Summary of 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
Prospective administrative directors: Oltea Sampetrean (Assistant Professor) and Haruhiko Siomi (Professor) Keio University School of Medicine

(1) Overall Framework of the Center Project

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 the 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

1) Research content: 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.

2) Interdisciplinary research: 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

1) International research environment: International up-and-coming multidisciplinary young researchers will be recruited by a dedicated recruitment team based on the policy that is designed to ensure fair and objective selection and decision processes. The working language will be English. We will ensure diversity among Bio2Q researchers by having a variety of nationalities, genders, and ages, with the goal of having at least 30% international and 50% female researchers. The administrative and support staff will help all researchers in a way that they can devote themselves to their research. From the outset of the WPI project, a total of more than 3,000 m^2 will be available for the center at Shinanomachi Campus, with 1,300 m^2 as the core facilities of a "globally visible" research center, which will include open labs, center support offices, and community space. After opening the WPI center, we will relocate and expand the center by considering the construction of a new building on Shinanomachi Campus in anticipation of a facility that will allow researchers to work together under one roof. In addition, a virtual research environment will be established to bring together research activities using web conferencing systems and other data-sharing tools, creating a strategy for close daily communication among researchers of Keio University and satellites (RIKEN, CIEA, Harvard, MRB-LMB, NTU, Rockefeller, MIT, Yale, NYU, Broad Institute, and Stanford).

2) Center management and system reform: 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. Decisions regarding the general management of the center will be at the discretion of the Center Director. We will establish a support office that will cover all facets of the center, including intellectual property, DX, early career researcher training, and fundraising. In order to make the center self-sufficient and sustainable, the host institution will work to support the acquisition of external funding, strengthen intellectual property management, and establish a governance system that ensures compliance while allowing freedom of research. Compensation will be determined by the Center Director in line with a global standard (those implemented by the National Institutes of Health, USA) and based on evaluations of research performance and other factors. 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.

(4) Values for the Future

1) Generating and disseminating the societal value of basic research

The mission of the center is to contribute to the sustainable development of society by creating knowledge that leads to improved prophylactics and therapeutics for promoting healthy aging. We are committed to promoting the translation of basic research findings into practice in relevant healthcare settings. We will encourage researcher entrepreneurship and industry-academia collaboration. To this end, we will create a team dedicated to active outreach and publicity activities. We will develop ways to share the details of our research findings and their value, particularly to the younger generation via lectures, workshops, and social media.

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

The center will strive to create positive feedback loops where faculty, researchers, and students are encouraged to work freely beyond academic disciplines. To achieve this objective, three Graduate Schools of Medicine, Pharmaceutical Sciences, and Science and Technology will establish a joint cross-disciplinary graduate English program tentatively named **STaMP** (**S**cience and **T**echnology, **a**nd **M**edicine, **P**harmacy) in FY2023, inviting PIs and early career researchers from the center to participate in graduate education. PIs will be qualified to supervise graduate research at STaMP, and students will be able to receive guidance from multiple mentors across the different graduate schools. Keio University entered into a basic research and education agreement with RIKEN and the Central Institute for Experimental Animals (CIEA). The center will leverage these agreements to build stronger feedback loops to foster talent and expand joint research opportunities. In addition, undergraduates and high school students will be considered as potential WPI researchers, and we will encourage their participation in the activities of the center.

3) Self-sufficient and sustainable center development

The Bio2Q center will be a manifestation of the university's goal of "creation of convergence of knowledge" and will serve as a model international, interdisciplinary, and autonomously growing research center. After the WPI grant period ends, the center will remain in place in the form of the Institute for Advanced Studies (tentative), which will function as a "globally visible" research center. Keio will continuously uphold university-wide commitment by bridging faculties/graduate schools across departments and enhancing a virtuous cycle. We continue to aim to translate research results into society via industry-government-academia collaboration and startup supports. Keio will implement structural reform to employ excellent researchers at all career stages, and foster early career researchers via graduate education, etc. Through the above actions, Keio aims to serve as a model for international research centers at private universities, which have to generate their own financial resources in contrast to national universities.