World Premier International Research Center Initiative (WPI)

FY2022 WPI Project Progress Report

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Research Center	Human Biology-Microbiome-Quantum Research Center (Bio2Q)		
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Common instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2023) situation of your WPI center.
* So as to execute this fiscal year's follow-up review on the "last" center project plan, prepare this report based on it.
* Use yen (\) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.
- Prepare this report within 10-20 pages (excluding the appendices, and including Summary of State of WPI Center Project Progress (within 2 pages)).

Summary of State of WPI Center Project Progress (write within **2 pages**)

To successfully initiate joint research between different fields in the center, all members of the Bio-1, Bio-2, and Q cores participated in several discussions as well as the 1st WPI symposium. The Microbiome, Human disease analysis, Organoids, Metabolomics, and Q teams have begun to work together to investigate the functions of metabolites produced by microbiota in the interaction between microbes and the host by sharing clinical samples, organoids, gnotobiotes, metabolomics, and computational analysis technologies. In addition, to fuse the disciplines of microbiome, molecular neurobiology and structural biology, the Structural analysis, Microbiome, and Neuroregulation teams held numerous discussions and meetings and have begun working together on projects related to synapse connectors and enteroendocrine cell biology.

The team members of **Bio-1 core** have begun collecting plasma, fecal and tissue samples from humans and model animals. We have also begun developing advanced analytical methods based on highly accurate quantification and measurement, with particular emphasis on the causal relationships between the intestinal microbiota and the maintenance of human homeostasis. Using a reductionist approach that combines microbiome profiling, gnotobiotic animals, and targeted/non-targeted metabolomics, we have attempted to develop new methods for identifying previously undefined microorganism-derived metabolites associated with diseases and specific conditions. We are currently looking for ways to accelerate a series of experimental steps, including the isolation of bacterial strains, sequencing of bacterial genomes, and generation of mutant strains, to identify bacterial enzymes/pathways that contribute to the production of specific metabolites, thereby influencing human physiology. By advancing non-targeted lipidomics with mass spectrometry (MS)/MS molecular spectral networking, which supports the structural estimation of unknown molecules, we are making significant progress in elucidating the lipid diversity arising from the intestinal microbiota and the molecular mechanisms that regulate the complex metabolic network. In addition, we have established capillary electrophoresis (CE)-MS based metabolomics techniques, including sample preparation, metabolite separation and detection, and data analysis to measure polar and charged metabolites. Moreover, using state-of-the-art technologies, such as organoids, single-cell multi-omics platforms, and CRISPR-based nucleotide editing, we have conducted experiments to elucidate how genetic variation affects cell- and tissue-specific molecular phenotypes associated with host-microbiome interactions. Additionally, we are working with the Q core to develop new pipelines to infer the complex interactions between microbiomes, metabolites, and host genetic factors.

Bio-2 core seeks to provide additional insight into the multifaceted mechanisms underlying multi-organ networks in humans, with particular emphasis on the role of the gut microbiota. Bio-2 core is developing innovative experimental platforms to demonstrate how metabolites from the gut microbiota

activate enteroendocrine cells (EECs), which in turn transmit signals to the brain. The Imaging metabolomics team is extending surface-enhanced Raman spectroscopy (SERS) imaging techniques to visualize and analyze in situ complex metabolites in the gut and surrounding organs. The Organoid team established an in vitro and intravital imaging system to observe stemness and cell cycle in the human colonic epithelium. These organoids encompass a diverse range of cell types, including EECs, which can interact with gut microbiota and metabolites. G protein-coupled receptors (GPCRs) are prime candidates for sensing metabolites generated by the microbiota. To streamline the identification of the GPCR-metabolite pair, the Structural analysis team is constructing a new structural biology facility that will decipher intricate host-bacterial communication. To elucidate the functional relationship between EECs and neurons, Neuroregulation team has established a gene-manipulation system for neural synapses. Upon metabolite-GPCR engagement, EECs transmit signals through neuroepithelial synapses to the sensory vagal nerves. This newly developed genetic manipulation system will improve our understanding of how EECs regulate vagal nerve activation. Neuroregulation team has also initiated investigation of the effect of the gut microbiota on the mother-infant attachment. There is still a gap between gut microbiota and host behavior, but our brain connectivity mapping together with microbiome analysis will provide unique phenotype-association data.

Q-core works on the application of quantum computing technology to the fields of human biology and the microbiome. We have been working on three research projects: causal discovery using quantum computing, the proposal of a new graph kernel applying quantum-computing technology, and the construction of a black-box optimization framework using quantum-computing technology. Quantum computing has the following three advantages: 1. theoretical, 2. empirical, and 3. operational. The first two are mathematical and physical concepts; the third refers to the situation-specific advantages of using quantum computing in a particular situation or index. Past studies have not clearly demonstrated operational advantage in medicine and biology, and predictions of when this will occur in the future vary extensively; however, experimental verification of the sample size advantage is expected to yield significant operational benefits. In medical research and clinical practice, generating and acquiring samples is generally costly because of the long duration of wet lab protocols, procedural invasiveness, high financial costs, and low incidence of disease. Therefore, we propose a roadmap comprising the following plans and milestones: 1. identification of tasks for which quantum computing can be utilized; 2. application of existing quantum computing algorithms; 3. development of new quantum computing algorithms; and 4. verification of the advantages of utilizing quantum computing in medical and biological research. In fiscal year (FY) 2022, we implemented Part 1 of the roadmap and initiated interdisciplinary research and the selection of associated tasks. Conversely, without careful consideration of Part 1 of the roadmap, research activities in Part 2 and beyond would be rendered futile. To expand the scale of the WPI program in future, we will carefully investigate Part 1 of the roadmap and aim to achieve Part 2 and beyond.

Under the leadership of the center director and the guidance of the newly established executive- and steering committees, the center is advancing its operational and administrative structures. Bio2Q has implemented the positions of junior principal investigator (Jr. PI), and WPI postdoctoral fellowships based on a globally competitive salary structure. We welcomed junior PIs and a postdoctoral fellow (an international female researcher) with expertise in microbiome, biological, and computer sciences. Our scientific results, recruitment, and outreach activities have been extensively disseminated via the newly established center's homepage and university publications. We also launched a joint cross-disciplinary graduate English program called Science and Technology and Medicine, Pharmacy (STaMP). The administrative branch expanded its Division of Planning and Operations, opened a new office, and added three bilingual support staff. The host organization strongly supports the center through measures such as allocating indirect expenses to improve its operating funds, diversifying funding sources, and planning its establishment under the Keio Global Research Institute (KGRI).

* Describe clearly and concisely the progress made by the WPI center project from the following viewpoints.

1. World-Leading Scientific Excellence and Recognition

1-1. Advancing Research of the Highest Global Level

* Among the research results achieved by the center, concretely describe those that are at the world's highest level. In Appendix 1, list the center's research papers published in 2022.

Bio-1 Multidimensional Data Analysis Core

Microbiome Team (Honda, Atarashi, Tuganbaev)

The human body is colonized by microbes from all three domains of life, with the gastrointestinal tract exhibiting the highest microbial density and diversity. Gut microbes outnumber their host by more than 25 times in terms of their genetic composition. This vast microbial ecosystem interacts intimately and, for the most part, mutually with the human host to perform essential metabolic functions. While sequence-based microbiome-wide association studies provide correlative support for the notion that microbiota influences human health and disease, they neither address the causality nor directionality of the host-microbiota relationship. Therefore, we have begun to conduct causal studies to identify bacterial species that directly contribute to human homeostasis in specific ways. We have been creating an effective feedback cycle between bacterial isolation, generation of mutant bacterial strains, proteomic and metabolomic analyses combined with gnotobiotic studies to facilitate a detailed mechanistic understanding of the microbiota-mediated maintenance of homeostasis and multi-organ systems where specific bacterial species and their products play causal roles and ultimately identify causally effective and therapeutically applicable minimal microbes and microbial products.

In the process of building such a research pipeline, one of the outcomes was the following research results. Although certain reports suggest that excessive gut protease activity may contribute to the pathogenesis of intestinal inflammatory and infectious diseases, the actual physiological implications of high and low intestinal protease levels remain unclear. Importantly, the components and mechanisms controlling intestinal proteases are unknown. Using a newly developed deep and highly sensitive proteomic assessment, we identified trypsin originating from the pancreas as one of the most abundant proteins in the large intestine of germ-free mice compared to conventional SPF mice. We mined healthy human microbiota using gnotobiotic techniques and for the first time identified Paraprevotella strains as potent trypsin-degrading commensals. By generating a panel of mutant Paraprevotella strains, we identified the type IX secretion system (T9SS) and two previously undefined T9SS effector proteins (PROKKA00502 and 00509) as essential components mediating trypsin degradation. By comparing gnotobiotic mice colonized with trypsin-degrading Paraprevotella and non-trypsin-degrading mutants, we demonstrated that intestinal colonization with Paraprevotella and the consequent trypsin reduction prevented the degradation of IgA. Moreover, Paraprevotella colonization can inhibit the systemic dissemination of intestinal coronaviruses that depend on trypsin for entry into host cells. Therefore, trypsin-degrading commensal colonization may provide protective benefits against coronavirus infections. In summary, this study used a newly developed deep and highly sensitive proteomic assessment, gnotobiotic techniques, and mutant Paraprevotella strains to demonstrate the causality and directionality of the host-microbiota relationship in maintaining homeostasis and preventing diseases. This study was published in *Nature* in 2022 (Appendix 1 – Refereed papers serial number 1).

Metabolome Team (Arita, Soga)

Gut microbes have unique metabolic systems, and many of their complex metabolic networks and structural diversity, as well as their interactions with the food environment and host, are unknown. Advances in non-targeted lipidomics technology developed by the Arita lab have revealed a much greater variety of lipid molecules in living organisms than previously thought (Tsugawa et al, 2020). By combining non-targeted lipidomics, which enables comprehensive analysis, including that of unknown metabolites,

with MS/MS molecular spectral networking, which supports the structural estimation of unknown molecules, we aimed to elucidate the lipid diversity formed by the intestinal microbiota and the molecular mechanisms that regulate the complex metabolic network. The diversity of lipid species and their modifications have the potential to perform various biological functions. The identification of new functional lipids often elucidates the biology and pathophysiology of diseases. In addition to the conventional MS/MS fragmentation method, i.e., collision-induced dissociation, we have developed a new structural analysis method to obtain more detailed structural annotation, such as double bond positions of lipid structures, using oxygen attachment dissociation (Uchino et al, 2022, App.1 – 46).

