consist of a group of international and interdisciplinary research centers and institutes modeled after the WPI center.

1) Shared mentor program: We plan to implement a system for graduate students to receive guidance from multiple mentors in graduate schools. Mentors will not only participate in research guidance, but also join degree reviews and promote research in their respective graduate school laboratories and at research institutions abroad. We expect this system to not only promote the development of interdisciplinary researchers, but also to encourage interdisciplinary research among mentors through their graduate student mentees. The faculty members of the Graduate School of Medicine, Graduate School of Pharmaceutical Sciences, and Graduate School of Science and Technology who are not part of the WPI center will be actively registered as members of the STaMP Graduate School Committee as the center develops, allowing them to take part in research guidance and personnel exchanges that transcend academic disciplines.

2) Research internship program: We will establish a system that allows graduate students to intern at other laboratories (within their graduate school, at another graduate school, or overseas) for up to six months. PIs and WPI offices can assist graduate students in selecting a laboratory, but the decision will be ultimately left to the student.

3) Symposiums and retreats organized by graduate students and early-career researchers: International symposiums and retreats will be organized and held approximately once a year at the initiative of early career researchers, including graduate students and postdocs, with support from PIs

and the WPI administrative offices. We hope that these symposiums and retreats will lead to the creation of researcher networks that will extend across academic disciplines.

4) Cross-listed graduate workshops: We will establish workshops, including lectures and practical exercises, as programs for acquiring the skills and knowledge required of early career researchers who can work across academic disciplines. Workshops will be open not only to graduate students, but also to undergraduate students and early career researchers. Upon completion, participants will receive a certificate signed by the three deans of STaMP graduate schools. For example, in the Presentation Workshop, an international lecturer will present in English on how to give a presentation (oral, poster, or online), followed by practical training in small groups (e.g., four groups of five students each year) with PIs from the three graduate schools participating as tutors for each group. In the Medical Bioinformatics Workshop, participants will receive lectures and take part in practical training on genome analysis, gene expression analysis, and image analysis. PIs from each of the three graduate schools will be in charge of lectures and online training.

5) Accepting undergraduate students from the Faculty of Science and Technology and the Faculty of Pharmacy to conduct their graduate research at the School of Medicine: Unlike the Faculty of Medicine, undergraduate students at the Faculty of Science and Technology and the Faculty of Pharmacy participate in graduate research. Although students were previously accepted on an irregular basis, we plan to accept approximately 20 undergraduate students each year, in coordination with the Medical Educational Center at the School of Medicine as part of this new center. We expect that the master's and doctoral program students who experience this kind of cross-disciplinary graduate research will lead this center in the future.

6) High school outreach program: The center will support high school outreach programs that are already in place at each of Keio's undergraduate faculties to foster the future leaders who will help drive the next generation of research at the center.

4) -3 Self-sufficient and sustainable center development

* The center needs to become self-sufficient and sustainable after the funding period of 10 years ends. Describe the host institution's mid- to long-term plan and schedule for supporting the center's development, including the reform of the host institution's organization, the provision of personnel with priority allocation of tenured posts to the center, fundamental financial support, and material support including land and buildings.

Reorganization to become self-sufficient and sustainable: The center will be positioned as an independent research institute under the administrative jurisdiction of Keio University. In the future, we will establish the **Institute for Advanced Studies** (tentative), which will consist of a group of international and interdisciplinary research centers and institutes modeled after the WPI center. As an intramural special zone within the university, we will implement various bold measures to enhance research, ensure independent management, and attract the attention of researchers from around the world for its research performance, environment, support systems, and the ability to obtain funding. After reaching a consensus on these issues, we will reorganize existing cross-departmental research centers and institutes at the university, consolidating and optimizing resources into the Institute for Advanced Studies by reallocating operational expenditure budgets, staff, and facilities. As social norms and values continue to undergo dramatic changes, we advocate a "Convergence of Knowledge" format that integrates the humanities and social sciences, which will serve as the nucleus for creating the future of Japan and will be the driving force for the evolution of the university into a space that nurtures the world's leaders. Entry into the Institute for Advanced Studies will be based on the same criteria as the WPI center, requiring an impact and presence that attracts frontline researchers from around the world. While strict entry requirements will be set for research centers and institutes to receive accreditation, various incentives will be provided to affiliated researchers. By promoting the systems and policies of the Institute for Advanced Studies across the university, the

institute will become a driving force for Keio University to make further progress as a research university.

Provision of personnel with priority allocation of tenured posts to the Center: Researchers affiliated with the WPI or the Institute for Advanced Studies may also remain affiliated with their home institutes (concurrent appointment). Simultaneously, through the above-mentioned organizational reforms, we will be able to allocate or increase the number of tenured positions, and we will develop a system for establishing several tenured positions at the Institute for Advanced Studies at the discretion of the President of Keio University. These positions will be allocated to contribute to the sustainable development of the center through tenure-track positions for early career researchers and the acceptance of promising researchers from outside the university and overseas, primarily through the generational succession of PIs and the acquisition of external funding to exponentially improve the center's reputation.

In addition, we will promote the existing system of Advanced Research Project Professors (externally funded fixed-term faculty members not subject to compulsory retirement regulations). The income of the center (external funds) will also be used to bring 'world knowledge' from outside the university to the center and leveraged to further acquire external funding. Graduate students who participate in this center through the Early-Career Researcher Development Program at the Center for Quality Assurance in Higher Learning will be treated as researchers and paid an appropriate salary to broaden the center's base and ensure its sustainable development.

Mid- to long-term plan and schedule to support the center's development: The establishment and operation of the Institute for Advanced Study will be a part of the core project of Keio University following three goals specified in the "Mid-Term Plan 2022-2026": 1. creation of convergence of knowledge needed to lead society through collaboration between the humanities and natural sciences; 2. organic growth as a research university; 3. establishment of a 'globally visible' research center that can attract frontline researchers from around the world. These initiatives will remain in place in the form of the Institute for Advanced Studies after the WPI grant period ends. The operational budgets of the Institute for Advanced Studies are provided to maintain a secure and well-performing environment for researchers. We support the translation of research findings into social contributions and the acquisition of competitive research fundings with minimal interference. Furthermore, we plan to build updated infrastructures and commit to operating the institute where both international and domestic researchers can fully dedicate themselves to their research. Specifically, the university will support various new initiatives to secure research fundings. At the start point of WPI center, Keio University will bear a portion of the personnel expenses for PIs and other researchers (approximately 150 million yen/year) as well as the cost of renting space (approximately 300 million yen/year). All indirect expenses from public funds will be used to develop and improve the research infrastructure of the center (regarding private funding from companies, etc., 30% indirect costs will be charged). Through these measures, approximately 200 million yen will be available to the center in the final year of the project. Personnel expenses for the center's research and administrative support teams under this grant will be gradually reduced from the project's sixth year onward and will be halved in the final year (we expect to use approximately 360 million yen/year). By gradually shifting financial resources to external funds, and indirect expenses/overhead to be secured as detailed above, we estimate that it will be possible to maintain the center even after the WPI grant period ends, but we will invest university operational expenditure as necessary to achieve the project proposal.