Regarding polar and charged metabolites, Soga Lab is the world's largest platform for metabolome analysis, with over 60 metabolomics instruments, including CE-MS, LC-MS, GC/MS, and SFC-MS, and has analyzed more than 20,000 samples from various research areas by national and international collaborators. Most metabolites from central carbon and nitrogen metabolism are hydrophilic and charged compounds (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 for all of these metabolites because of their high polarity, non-volatility, and identification complexity. Furthermore, the coexistence of more than 1,000 metabolites with similar physical and chemical characteristics in the cell complicates analysis. Focusing on these characteristics, Soga et al. developed a metabolomic profiling method based on CE-MS of polar and charged metabolites (Soga T et al, 2003). They have already established CE-MS based metabolomics techniques, including sample preparation, metabolite separation and detection, and data analysis, for measuring fecal metabolites, and has already reported some interesting findings on microbiome research (Yachida et al, 2019, Kikuchi et al, 2019). Therefore, the research environment for this project was comprehensively prepared.

Genome Dynamics Team (Siomi, Ishigaki)

Human health is maintained by complex interactions between the microbiome and host genetics, which are mainly unclear. The genome dynamics team investigated the biological mechanisms of transposable elements (Siomi Lab) and genetic polymorphisms (Ishigaki Lab) and aimed to study their interactions with microbiomes. The abundance of transposable elements (TEs) is one of the most striking characteristics of mammalian genomes. Their ability to mobilize and embed at any point in the genome can cause mutations that are generally detrimental to the host and sometimes cause disease in humans. TEs influence higher-order genomic structure and function by initiating DNA and histone modifications and chromatin remodeling. Host immune system uses TEs to communicate with the microbiota, which controls tissue homeostasis and inflammation. To investigate the functions of TEs, Siomi et al. developed an approach to effectively deplete the production of multi-copy TEs, which led to the discovery that the expression of a TE (MERVL) with more than 600 full-length copies in the mouse genome is required for accurate regulation of the host transcriptome and chromatin state during preimplantation development (Sakashita et al, 2023). TE bursts, however, pose a major threat to genome integrity by transposing copies in the genome. We identified TDP-43 as a factor that safeguards embryos against LINE1 transposition (Li et al, 2022). Because TDP-43 is a major risk factor for amyotrophic lateral sclerosis (ALS), our findings imply defects in TDP-43 in human diseases by increasing LINE1 transposition in embryos, perhaps providing an alternative view of the etiology of ALS.

Ishigaki et al. are committed to elucidating the functions of genetic polymorphisms that affect human health. To this end, they joined an international consortium to conduct large-scale genetic studies to identify risk polymorphisms and reported 34 novel loci for rheumatoid arthritis (Ishigaki et al, 2022a). The group also collaborated with clinical researchers to examine the impact of risk polymorphisms on immune cell functions using samples obtained from patients with autoimmune diseases, and illuminated the pathology of systemic lupus erythematosus (Nakano et al, 2022). The group developed a novel method

for analyzing T cell receptors (TCRs) to infer the impact of *HLA* polymorphisms, the most powerful risk factors of autoimmunity, and modified the method for inferring the TCR features of regulatory T cells (Ishigaki et al, 2022b; Lagattuta et al, 2022). These studies elucidate the functional underpinnings of genetic polymorphisms, which form the basis for investigating host and microbiome interactions.

Human Disease Analysis Team (Seki, Yoshino)
The clinical picture of chronic diseases and conditions is extremely diverse, and a comprehensive analysis of large amounts of patient information is essential to comprehensively understanding disease concepts. Seki et al. used a multicenter database of more than 1,000 patients with Parkinson's disease. The incidence of Parkinson's disease (PD) is rapidly increasing in our aging society, and the microbiome influences the pathogenesis of Parkinson's disease and drug metabolism. Improving the medical care of patients with Parkinson's disease necessitates the optimization of treatment and provision of tailor-made medication based on microbiota assessments. Seki obtained clinical fecal samples from patients with Parkinson's disease at the Keio University Hospital with informed consent and provided them to the Microbiome Team for further analysis.

Bio-2: Homeodynamics mechanistic analysis core
Imaging Metabolomics Team (Suematsu, Hishiki)
The Imaging Metabolomics team developed a novel method for visualizing metabolites in situ using SERS imaging, which has potential implications for collaborative work with Bio2Q. Formalin-fixed paraffin-embedded (FFPE) tissue is the standard for diagnosing diseases such as cancers but is inappropriate for detecting marker metabolites in situ. To address this challenge, the Imaging Metabolomics team integrated imaging metabolomics (IM), imaging mass spectroscopy, and gold nanoparticle-based SERS imaging. Using these technologies, the team revealed the novel roles played by polysulfides generated in intractable ovarian cancer, detoxifying anti-cancer drugs to render them chemoresistant (Honda et al, 2021). The team also revealed that invasive breast cancers exhibit greater levels of polysulfides than noninvasive cancers (Kubo et al, 2023, App.1 – 57). In this study, infrared laser scanning large-area SERS was fitted with a gold nanoparticle-based SERS substrate to visualize metabolites in freshly frozen needle-biopsied samples. The application of supervised machine learning to multiple stroma-specific SERS signals enabled automated differential diagnosis of invasiveness of cancer with high accuracy. This technology demonstrates that redox metabolite-derived SERS fingerprints can determine the invasiveness of human breast cancer.

Organoid team (Sato)
The intestinal epithelium maintains homeostasis through nutrient absorption and antibacterial protection. Deregulation of these epithelial functions leads to an imbalance in the gut microbiota associated with systemic disorders such as chronic inflammation, obesity, and cancer. However, the biological mechanism by which the epithelium regulates the gut microbiota and host homeostasis is unclear owing to the lack of experimental systems. In FY 2022, the team established three advanced technologies using organoids. (i) They developed a high-throughput drug screening system for normal human colon and cancer organoids (Toshimitsu et al, 2022, App.1 – 11). In the present study, newly optimized culture conditions were used to establish a scalable culture system for normal human colon organoids suitable for high-throughput applications. (ii) The combination of an intravital imaging system and genetic tracing system identified drug-resistant cancer stem cells (Ohta et al, 2022, App.1 – 12). Using multiphoton microscopy, the team established an intravital imaging system that enabled long-term live tracing of genetically labeled stem cells. This study also revealed the molecular mechanism by which the cell-matrix interface regulates the dormancy of cancer stem cells and proposes a new therapeutic strategy to prevent cancer recurrence. (iii)

The team refined Orthotopic xenotransplantation of human colon organoids. This study demonstrated the existence of slow-cycling human colon stem cells using a genetic lineage tracing system (Ishikawa et al, 2022, App. 1 – 10). This technology will elucidate the interaction between the human colon epithelium and the microbiome in the Bio2Q project. The team will share these technologies with other teams In Bio2Q to elucidate gut microbiota and host homeostasis.

Structural Analysis Team (Aricescu, Suzuki):
In FY 2022, the team supported the establishment of a new structural biology facility at the Keio University. In the present phase of the project, we are selecting equipment for cryo-electron microscopy and establishing a laboratory for the purification of proteins. In addition, we are hiring a junior principal investigator who will operate the cryo-EM laboratory. It is anticipated that the facility will begin operating in FY 2023.

Neuroregulation Team (Yuzaki, Minagawa):
Various metabolites produced by the microbiome, nutrients, and bile acids are sensed by receptors expressed by enteroendocrine cells (EECs) scattered throughout the intestinal epithelium. EEC signals are transmitted to the nucleus tractus solitarii (NTS) in the medulla oblongata via the sensory vagal nerve and are further integrated with various types of information in higher-order centers in the brain to control visceral, cognitive, and emotional functions, which are relevant to certain psychiatric and neurological disorders. To comprehensively understand the relationship between the microbiome and nervous system, the team aimed 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 are integrated in higher-order centers. To achieve these goals, Yuzaki et al. developed a viral vector tool kit to specifically manipulate gene expression in different subpopulations of EECs and vagal nerves. In FY 2022, the group established the X10 Expansion microscopy (X10 ExM) technique, which does not rely on optics but on the isotropic physical expansion of fixed specimens to clarify how nanodomains formed by various synaptic proteins interact with each other to organize synapses in the central nervous system *in vivo* (Nozawa et al, 2022, App.1 - 5). As EECs and vagal nerves form a synapse-like complex structure, Yuzaki et al. will apply this technique to elucidate the molecular mechanisms by which the EEC-vagal nerve contact site is organized. The X10 ExM technique will be shared with the other teams at Bio2Q.

In collaboration with the microbiome team, the Minagawa group aimed to elucidate the effect of the gut microbiome on neurodevelopmental disorders by focusing on mother-infant attachment. In FY 2022, the group established a new analysis pipeline to efficiently examine infants' brain connectivity in relation to their diverse demographic data (e.g., gestation and post-menstrual age). They found that long-range connectivity (e.g., frontal area to temporal area) developed very slowly in early preterm infants born before 30 weeks, suggesting that neurodevelopmental disorders occur more frequently in early preterm infants (Arimitsu et al, 2022, App.1 - 56). The Minagawa group also conducted a longitudinal cohort study and collected behavioral and physiological data from typically developing infants (TL) and infants with an elevated likelihood for autism (EL). In FY 2022, the group showed that parent training via the online system during the COVID pandemic situation improved children's social skills (Togashi et al, 2022, App.1 - 53).

Humanized Animal Model Team (Sasaki)
The common marmoset is a small, easy-to-handle, and highly reproductive species closely related to humans. It is a well-developed cerebral cortex, making it excellent for analyzing brain function, and a long average lifespan, which makes them excellent models for chronic diseases, lifestyle-related diseases, and aging. Genetic and embryonic manipulations are possible. Recently, the team produced a genetically

engineered Alzheimer's disease model and a sterile marmoset. They also developed an autoinduction monitoring system. This year, a gnotobiotic experimental system for marmosets was established. In the first trial, bacterial isolates from centenarians that generated the biosynthetic pathway of specific bile acids, including isoalloLCA, which is only naturally observed in humans (Sato et al, 2021), were inoculated into a *Staphylococcus aureus* mono-colonized marmoset. Fecal sample analyses of the gnotobiotic marmoset indicated reproduction of the bile acid metabolic pathway in in vitro studies. Furthermore, an inhibitory effect on *S. aureus* colonization was observed. These findings suggest the significance of gnotobiotic marmosets for evaluating bacterial functions in primate hosts, such as bile acid metabolism, which are difficult to reproduce in mouse studies. A gnotobiotic experiment was performed in non-human primates for the first time. To investigate gnotobiotic marmosets, we established a multidimensional phenotyping system for marmosets, including a 3D tracking system, vocal communication analysis system, automated fecal ophthalmoscopy analysis, MRI, functional MRI, and a touch panel-based cognitive function analysis system. This system will facilitate the elucidation of the relationship between the gut microbiota and behavioral and cognitive functions in non-human primates. The cognitive function of germ-free marmosets will be analyzed to compare the cognitive functions of wild-type marmosets.

Q-core

Q-core works on the application of quantum computing technology to the fields of human biology and the microbiome. This year, we have been working on three research projects: causal discovery using quantum-computing technology, the proposal of a new graph kernel applying quantum-computing technology, and the construction of a black-box optimization framework using quantum-computing technology.

Causal discovery has attracted considerable attention as an application of biomedical data. However, in situations such as rare and emerging infectious diseases, where sample sizes are insufficient for the detection of valid causal relationships, the development of new causal discovery algorithms suitable for small data is necessary. Therefore, we aimed to develop a new causality discovery algorithm suitable for small datasets by utilizing quantum computing, which has attracted attention for its application in machine learning. Specifically, Kawaguchi developed qLiNGAM, a new causal-discovery algorithm that applies a quantum kernel to a linear non-Gaussian acyclic model. This study was the first attempt to use quantum computing in a causal discovery algorithm. Experiments on multiple artificial datasets demonstrate that the algorithm is more accurate than existing methods that use the Gaussian kernel, a common conventional kernel, under various conditions in low-data regimes (Kawaguchi, 2023). In addition, when applying qLiNGAM to real-world medical data, Kawaguchi confirmed a case where the causal structures that could not be identified by existing methods were correctly estimated even when the amount of data were small. This result indicates the feasibility of qLiNGAM, compared to other causal discovery algorithms in low-data regimes, for obtaining novel medical knowledge.

We developed a novel graph kernel that uses a "quantum computer" to measure the similarity obtained from all subgraphs by fully exploiting the power of quantum superposition to encode every subgraph into a feature of particular form. Graph kernels are often used in bioinformatics and network applications to measure similarities between graphs. To construct a quantum kernel, we developed an efficient protocol that clears the index information of the subgraphs encoded in the quantum state. We also demonstrated that a quantum computer requires less query complexity to construct a feature vector than a classical sampler used to approximate the same vector. A detailed numerical simulation of a bioinformatics problem was used to demonstrate this; in many cases, the proposed quantum kernel achieved more optimized classification accuracy than the existing graph kernels (Kishi K et al, 2022, App.1 - 19).

To establish a fast and accurate method for performing many combinatorial optimization problems behind multi-organ algebras, an algorithm that can efficiently handle optimization problems where the

objective function is not explicitly given, that is, black-box optimization problems, needs to be constructed. Tanaka developed a new optimization method combining quantum annealing and machine learning to efficiently handle black-box optimization problems (Seki et al, 2022). Quantum annealing machines have an architectural bottleneck in that their input format is limited; however, this method facilitates the application of a quantum annealing to black-box optimization problems by estimating functions using machine learning. This method applies a quantum annealing to black box optimization problems by estimating a function using machine learning.

1-2. Generating Fused Disciplines

* Describe the content of measures taken by the center to advance research by fusing disciplines. For example, measures that facilitate doing joint research by researchers in differing fields. If any, describe the interdisciplinary research/fused discipline that have resulted from your efforts to generate fused disciplines. You may refer to the research results described concretely in "1-1. Advancing Research of the Highest Global Level."

As an initial step towards successful international joint research in different fields, all members of Bio-1, Bio-2, and Q cores participated in the 1st WPI kickoff meeting. Aricescu introduced cutting-edge technology to the Structural Analysis Team to facilitate international collaboration. For the fused disciplines of molecular neurobiology and structural biology, the structural analysis team (Aricescu and Suzuki) had many discussions and meetings with the neuroregulation team (Yuzaki) about an ongoing project related to synapse connectors. The structural analysis team conducted several tests in the MRC Laboratory of Molecular Biology (LMB) and product factory to identify the optimal equipment for in situ structural biology of biological samples that Bio-1 and Bio-2 were interested in. The equipment will soon be installed in Cambridge, and later in Keio. Personnel exchange between the two sites is scheduled to promote interdisciplinary research at the highest global level.

The organoid team collaborated with the imaging metabolomics team to investigate the metabolic functions of human hepatocytes. Using a new human hepatocyte organoid culture system, these teams streamlined the pipeline for efficient metabolic analysis of functional hepatocyte organoids. Sato, Clevers, and Honda are studying host-microbe interactions as a global collaboration. In this collaborative study, the three PIs share organoids, gnotobiotes, and whole-genome sequencing technologies and attempt to understand the biological mechanisms of underlying the introduction of somatic mutations by microbiomes to the host epithelium and ultimate induction of colon cancers.

To facilitate collaboration between the microbiome and metabolomics teams, Suematsu and Hishiki developed an analytical system for low-molecular-weight bioactive metabolites produced by gut microbiota. They fitted their mass spectrometer with a new high-energy 532 nm laser to cover broader molecular weight metabolites. They combined silver nanoparticles and the new laser enhanced resolution and sensitivity. These technologies will further connect the metabolomics team with other teams.

In collaboration with a human disease analysis team, the microbiome of centenarians (n = 106) was examined, and centenarians were found to have a distinct gut microbiome enriched in microorganisms capable of generating unique secondary bile acids, including various isoforms of lithocholic acid (LCA): iso-, 3-oxo-, allo-, 3-oxoallo-, and isoallolithocholic acid. Among these bile acids, the biosynthetic pathway of isoalloLCAs has not been previously described. By screening 68 bacterial isolates from the fecal microbiota of a centenarian, we identified Odoribacteraceae strains as effective producers of isoalloLCAs, both in vitro and in vivo. Furthermore, the team found that enzymes 5α-reductase (5AR) and 3β-hydroxysteroid dehydrogenase (3β-HSDH) were responsible for the production of isoalloLCA. IsoalloLCA exerts potent antimicrobial effects against gram-positive (but not gram-negative) multidrug-resistant pathogens, including *Clostridium difficile* and *Enterococcus faecium*. These findings suggest that the metabolism of specific bile acids may be involved in reducing the risk of infection by pathobionts, thereby potentially contributing to the maintenance of intestinal homeostasis. In a follow-up analysis of isoalloLCA-producing microbes, we found that bile acid-metabolizing bacterial strains were capable of converting testosterone

to dihydrotestosterone (DHT) and further to 3β-androstanediol. Testosterone and DHT are potent ligands for the androgen receptor, while 3β-androstanediol is no longer an androgen receptor ligand, but acts as a ligand for the estrogen receptor. Although controversial, estrogens are thought to have cancer-preventive effects, whereas androgens have detrimental effects on various cancers, including melanoma and prostate cancer. Therefore, steroid-metabolizing microbes may play a systemic role in cancer prevention. Within a few hours of incubation with testosterone, high levels of DHT and 3β-androstanediol were detected in the culture supernatants of a centenarian-associated Odoribacter strain. Notably, the same bacterial strains, particularly the *Odoribacter* strain, were capable of producing several undefined metabolites after incubation with testosterone. Although the chemical formulas can be predicted, the chemical structures of these metabolites have not yet been defined. Therefore, by teaming up the metabolomics team and the Q-core, the microbiome team aims to define the chemical structures of these undefined testosterone derivatives. These are good examples of interdisciplinary research projects at our center because they involve collaboration between multiple teams with different areas of expertise. This study combined microbiology, biochemistry, and metabolomics to investigate the gut microbiome of centenarians and its potential impact on aging-related illnesses and cancer prevention. In this project, advanced techniques were used to identify specific bacterial strains that produce unique secondary bile acids and metabolize steroids. These findings suggest that microbial activity may reduce the risk of infection with pathogens and potentially prevent cancer. Collaboration between multiple teams allows for comprehensive elucidation of the complex interactions between the gut microbiome and human health.

The cutting-edge technologies of the metabolome team, which widely cover both hydrophobic and hydrophilic metabolites, will be applied to the metabolite-based approach for a detailed mechanistic understanding of the microbiota-mediated maintenance of homeostasis and multi-organ systems in the WPI-Bio2Q program. In collaboration with a microbiome team, we built a microbiome-specific metabolome database. To verify the structure-activity relationship of functional lipids and the causal relationship with the obtained phenotype, lipids, including structural isomers, will be chemically synthesized and subjected to various assays, including receptor screening, in collaboration with the Bio-2 Homeodynamics Mechanistic Analysis Core. In addition, we will develop a mass spectrometry platform that facilitates the annotation of metabolites by integrating collision cross-sections and MS/MS spectra, and will develop a spatial lipidomics platform to visualize the distribution of functional lipids in tissues and cells in collaboration with the imaging metabolomics team in Bio-2 core.

Activation of TEs in response to environmental stress induces mutations and/or epigenetic modifications that initiate a highly programmed sequence of events within the cell to cushion the effects of stress and help the organism adapt to new environmental conditions. Recent studies have shown that the host immune system uses TEs to communicate with the microbiota, which control tissue homeostasis and inflammation. In collaboration with the microbiome and homeodynamics mechanistic analysis teams, Siomi addressed how TEs sense the microbiome to initiate the host immune response. To this end, we will set up a platform consisting of an intestinal hemi-anaerobic co-culture system (iHACS), a simple 2-chamber culture system for the human colonic epithelium, and various microbiome cultures, developed by the Organoid team. After co-culturing organoids with a set of microbiomes, we analyzed gene expression and epigenome modifications using state-of-the-art genomics tools and bioinformatics to determine how TEs in the genome respond to microbiota and to elucidate the consequences of the response.

Most risk polymorphisms occur in cell-type-specific enhancer regions and affect disease risk by altering gene expression. Ishigaki et al. hypothesized that the microbiome influences the pathogenic functions of risk polymorphisms. To prove this hypothesis, they will perform in vitro functional genetics studies to test how the metabolites released by the microbiome affect the molecular functions of risk polymorphisms using transcriptome and epigenome studies. To this end, they will collaborate with the microbiome and metabolome team to obtain expertise on microbiome-derived metabolites and collaborate

with the quantum computing group to develop a novel algorithm for inferring the complex interaction between the microbiome and genetic factors.

The Human Disease Analysis Team has been collecting 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 anemia at Keio University Hospital and related hospitals over time. Clinical information and samples will be shared among the Bio-1, Bio-2, and Q cores, and a multidisciplinary analysis will be conducted.

To promote research on the medical applications of quantum computing, active discussions among researchers who are close to each other in the field, under one roof with the Q, Bio-1, and Bio-2 cores, are essential. For example, mutual recognition, sharing of objectives and preconditions, task selection on how quantum computing can be used, and the identification of issues in actual applications are important. In particular, the sole application of quantum computing algorithms to existing biodata is insufficient; it is essential to start discussions from the data generation stage. Therefore, there is an urgent need to utilize, acquire, and train human resources familiar to both fields. In this regard, Kawaguchi, who belongs to the Q core and has a background in the medical field, actively engaged in discussions with the Bio-1 and Bio-2 cores and conducted the following interdisciplinary research: To reinforce this cooperative system and facilitate discussions under one roof, Kawaguchi moved to the Shinanomachi campus in FY 2023.

As an interdisciplinary research in FY 2022, we begun to apply qLiNGAM described in section 1-1 to all brain activities of mice captured by fMRI imaging to search for causal relationships among brain regions, which cannot be estimated by existing algorithms. Until now, the association between brain regions has often been examined in terms of brain activity correlations, thereby complicating the determination of causal relationships between them. For example, determining the group of brain regions affected by deep brain stimulation therapy was difficult. Furthermore, because the acquisition of data on whole-mouse brain activity is expensive, this study was considered a suitable task for qLiNGAM, which can potentially perform causal discovery from a small amount of data. As a prerequisite for causal discovery, it is important to acquire precise functional image data from mouse brain images, and in this process, it is crucial to align the structural and functional images of the mouse brain images. Statistical Parametric Mapping is often used to preprocess mouse brain MRI images, but causes misalignment between structural and functional MRI images. In addition, because this technique is designed for human MRI images, it can cause different problems than when using human MRI images; for example, extracting the brain region only from the MRI of a mouse head is difficult.

This necessitated the development of a new protocol for preprocessing mouse brain MRI images before applying the causal discovery algorithm. Specifically, we incorporated Advanced Normalization Tools into the alignment of mouse brain MRI images and visualized the results as a Quality Check. We constructed this protocol according to the Brain Imaging Data Structure format, which is a unified standard for storing and naming brain image data, and established a system that enables batch processing and reuse of brain images if they are stored according to this format. From FY 2023 onward, the brain images stored in the Brain Imaging Data Structure format were appropriately transformed, and the causal discovery algorithm was executed after optimizing the shape and number of regions of interest to analyze brain activity. Specifically, we plan to analyze the functional connectivity between brain regions using conventional methods, focus on a group of brain regions with high connectivity, and compare the results of qLiNGAM with those of conventional causal discovery algorithms.

Sakakibara, the PI in the Q-core, initiated discussions regarding collaborative research with the Honda Lab on the analysis of gut microbiomes. Based on our previous research (Uehara et al, m Systems, App.1 -18), we expect to gain new insights by applying bioinformatics methods to large-scale multi-omics experimental data on gut microbiomes conducted by the Honda Lab.

2. Global Research Environment and System Reform

2-1. Realizing an International Research Environment

* Describe what's been accomplished in the efforts to raise the center's recognition as a genuine globally visible research institute, along with innovative efforts proactively being taken in accordance with the development stage of the center, including the following points, for example:
- Efforts being developed based on the analysis of number and state of world-leading, frontline researchers (in Appendix 2); exchanges with overseas entities (in Appendix 4); number and state of visiting researchers (in Appendix 5)
- Proactive efforts to raise the level of the center's international recognition and to obtain diversity within the center including gender balance.
- Efforts to make the center into one that attracts excellent young researchers from around the world (such as efforts fostering young researchers and contributing to advancing their career paths)

Recruiting and Hiring Researchers and Research Support Personnel

Recruiting international researchers and English-speaking administrative personnel are crucial for establishing a globally visible institute. The Center established its policy for the recruitment process and treatment of Jr. PIs and postdoctoral fellows. International recruitment of researchers was launched on the center's website, with a proactive emphasis on the WPI guidelines of globalization and diversity. A scientist with expertise in both medical and computer sciences has been hired as the first Jr. PI and an international female researcher joined the center as the first postdoctoral fellow. In addition, three research support staff members who are fluent in English have been hired this fiscal year, and four more will be hired as of April 1 of the subsequent fiscal year. The center will further expand its administrative support system by hiring additional bilingual staff for the divisions of planning and management, human resources and public relations, finance, and secretarial services.

Efforts to Attract Young Researchers

The Center has implemented a globally competitive salary structure designed to attract and support world-class researchers, and the first postdoctoral researcher has been selected. Internal regulations regarding travel expenses for postdoctoral fellows and start-up funds were implemented and adjusted as necessary. In addition, a list of domestic and international grants available to young researchers is currently being compiled and a support system for overseas researchers to apply for research funds is being developed. From April, the Center and host institutions will jointly offer support services to international researchers who will come to Japan to work at the center.

Ensuring Diversity, including Gender Balance

In cooperation with the Office for Promotion of Collaborative Environment, which is responsible for promoting diversity throughout Keio University in areas such as the support of female scientists, childcare, nursing, and disability, meetings were held to promote the activities of the Bio2Q Center.

For events organized by the center, such as symposiums and workshops, female scientists are proactively invited to participate. For instance, in the Presentation Workshop (described in detail in 3-1), the tutoring team constituted 50% female researchers and the audience approximately 40% female students.

2-2. Making Organizational Reforms

* Describe the system reforms made to the center's research operation and administrative organization, along with their background and results.
* If innovated system reforms generated by the center have had a ripple effect on other departments of the host institutions or on other research institutions, clearly describe in what ways.
* Describe the center's operation and the host institution's commitment to the system reforms.

Visits to Other WPI Research Centers

The Administrative Director, Bio2Q staff, and Facilities and Supply Management Office staff visited the following four centers to learn about reform precedents and tour the research facilities.
Nagoya University ITbM on November 17, 2022
Tokyo University Kavli-IPMU on November 18, 2022
Kyoto University ASHBi on November 25, 2022
Tohoku University AIMR on December 14, 2022

Development of Internal Rules and Research Support System

We are progressing in both the development of the operational structure within the center and the reform of the university-wide research support organization. We have established an "Executive Committee" within the center as a meeting body including the director, deputy director, vice-directors, and administrative directors which meets approximately every two weeks to discuss the center's operation. In addition, we have established a "Steering Committee" as a meeting body to coordinate and communicate about the center's operation among the facility and related departments such as faculties, graduate schools, and the university's executive office, and are conducting discussions and consultations with them as necessary. Furthermore, we are in the process of establishing internal regulations for the center. These will be associated with the internal regulations of Keio University in such a way as to allow the promotion of reforms in both directions.

Under the leadership of the center director, we have achieved an agile and flexible organizational operation by appointing two Administrative Directors: one for external affairs and one for internal affairs. With researchers serving as Administrative Directors, the administrative branch strives to provide support that is deeply committed to research.

The research support staff, including the Academic Research Support Department at the headquarters organization and the staff in charge of Bio2Q at the Faculty of Medicine, Faculty of Pharmacy, and Faculty of Science and Engineering, meet every two weeks to share information and coordinate so that the center develops in sync with the host organization.

As a university-wide effort to comprehensively support world-class international research, the host organization has established a system consisting of three departments: the "Office for Research Coordination and Administration" which supports the promotion of research activities, the "Office of Innovation and Entrepreneurship" which promotes the social implementation of research results through industry, academia, and government collaboration and startup support, and the "KGRI/Keio University Global Research Institute," which serves as the parent organization for various interdisciplinary research projects. Keio University plans to position Bio2Q as a specially designated, advanced international research center within the KGRI and thereby build a system to support the center's activities throughout the university.

Regarding support personnel for research activities, we are advancing the employment of both University Research Administrators (URAs) with a background in administration as well as URAs with a background in research to provide comprehensive support and work closely with researchers throughout the research process.

In preparation for establishing the Advisory Council, the first two members were selected and began to provide scientific advice. The Council will be established as an official organization in the following fiscal year.

3. Values for the Future

3-1. Creating and Disseminating the Societal Value of Basic Research

* Describe the content of measures taken by the center to widely disseminate the results of its basic research to the general public.
* Describe what was accomplished in the center's outreach and other activities last year and how they have contributed to creating the

Societal Value of Basic Research. In Appendix 6, describe concretely the contents of these outreach activities. In Appendix 7, describe media reports or coverage, if any, of the activities.

Outreach Activities

An international design company developed a branding and design strategy for Bio2Q and its center's logo. The name Bio2Q and its logo were used for trademark registration. In addition, an English version of the website (https://www.bio2Q.keio.ac.jp) has been created and launched. In cooperation with Keio University's Public Relations Department, articles about the center's activities were made available on a university-wide website. Promotional materials for different target audiences, such as donors and junior and senior high school students, were initiated.

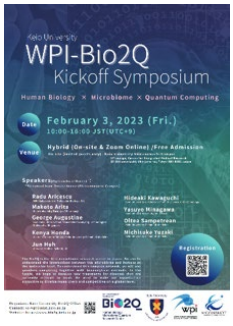
The Bio2Q administrative director and management staff members participated in the 11th WPI Science Symposium in November 2022, explaining Bio2Q's activities to middle and high school students and general visitors. Simultaneously, we had the opportunity to interact with staff members from other centers and learn about their operational expertise. In October and early November 2022, prior to the official launch of Bio2Q, international PI Dr. George Augustine visited Japan and held the Presentation Workshop 2022 as a WPI pre-event. Twenty-two graduate students in medicine, pharmacy, science, and engineering learned how to present research outcomes and received one-on-one mentoring from Dr. Augustine and other professors.

In February 2023, a Bio2Q Kick-off Symposium was held in a hybrid onsite and online format to bring together the PIs. Dr. Radu Aricescu, an international PI, visited Japan and held meetings with other PIs from the center to discuss future research activities and coordinate the setup of the necessary research space.

3-2. Human Resource Building: Higher Education and Career Development

* Describe the content of measures taken by the center to foster young researchers, including doctoral students, through their participation in a research system that creates new interdisciplinary domains within a rich international environment.

Bio2Q launched a joint interdisciplinary graduate English program called Science and Technology and Medicine, Pharmacy (STaMP) between the Graduate School of Medicine, Graduate School of Pharmaceutical Sciences, and Graduate School of Science and Technology. The Bio2Q STaMP program aims to create a "place of resonance" where faculty, researchers, and students from the three graduate schools can directly interact with each other, and each graduate student works with multiple mentors to receive guidance across graduate school boundaries. Detailed academic regulations, such as measures for the international recruitment of graduate students and examinations of degrees across the three graduate schools, are currently under discussion. In FY 2022, STaMP organized the first "Workshop for Research Presentation Skills 2022," which aimed to improve the research presentation skills of young researchers, particularly graduate students. After a one-day lecture, the workshop was conducted in small groups consisting of a tutor and four to five participants over the subsequent four days.



The Structural Analysis team, led by Aricescu and Suzuki, plans to establish a researcher exchange program between the LMB and Keio once research environments for Bio-2Q are established at both locations. Aricescu's lab at the LMB hosted several young researchers from Japan for short-term research and meetings in 2022. Keio and LMB will be active sites for the international exchange of young researchers,

facilitating a wide range of specialized research fields.

To promote young researchers, Keio University's Institute for Advanced Biosciences (IAB), of which Soga is a part, accepts high school students as "High School Student Interns" who dream of becoming world-class Ph.D. researchers in the future, and fully supports their research activities in their own topics. Since 2011, 194 high school students have participated in the program.

3-3. Self-sufficient and Sustainable Center Development

* Describe the state of implementation of the host institution's mid-to-long term measures for supporting the center toward becoming self-sufficient and sustainable after the 10-year funding period ends, such as reforming the host institution's organization, providing personnel with priority allocation of tenured posts to the center, providing fundamental financial support, and material support including land and buildings.

Regarding research projects related to Bio2Q, the university focuses on allocating indirect expenses to improve the operating funds of the center and diversify funding sources, such as possibly introducing crowdfunding. The university also reviewed its overhead rate across the entire university, not just the WPI Center, to enhance its research environment and promote research activities.
The university plans to assign a URA in charge of Bio2Q from the Office of Innovation and Entrepreneurship, which is a collaborative support division for industry, academia, and the government at Keio Headquarters. The Office of Innovation and Entrepreneurship is establishing a comprehensive support system to bring about an eco-cycle, from promoting joint research with companies to implementing research results in society and expanding license income through the utilization of intellectual property.

The university is also planning an incentive system for the PI's salary to increase researchers' motivation, and buyout systems to allow researchers more time to focus solely on research. Using these systems, the host institution and Bio2Q plan to attract, support, and retain excellent researchers from Japan and other countries. We are also developing systems that enable outstanding researchers to be active regardless of their age.

For physical spaces for research activities, the university plans to secure rental lab spaces for research centers and reconfigure existing spaces within Shinanomachi campus as the research progresses. As private universities depend on tuition fees as their main source of income and are, under the present system, not eligible for subsidies to build new facilities, there are significant barriers to establishing and securing research facilities. However, the university began negotiations and discussions with the Ministry of Education, Culture, Sports, Science and Technology (MEXT) by explaining its needs and requests regarding new buildings and construction funds.

4. Others

* In addition to the above 1-3 points, if there is anything else that deserves mention regarding the center project's progress, please note it.

5. Efforts to improve points indicated as requiring improvement in application review and results of such efforts

* Describe the status of responses to items in "Major points that need to be improved" in "The screening result for WPI centers launched in FY 2022."
* If you have already provided this information, please indicate where in the report.

Point 1. Quantum computers and their practical applications to science are still in very early stage, especially in biology and medicine. Achieving the goal of the project, therefore, will require thorough planning and a clear roadmap with milestones regarding applications of quantum computing. All pertinent PIs should fully engage in this planning and execution.

Medical and biological applications of quantum computing necessitated a comprehensive discussion of the advantages of using quantum computing. Quantum computing has theoretical, empirical, and operational advantages. The first two are mathematical and physical concepts, respectively, and the third refers to

the situation-specific advantages of using quantum computing in a particular situation or index. This operational advantage should be emphasized in medicine and biology. Currently, there are no results that clearly demonstrate operational advantage in medicine and biology, and predictions of when this will occur in the future vary widely, but experimental verification of the sample size advantage is expected to potentially yield significant operational benefits (Cordier et al., 2022). In medical research and clinical practice, the cost of generating and acquiring samples is generally high because of the long duration of wet lab protocols, procedural invasiveness, high financial costs, and low incidence of disease. Therefore, it is important to carefully examine whether these advantages exist in medical or biological settings.

Based on the above, the proposed roadmap, including plans and milestones to achieve this advantage, was assumed to be as follows: 1. identification of tasks for which quantum computing can be utilized; 2. application of existing quantum computing algorithms; 3. development of new quantum computing algorithms; and 4. verification of the advantages of utilizing quantum computing in medical and biological research. In FY 2022, we began with Part 1 of the roadmap. Consequently, interdisciplinary research was launched as described in Section 1-2 and the selection of associated tasks was accomplished. Conversely, unless Part 1 of the above roadmap is carefully continued in the future, the risk of research activities in Part 2 and beyond of the above roadmap becoming futile is assumed. To expand the scale of the WPI program in future, we will continue to carefully execute Part 1 and aim to achieve Part 2 and beyond of the above-mentioned roadmap.

To promote research on medical applications of quantum computing, it is essential to have active discussions among researchers who are close to each other in the field. For example, mutual recognition, sharing objectives and preconditions, task selection on how quantum computing can be used, and the identification of issues in actual applications are important. In particular, it is not sufficient to simply apply quantum computing algorithms to existing biological data; it is essential to begin discussions from the data generation stage. Therefore, there is an urgent need to utilize, acquire, and train human resources familiar to both fields. In this regard, we hired a junior PI with a background in quantum computing and medicine. As a full-time member of Bio2Q, he initiated discussions and collaborations between the cores. As an example of interdisciplinary research, we applied qLiNGAM to all brain activities of mice captured by fMRI to identify causal relationships among brain regions that cannot be estimated by existing algorithms. Connections between brain regions have often been examined using brain activity correlations, thereby complicating the inference of causal relationships between them. Statistical Parametric Mapping is often used to preprocess mouse brain MRI images; however, this technique causes misalignment between structural and functional MRI images. Therefore, a new protocol for preprocessing mouse brain MRI images was developed before applying the causal discovery algorithm. We plan to analyze the functional connectivity between brain regions using conventional methods, focus on a group of brain regions with high connectivity, and compare the results of qLiNGAM with those of conventional causal discovery algorithms.

Point 2. The proposal does not elaborate how the relationship will be clarified between microbiomes and each organ. For example, the center needs to make a plan on elucidating specifically how microbiomes affect brain functions and diseases such as Parkinson disease and Alzheimer disease at the molecular, biochemical, cellular, physiological and pathological levels.

To address this point, we established cohorts of patients with Parkinson’s and Alzheimer’s disease, as well as cohorts of older adults and centenarians. We generated a multicenter database that included more than 1,000 patients with Parkinson's disease. The incidence of Parkinson's disease is rapidly increasing in aging societies, and it is considered a systemic disease. The gut microbiome has attracted attention owing to 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 microbiota are paramount for improving the medical care of patients with Parkinson's disease. In addition to Parkinson's, we collected blood and clinical data from approximately 100 centenarians (including those aged > 110 years). Centenarians aged ≥100 years are less susceptible to age-related diseases such as hypertension, diabetes, obesity, cancer, and infectious diseases. There are centenarian-specific members of the gut microbiota, which might not be merely a consequence of adaptation to aging but rather actively contribute to maintaining homeostasis, resilience, and successful aging. Recent studies have shown that nutrient metabolism following digestion and absorption is regulated by the central nervous system (CNS). However, the pathways involved in the metabolic control of dietary nutrients are likely to be far more complex than currently understood. 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 the peripheral organs to the central nervous system. However, synaptic structures between the autonomic nervous system and peripheral organs are largely unknown. Therefore, we aimed to elucidate the mechanisms underlying the conversion of external environmental changes (including the microbiome) into internal signals and to examine the associated multi-organ regulatory networks (the gut-brain axis in particular) at a greater resolution than currently prevalent. 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 throughout the intestinal epithelium. EEC signals are transmitted to the nucleus tractus solitarii (NTS) in the medulla oblongata via the sensory vagal nerve and are further integrated with various types of information in 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 nervous system, we attempted 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 higher-order centers. To achieve these goals, we developed a viral vector toolkit that specifically manipulates gene expression in different subpopulations of EECs and vagal nerves. In addition, in collaboration with the Bio-1, Bio-2, and Q cores, we discussed the possibility of developing a pipeline for the computational analysis of multidimensional data obtained from microbiome, genomics, and metabolomics approaches, as well as functional imaging of the vagal nerve and higher-order centers. To do so, cognitive and motor functional abnormalities in animal models or patients with psychiatric and neurological disorders, such as Alzheimer's disease and autism spectrum disorders, must be quantified and integrated into the database. We have made efforts to establish a pipeline for sharing clinical information and specimens among the Bio-1, Bio-2, and Q cores to understand the factors influencing healthy longevity.

Point 3. There are few foreign PIs who stay at the center for a sustained period of time. More foreign PIs who resides on site should be hired to advance the internationalization of the center.

In response to the committee's recommendations, we revised our initial plan to include the concrete target of having at least five international PIs or Jr. PIs residing on site. The following specific measures are currently in place to achieve this goal.

One of the PIs initially invited to participate from abroad has now been invited to reside onsite, possibly as early as autumn 2023. To attract young, promising foreign PIs, the center first laid the organizational groundwork for the positions of Jr. PIs. We also launched a global call for Jr. PIs, and both the recruitment materials and center webpage prominently and specifically highlighted the WPI missions of globalization and diversity. Two international Jr. PIs are already undergoing the evaluation process, and the call will remain open throughout 2023. Concrete plans to increase the participation of PIs residing

onsite have also been initiated at the individual core and team levels. For instance, the structural analysis team will actively promote researcher exchange between Japan and the UK. Once a structural biology facility is established in Bio2Q, additional international structural biologists will be recruited.

While increasing the number of foreign PIs residing at the center is the main priority, we also aim to support all international PIs in spending as much time at the center as possible. The center has already started employment negotiations for the international PIs invited from the time of the application, and the contract documents are drafted to specifically mention the WPI "under one roof" policy. Furthermore, we implemented a financial support plan meant to cover frequent but shorter (up to two weeks) stays, with special consideration given to the families of the PIs. We plan to implement housing support in the coming fiscal year.

Point 4. While the host institution's strong support for the center is greatly appreciated, a space of 3,000 m2 will be insufficient to gather all its researchers "under one roof," which is an overarching concept of the WPI. Effort is needed on the part of Keio University to provide a research environment in line with this concept.

In the first year (2022), the WPI began its activities using the research space of its PIs (approximately 1700 m^2) and an additional 1300 m^2 of existing rental lab space at the Shinanomachi campus. Regarding the realization of "under one roof," as mentioned in 3-3, we are negotiating with the MEXT to secure funds for the construction of a new building. We are also considering raising independent funds through other means, such as donations. We will maintain our efforts toward securing funds, both within the construction plan of the Shinanomachi campus and at the university-wide level.

Appendix 1 FY 2022 List of Center's Research Results and Main Awards

1. Refereed Papers

- List only the Center's papers published in 2022. (Note: The list should be for the calendar year, not the fiscal year.)

(1) Divide the papers into two categories, A and B.
   A. WPI papers
      List papers whose author(s) can be identified as affiliated with the WPI program (e.g., that state "WPI" and the name of the WPI center (WPI-center name)). (Not including papers in which the names of persons affiliated with the WPI program are contained only in acknowledgements.)
   B. WPI-related papers
      List papers related to the WPI program but whose authors are not noted in the institutional affiliations as WPI affiliated. (Including papers whose acknowledgements contain the names of researchers affiliated with the WPI program.)

      Note: On 14 December 2011, the Basic Research Promotion Division (the Basic and Generic Research Division at present) in MEXT's Research Promotion Bureau circulated an instruction requiring paper authors to include the name or abbreviation of their WPI center among their institutional affiliations. From 2012, the authors' affiliations must be clearly noted.

(2) Method of listing paper
   - List only refereed papers. Divide them into categories (e.g., original articles, reviews, proceedings).
   - For each, write the author name(s); year of publication; journal name, volume, page(s) (or DOI number), and article title. Any listing order may be used as long as format is consistent. (The names of the center researchers do not need to be underlined.)
   - If a paper has many authors (say, more than 10), all of their names do not need to be listed.
   - Assign a serial number to each paper to be used to identify it throughout the report.
   - If the papers are written in languages other than English, underline their serial numbers.
   - Order of Listing
      A. WPI papers
         1. Original articles
         2. Review articles
         3. Proceedings
         4. Other English articles

      B. WPI-related papers
         1. Original articles
         2. Review articles
         3. Proceedings
         4. Other English articles

(3) Submission of electronic data
   - In addition to the above, provide a .csv file output from the Web of Science (e.g.) or other database giving the paper's raw data including Document ID. (Note: the Document ID is assigned by paper database.)
   - The papers should be divided into A or B categories on separate sheets, not divided by paper categories.

(4) Use in assessments
   - The lists of papers will be used in assessing the state of WPI project's progress.
   - They will be used as reference in analyzing the trends and whole states of research in the said WPI center, not to evaluate individual researcher performance.
   - The special characteristics of each research domain will be considered when conducting assessments.

(5) Additional documents
   - After all documents, including these paper listings, showing the state of research progress have been submitted, additional documents may be requested.

A. WPI papers

1. Original articles N/A
2. Review articles N/A
3. Proceedings N/A
4. Other English articles N/A

B. WPI-related papers

1. Original articles

(1) Li Y, Watanabe E, Kawashima Y, Plichta DR, Wang Z, Ujike M, Ang QY, Wu R, Furuichi M, Takeshita K, Yoshida K, Nishiyama K, Kearney SM, Suda W, Hattori M, Sasajima S, Matsunaga T, Zhang X, Watanabe K, Fujishiro J, Norman JM, Olle B, Matsuyama S, Namkoong H, Uwamino Y, Ishii M, Fukunaga K, Hasegawa N, Ohara O, Xavier RJ, Atarashi K, Honda K* "Identification of trypsin-degrading commensals in the large intestine", *Nature 609* (7927), DOI10.1038/s41586-022-05181-3, (2022)

(2) Kawano Y, Edwards M, Huang Y, Bilate AM, Araujo LP, Tanoue T, Atarashi K, Ladinsky MS, Reiner SL,

Wang HH, Mucida D, Honda K, Ivanov II, "Microbiota imbalance induced by dietary sugar disrupts immune-mediated protection from metabolic syndrome", *Cell 185* (19), DOI10.1016/j.cell.2022.08.005, (2022)

(3) Federici S, Kredo-Russo S, Valdés-Mas R, Kviatcovsky D, Weinstock E, Matiuhin Y, Silberberg Y, Atarashi K, Furuichi M, Oka A, Liu B, Fibelman M, Weiner IN, Khabra E, Cullin N, Ben-Yishai N, Inbar D, Ben-David H, Nicenboim J, Kowalsman N, Lieb W, Kario E, Cohen T, Geffen YF, Zelcbuch L, Cohen A, Rappo U, Gahali-Sass I, Golembo M, Lev V, Dori-Bachash M, Shapiro H, Moresi C, Cuevas-Sierra A, Mohapatra G, Kern L, Zheng D, Nobs SP, Suez J, Stettner N, Harmelin A, Zak N, Puttagunta S, Bassan M, Honda K, Sokol H, Bang C, Franke A, Schramm C, Maharshak N, Sartor RB, Sorek R, Elinav E., "Targeted suppression of human IBD-associated gut microbiota commensals by phage consortia for treatment of intestinal inflammation.", *Cell, 185* (16), DOI10.1016/j.cell.2022.07.003, (2022)

(4) Ojima K, Kakegawa W, Yamasaki T, Miura Y, Itoh M, Michibata Y, Kubota R, Doura T, Miura E, Nonaka H, Mizuno S, Takahashi S, Yuzaki M*, Hamachi I*, Kiyonaka S**, "Coordination chemogenetics for activation of GPCR-type glutamate receptors in brain tissue.", *Nature Communications 13* (1), DOI10.1038/s41467-022-30828-0, (2022)

(5) Nozawa K, Sogabe T, Hayashi A, Motohashi J, Miura E, Arai I, Yuzaki M*., "In vivo nanoscopic landscape of neurexin ligands underlying anterograde synapse specification." *Neuron 110* (19), DOI10.1016/j.neuron.2022.07.027, (2022)

(6) Ito S, Hashimoto H,Yuzaki M, Fukuda K, Yuasa S., "The complement C3-complement factor D-C3a receptor signalling axis regulates cardiac remodelling in right ventricular failure." , *Nature Communications 13* (1), DOI10.1038/s41467-022-33152-9, (2022)

(7) Li TD, Murano K, Kitano T, Guo Y, Negishi L, Siomi H., "TDP-43 safeguards the embryo genome from L1 retrotransposition", *Science Advances 8* (47), DOI10.1126/sciadv.abq3806, (2022)

(8) Takeuchi C, Yokoshi M, Kondo S, Shibuya A, Saito K, Fukaya T, Siomi H, Iwasaki YW., "Mod(mdg4) variants repress telomeric retrotransposon HeT-A by blocking subtelomeric enhancers", *Nucleic Acids Research 50* (20), DOI10.1093/nar/gkac1034 PublishedNOV 11 2022, (2022)

(9) Abe K, Kabe Y, Uchiyama S, Iwasaki YW, Ishizu H, Uwamino Y, Takenouchi T, Uno S, Ishii M, Maruno T, Noda M, Murata M, Hasegawa N, Saya H, Kitagawa Y, Fukunaga K, Amagai M, Siomi H, Suematsu M, Kosaki K, Keio Donner Project., "Pro108Ser mutation of SARS-CoV-2 3CLpro reduces the enzyme activity and ameliorates the clinical severity of COVID-19", *Scientific Reports 12* (1), DOI10.1038/s41598-022-05424-3,(2022)

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2. Review articles

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3. Proceedings N/A

4. Other English articles

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2. Invited Lectures, Plenary Addresses (etc.) at International Conferences and International Research Meetings

- List up to 10 main presentations during FY 2022 in order from most recent.
- For each, write the date(s), lecturer/presenter's name, presentation title, and conference name.

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
Feb.8, 2023	Toshiro Sato	Understanding of Human Gastrointestinal Diseases using Organoid Technology	Keystone Symposia 2023: Keystone, CO USA
Nov.29, 2022	Naoki Yamamoto	Statistical method for quantum estimation algorithms	Quantum Innovation: Tokyo, Japan
Nov.5, 2022	George Augustine	A synapsin SNP associated with schizophrenia impairs synaptic function	2nd Pan-Asia Symposium on the Genetics of Brain Disorders
Nov.1, 2022	Makoto Arita	Cutting-edge lipidomics technology reveals the biology of lipid diversity and disease control	17th International Conference on Bioactive Lipids in Cancer, Inflammation and Related Diseases: New Orleans, LA, USA
Sep.19-22, 2022	Michisuke Yuzaki	C1qFamily Proteins and Beyond: Bridging Synapses to Understand and Repair	The 4th Japan-UK Neuroscience Symposium 2022: Karuizawa, Japan
Jul.17, 2022	Yasuyo Minagawa	Exploring neurodiversity in cognitive development: mother-infant interaction and language acquisition.	Seminar Series for Joint East-West Early Language Project (JEWEL), Online: Kyoto, Japan
Jun.16, 2022	Kenya Honda	Toward the development of defined microbial therapeutics	Microbiome Virtual International Forum: USA
May 26, 2022	Makoto Suematsu	Imaging metabolomics and medical application	Special Lecture, Society for Free Radicals International: London, UK

Apr.26, 2022	Jun Huh	Precision Probiotic Therapies- Challenges and opportunities	National Center for Complementary and Integrative Health, U.S. National Institutes of Health (online)
Apr.6-9, 2022	Haruhiko Siomi	piRNA-guided transcriptional silencing and Epigenetic regulation	EMBO piRNA Workshop 2022 on PIWI proteins and piRNAs (the virtual Zoom meeting due to the SARS-Cov-2 pandemic): Germany

3. Major Awards

- List up to 10 main awards received during FY 2022 in order from the most recent.
- For each, write the date issued, the recipient's name, and the name of award.
- In case of multiple recipients, underline those affiliated with the center.

Date	Recipient's name	Name of award
Mar.20, 2023	Jun Huh	John and Virginia Kaneb Fellowship Award, Harvard Medical School
Mar.16, 2023	Michisuke Yuzaki	The Naito Foundation Prize for Science Promotion
Feb.20, 2023	Toshiro Sato	Kobayashi Foundation Award
Nov.15, 2022	Kenya Honda	2022 Highly Cited Researchers 2022 (Clarivate Analytics)
Nov.15, 2022	Toshiro Sato	2022 Highly Cited Researchers 2022 (Clarivate Analytics)
Nov.11, 2022	Tomoyoshi Soga	Fukuzawa Award
Nov.3, 2022	George Augustine	Stanford "Updated science-wide author databases of standardized citation indicators" 2022

Appendix 2　FY 2022 List of Principal Investigators

NOTE:

*Underline names of principal investigators who belong to an overseas research institution.

*In the case of researcher(s) not listed in the proposal for newly selected centers in FY2022, attach a "Biographical Sketch of a New Principal Investigator"(Appendix 2a).

*Enter the host institution name and the center name in the footer.

		<Results at the end of FY2022>					**Principal Investigators Total: 15**
Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Center director Kenya Honda	54	Professor, Keio University School of Medicine	M.D., Ph.D. Microbiome, Immunology	90	November 11, 2022	Usually stays at the center	
Toshiro Sato	50	Professor, Keio University School of Medicine	M.D., Ph.D. Gastroenterology	90	November 11, 2022	Usually stays at the center	
Makoto Arita	53	Professor, Keio University Faculty of Pharmacy	Ph.D. Lipid biology, Lipidomics	80	November 11, 2022	Usually stays at the center	
Shu Tanaka	42	Associate Professor, Keio University Faculty of Science and Technology	Ph.D. Quantum annealing, Statistical mechanics, Computational physics	80	November 11, 2022	Usually stays at the center	
Haruhiko Siomi	63	Professor, Keio University School of Medicine	Ph.D. Epigenetics	90	November 11, 2022	Usually stays at the center	
Michisuke Yuzaki	63	Professor, Keio University School of Medicine	M.D., Ph.D. Neuroscience, Synaptopathy	90	November 11, 2022	Usually stays at the center	
Jun Huh	49	Associate Professor, Department of Immunology, Harvard Medical School, Harvard University	Ph.D. Microbiome and Neuroimmunology	10	November 11, 2022	Usually stays at home institution and attends meetings online	Attended the Bio2Q Symposium and delivered an online presentation

Erika Sasaki	56	Director, Department of Marmoset Biology and Medicine, Central Institute for Experimental Animal	Ph.D. Laboratory animal science, Reproductive biology	80	November 11, 2022	Usually stays at the center	
Yasuyo Minagawa	52	Professor, Keio University Faculty of Letters	Ph.D. Developmental cognitive neuroscience, Developmental psychology, Psycholinguistics	80	November 11, 2022	Usually stays at the center	
Radu Aricescu	50	Programme Leader, Neurobiology Division, MRC Laboratory of Molecular Biology	Ph.D. Neuroscience & Structural Biology	TBD	November 11, 2022	Usually stays at home institution and attends meetings online or onsite	Attended the Bio2Q Symposium and delivered a presentation Attended meetings for laboratory setup
Tomoyoshi Soga	63	Professor, Keio University Faculty of Environment and Information Studies	Ph.D. Analytical chemistry, Metabolomics, Cancer metabolism	80	November 11, 2022	Usually stays at the center	
Naoki Yamamoto	46	Professor, Keio University Faculty of Science and Technology	Ph.D. Quantum computation, Quantum control	80	November 11, 2022	Usually stays at the center	
Yasubumi Sakakibara	62	Professor, Keio University Faculty of Science and Technology	Ph.D. Bioinformatics	80	November 11, 2022	Usually stays at the center	
Makoto Suematsu	65	Director, Live Imaging Center, Central Institute for Experimental Animals / Professor, Keio University School of Medicine	M.D., Ph.D. Biochemistry	80	November 11, 2022	Usually stays at the center	
George Augustine	67	Professor, Neuroscience & Mental Health, LeeKong Chian School of Medicine, Nanyang Technological University	Ph.D. Neurobiology	30	November 11, 2022	Usually stays at home institution and attends meetings online or onsite	Conducted presentation skills seminar and provided tutoring at the center Attended the Bio2Q Symposium and delivered an online presentation

*Percentage of time that the principal investigator devotes to working for the center vis-à-vis his/her total working hours.

Principal investigators unable to participate in project in FY 2022

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken

Appendix 3-1 FY 2022 Records of Center Activities

1. Researchers and center staff, satellites, partner institutions

1-1. Number of researchers in the "core" established within the host institution

- Regarding the number of researchers at the Center, fill in the table in Appendix 3-1a.

Special mention

- Enter matters warranting special mention, such as concrete plans for achieving the Center's goals, established schedules for employing main researchers, particularly principal investigators.
- As background to how the Center is working on the global circulation of world's best brains, give good examples, if any, of how career paths are being established for the Center's researchers; that is, from which top-world research institutions do researchers come to the Center and to which research institutions do the Center's researchers go, and how long are their stays at those institutions.

We started an international call to recruit foreign Jr. PIs in December 2022 and are currently in the selection process. These new foreign PIs are scheduled to join Bio2Q in FY 2023.

1-2. Satellites and partner institutions

- List the satellite and partner institutions in the table below.
- Indicate newly added and deleted institutions in the "Notes" column.
- If satellite institutions have been established overseas, describe by satellite the Center's achievements in coauthored papers and researcher exchanges in Appendix 4.

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes
N/A		

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
The Medical Research Council Laboratory of Molecular Biology (MRC-LMB)	Radu Aricescu	
Harvard Medical School	Jun Huh	
Nanyang Technological University	George Augustine	
The Central Institute for Experimental Animals (CIEA)	Erika Sasaki Makoto Suematsu	

2. Holding international research meetings

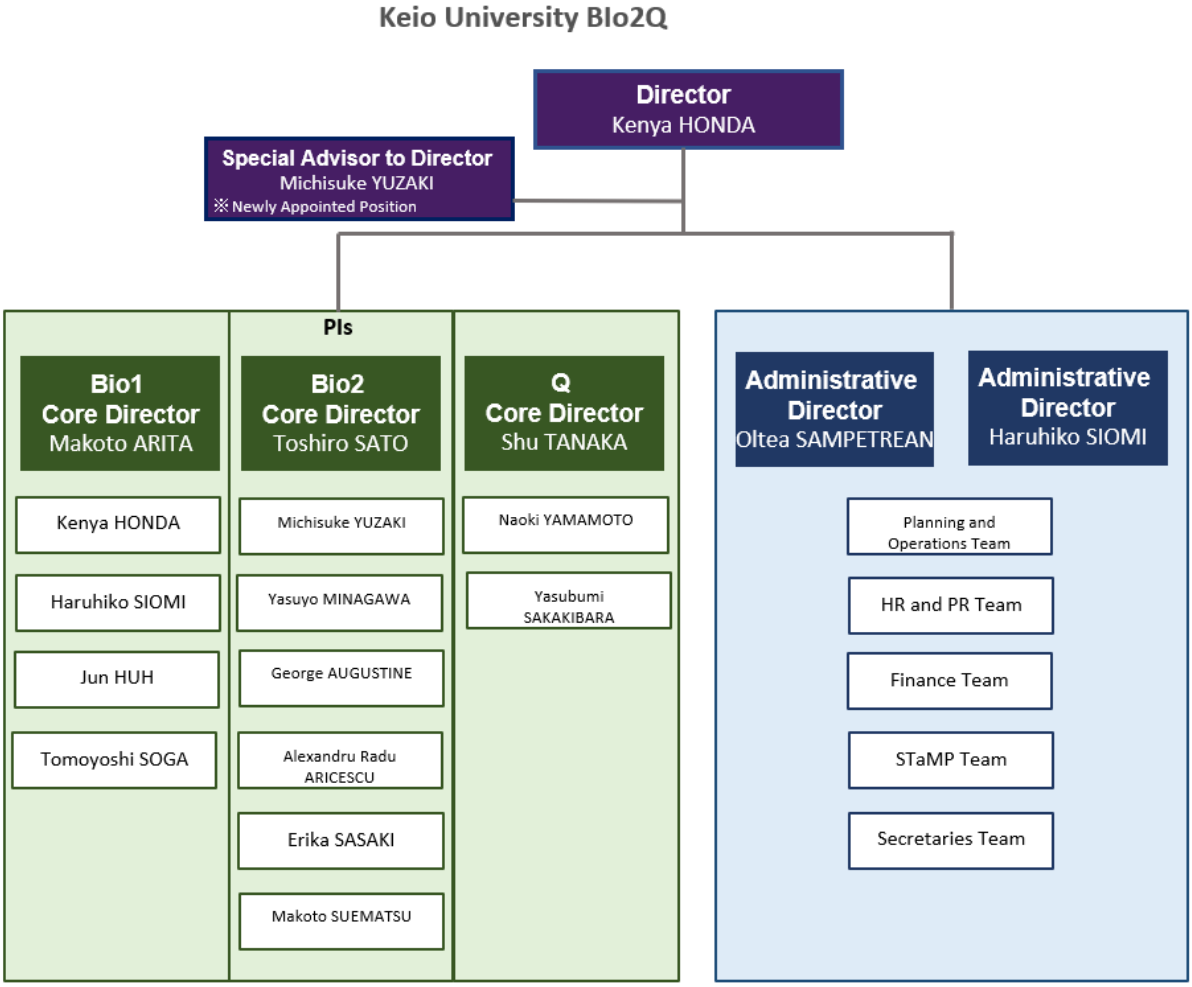
- Indicate the number of international research conferences or symposiums held in FY2022 and give up to three examples of the most representative ones using the table below.

FY 2022: 1 meeting

Major examples (meeting titles and places held)	Number of participants
WPI-Bio2Q Kickoff Symposium at Shinanomachi Campus, Keio University, Tokyo, Japan on February 3, 2023 by Hybrid (On-site & Zoom Online)	From domestic institutions: 184 From overseas institutions: 15

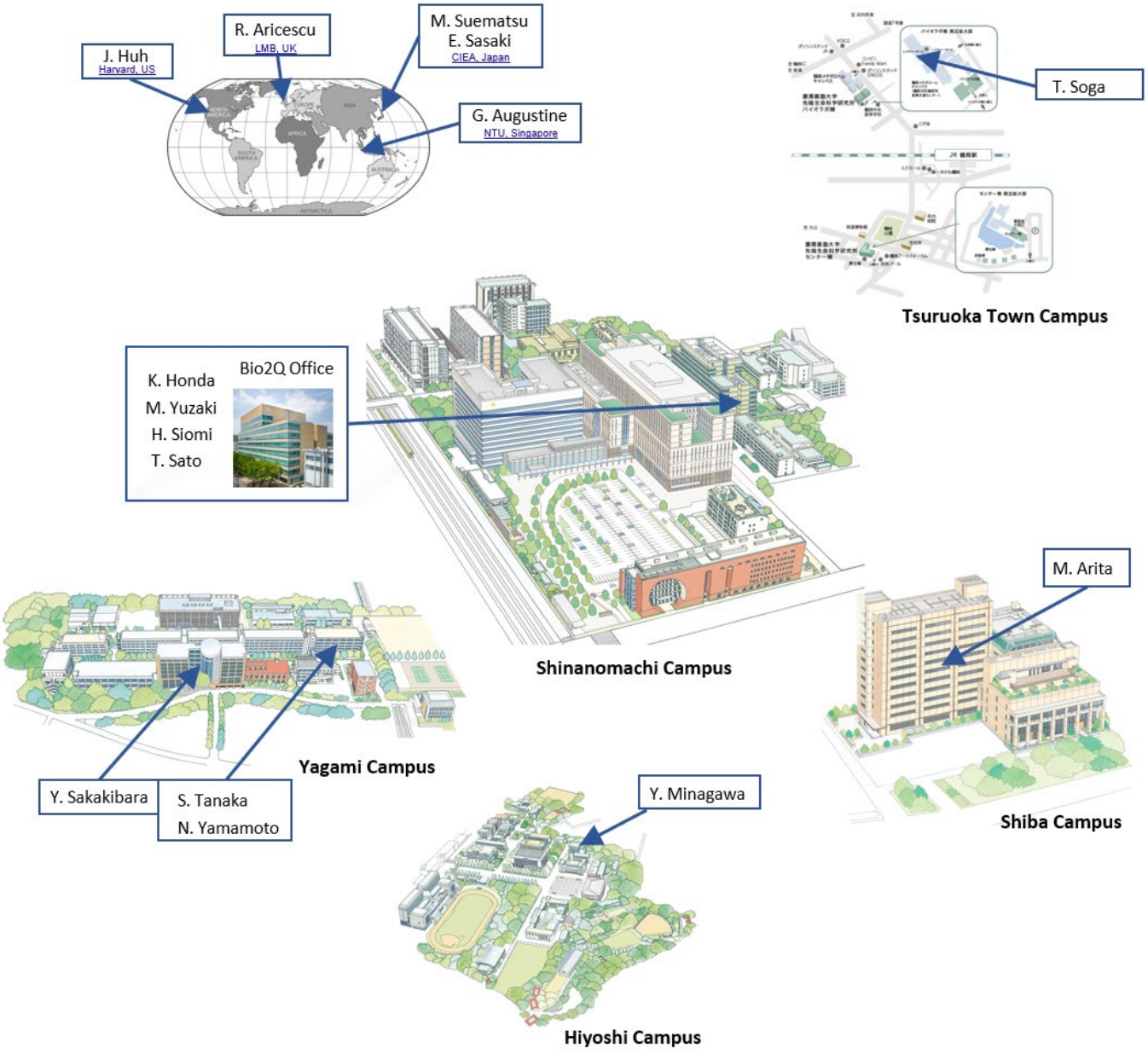
3. Diagram of management system

- Diagram the center's management system and its position within the host institution in an easily understood manner.
- If any new changes have been made in the management system from that in the latest "center project" last year, describe them. Especially describe any important changes made in such as the center director, administrative director, head of host institution, and officer(s) in charge at the host institution (e.g., executive vice president for research).



4. Campus Map

- Draw a simple map of the campus showing where the main office and principal investigator(s) are located.



5. Securing external research funding*

External research funding secured in FY2022

Total: 1,530,516,870 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.
* External research funding includes "KAKENHI," funding for "commissioned research projects," "joint research projects," and for others (donations, etc.) as listed under "Research projects" in Appendix 3-2, Project Expenditures.

Organization	Fund name	Name	Period	Funding amount (Allowable amount)
AMED	Moonshot Research and Development Program	Kenya Honda Makoto Arita Michisuke Yuzaki Makoto Suematsu Erika Sasaki Koji Atarashi Timur Tuganbaev	2022-2027	Total 1,000,000,000 yen
AMED	Project Focused on Developing Key Technology for Discovering and Manufacturing Drugs for Next-Generation Treatment and Diagnosis	Kenya Honda Koji Atarashi Oltea Sampetrean Timur Tuganbaev	2021-2026	Total 1,227,771,400 yen
AMED	Advanced Research & Development Programs for Medical Innovation (AMED-CREST)	Toshiro Sato	2018-2023	Total 537,406,108 yen
JST	ERATO	Makoto Arita	2021-2026	Total 548,280,000 yen
National Institutes for Quantum Science and Technology	SIP	Shu Tanaka	2021-2022	Total 104,650,000 yen

Appendix 3-1a FY 2022 Records of Center Activities

Researchers and other center staff

Number of researchers and other center staff

* Fill in the number of researchers and other center staff in the table blow.
* Describe the final goals for achieving these numbers and dates when they will be achieved described in the last "center project."

a) Principal Investigators

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

(number of persons)

	At the beginning of project	At the end of FY 2022	Final goal (Date: March, 2025)
Researchers from within the host institution	10	10	11
Researchers invited from overseas	3	3	3
Researchers invited from other Japanese institutions	2	2	2
Total principal investigators	15	15	16

b) Total members

	At the beginning of project		At the end of FY 2022		Final goal (Date: March, 2025)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	33		34		90	
Overseas researchers	13	39	13	38	28	31
Female researchers	8	24	9	26	45	50
Principal investigators	15		15		16	
Overseas PIs	3	20	3	20	3	19
Female PIs	2	13	2	13	2	13
Other researchers	18		19		62	
Overseas researchers	10	56	10	53	19	31
Female researchers	6	33	7	37	36	58
Postdocs	0		0		12	
Overseas postdocs	0	###	0	####	6	50
Female postdocs	0	###	0	####	7	58
Research support staffs	1		1		15	
Administrative staffs	6		8		11	
Total number of people who form the "core" of the research center	40		43		116	

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

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

Appendix 3-2 Project Expenditures

1) Overall project funding

* In the "Total costs" column, enter the total amount of funding required to implement the project, without dividing it into funding sources.
* In the "Amount covered by WPI funding" column, enter the amount covered by WPI within the total amount.
* In the "Personnel," "Project activities," "Travel," and "Equipment" blocks, the items of the "Details" column may be changed to coincide with the project's actual content.

(Million yens)

Cost items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):10	39	
	Jr.Principal investigators (no. of persons):4	14	
	Research support staff (no. of persons):2	4	
	Administrative staff (no. of persons):3	4	4
	Subtotal	61	4
Project activities	Cost of international Kickoff symposium (no. of symposiums):1	1	1
	Cost of Website production	1	1
	Cost of Bio2Q branding design	3	3
	Logo trademark application fee	0	0
	Cost of outreach activity	0	0
	Cost of consumables	1	1
	Other costs	3	3
	Rental fees for facilities	28	0
	Cost of utilities	0	0
	Subtotal	37	9
Travel	Domestic travel costs	0	0
	Overseas travel costs	0	0
	Travel and accommodations cost for invited scientists (no. of domestic scientists):0 (no. of overseas scientists):1	1	1
	Travel cost for scientists on transfer (no. of domestic scientists):0 (no. of overseas scientists):1	1	1
	Subtotal	2	2
Equipment	Facility renovation and improvement	50	50
	Costs of research equipments	9	9
	Costs of office equipments	16	16
	Subtotal	75	75
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1	0	
	KAKENHI	320	
	Commissioned research projects, etc.	1120	
	Joint research projects	17	
	Ohers (donations, etc.)	73	
	Subtotal	1530	0
Total		1705	90

Costs (Million yens)

WPI grant in FY 2022	0
Costs of establishing and maintaining facilities	50
Repairing facilities	50
(Center for Integrated Medical Research)	0
Others	0
Costs of equipment procured	12
Freezer	4
(Number of units:3)	
Workstation	4
(Number of units:2)	
Others	4

*1. Management Expenses Grants (including Management Enhancements Promotion Expenses (機能強化経費)), subsidies including National university reform reinforcement promotion subsidy (国立大学改革強化推進補助金) etc., indirect funding, and allocations from the university's own resources.
*2 When personnel, travel, equipment (etc.) expenses are covered by KAKENHI or under commissioned research projects or joint research projects, the amounts should be entered in the "Research projects" block.

*1 運営費交付金（機能強化経費を含む）、国立大学改革強化推進補助金等の補助金、間接経費、その他大学独自の取組による学内リソースの配分等による財源
*2 科研費、受託研究費、共同研究費等によって人件費、旅費、設備備品等費を支出している場合も、その額は「研究プロジェクト費」として計上すること

2) Costs of satellites

(Million yens)

Cost items	Details	Total costs	Amount covered by WPI funding
Personnel	Principal investigators (no. of persons):OO		
	Other researchers (no. of persons):OO		
	Research support staff (no. of persons):OO		
	Administrative staff (no. of persons):OO		
	Subtotal	0	0
Project activities	Subtotal		
Travel	Subtotal		
Equipment	Subtotal		
Research projects	Subtotal		
Total		0	0

Appendix 4 FY 2022 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

- List the refereed papers published in FY 2022 that were coauthored between the center's researcher(s) in domestic institution(s) (include satellite institutions) and overseas satellite institution(s). List them by overseas satellite institution in the below blocks.
- Transcribe data in same format as in Appendix 1. Italicize the names of authors affiliated with overseas satellite institutions.
- For reference write the Appendix 1 item number in parentheses after the item number in the blocks below. Let it free, if the paper is published in between Jan.-Mar. 2023 and not described in Appendix 1.

Overseas Satellite 1 **Name** (Total: OO papers)

1) N/A
2)
3)
4)

Overseas Satellite 2 **Name** (Total: OO papers)

1) N/A
2)
3)
4)

2. Status of Researcher Exchanges

- Using the below tables, indicate the number and length of researcher exchanges in FY 2022. Enter by institution and length of exchange.
- Write the number of principal investigator visits in the top of each space and the number of other researchers in the bottom.

Overseas Satellite 1:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022					

Overseas Satellite 2:

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022					

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022					

Appendix 5 FY 2022 Visit Records of Researchers from Abroad

* If researchers have visited/ stayed at the Center, provide information on them in the below table.
* Enter the host institution name and the center name in the footer.

Total: 2

	Name	Age	Affiliation		Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
			Position title, department, organization	Country				
1	Radu Aricescu	50	Programme Leader, Neurobiology Division, MRC Laboratory of Molecular Biology	UK	Ph.D. Neuroscience & Structural Biology	He has 28 years of research experience in protein biochemistry, molecular neuroscience and structural biology of cell surface receptors.	Feb. 2, 2023-Feb. 4, 2023 (3 days) Feb. 10, 2023- Feb. 15, 2023 (6 days)	Attended the Bio2Q Symposium and delivered an invited talk. Attended meetings for research and for lab facilities.
2	George Augustine	67	Professor, Neuroscience & Mental Health, LeeKong Chian School of Medicine, Nanyang Technological University	Singapore	Ph.D. Neurobiology	Stanford "Updated science-wide author databases of standardized citation indicators" 2022	Oct. 26, 2022- Nov. 4, 2022 (10 days)	Conducted presentation skills seminar and provided tutoring at the center. Attended research meetings.
3								
4								
5								
6								
7								
8								
9								
10								

Appendix 6 FY2022 State of Outreach Activities

* Fill in the numbers of activities and times held during FY2022 by each activity.
* Describe the outreach activities in the "3-1. Societal Value of Basic Research" of Progress Report, including those stated below that warrant special mention.

Activities	FY2022 (number of activities, times held)
Lectures, seminars for general public	1 - WPI-Bio2Q Kickoff Symposium
Participating, exhibiting in events	1 - 11th WPI Science Symposium
Press releases	2 news releases - Title: Keio Becomes First Private University to Be Selected under World Premier International Research Center Initiative (https://www.keio.ac.jp/en/news/2022/Oct/20/48-132779/) - Title: WPI-Bio2Q Holds Kickoff Symposium (https://www.keio.ac.jp/en/news/2023/Feb/21/48-135587/)
Others (Logo trademark application)	1 - Applied for Bio2Q Logo trademark in Japan
Others (Website)	1 - Launched Bio2Q website
Others (e-newsletter)	1 - *The Penmark*; Keio University monthly e-newsletter (https://mailchi.mp/global/the-penmark-march-6267597?e=dab315f4f7)

*If there are any rows on activities the center didn't implement, delete that (those) row(s). If you have any activities other than the items stated above, fill in the space between parentheses after "Others" on the bottom with the name of those activities and state the numbers of activities and times held in the space on the right. A row of "Others" can be added, if needed.

Outreach Activities and Their Results

List up to three of the Center's outreach activities carried out in FY 2022 that have contributed to enhancing the brand or recognition of your Center and/or the brand of the overall WPI program, and describe its concrete contents and effect in narrative style. (Where possible, indicate the results in concrete numbers.)

Examples:
- As a result of using a new OO press-release method, a OO% increase in media coverage was obtained over the previous year.
- By holding seminars for the public that include people from industry, requests for joint research were received from companies.
- We changed our public relations media. As a resulting of using OO to disseminate information, a OO% increase in inquiries from researchers was obtained over the previous year.
- As a result of vigorously carrying out OO outreach activity, \OO in external funding was acquired.

(1) Commissioned a designer with experience creating logos for renowned international brands to create the center's logo. The logo representing the essence of Bio2Q was completed and was later released to the public. Its visual impact, aesthetics and quality contributed to the increased recognition of Bio2Q both inside and outside the university. Additionally, we outsourced the website design and other design-related projects to the same company.

(2) Held the first Bio2Q symposium, which attracted 199 participants from both inside and outside the university and helped raise awareness of WPI-Bio2Q.

(3) Issued a press release announcing our selection as the first WPI Center at a private university, raising awareness of WPI-Bio2Q.

Appendix 7 FY 2022 List of Project's Media Coverage

* List and describe media coverage (e.g., articles published, programs aired) in FY 2022.

* Enter the host institution name and the center name in the footer.

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
1	**N/A**		
2			
3			
4			
5			
6			
7			
8			
9			
10			