# Center Director's Vision

I began my research career fascinated by the complexity of the immune system and later focused on the site where immune cells are the most active - the interface with the external environment, the mucosal surface. I realized that about 100 trillion symbiotic microorganisms (the microbiome), with their one million genes, functioned as if they were a single organ, profoundly influencing immune homeostasis. Given that the number of human genes is only 27,000, one can readily appreciate the functional impact of the microbiome. Moreover, the microbiome is an essential part of a **multiorgan network** that includes not only the mucosal immune system but also the entire immune system, along with the nervous, metabolic, and cardiovascular systems. Over the past decade, our own research, as well as next-generation sequencer-based large-scale projects including the human microbiome project (HMP), have uncovered significant associations between various diseases and the human microbiome. Moreover, the success of fecal microbiota transplantation, in which healthy human feces are transplanted into patients, revealed that the microbiota is manipulatable and is a good therapeutic target. However, despite the global development/progress of microbiome research, only a handful of studies have been able to identify truly "causative" bacterial species that causally contribute to disease progression or regression. Most of the research does not go beyond the "correlation" between gut microbiota and host phenotype. As a result, drug development still largely depends on empirical experiences. In infectious diseases, which are caused by a single pathogen, a standard practice is to isolate the responsible microorganism, infect animals with it, and see if it recapitulates the disease. In contrast to infectious diseases, the physiological functions of the microbiota are exerted by a "community" composed of multiple bacterial species. Therefore, it is critical to understand which combinations of bacteria constitute a functional unit. Current methodologies, however, are not best suited to the identification of such a functional unit at high throughput. Thus, the microbiome still remains the "dark matter" of the human body. To overcome this limitation, we have developed a unique approach that goes beyond the data-driven approach and instead narrows down the complex microbiota to minimal consortia that exert critical functions in the target phenotype. By taking full advantage of our strengths in the field of microbiome research (e.g., microbial culture techniques, gnotobiotic techniques, metabolomics, etc.), we have made seminal contributions in the microbiome field by identifying immune-activating microbial consortia. However, there is a limit to what a single laboratory can reveal about the highly complex network of the microbiome and multiple organs.

The human body's homeostasis is maintained through "**multiorgan homeodynamics"**, a complex interaction that connects multiple organs throughout the nervous, immune, metabolic, and digestive systems, in which the microbiome plays a central role. The interactions between multiple organ systems likely enable the **optimization** of biological processes. However, conventional analyses of single networks of cells or genes cannot fully reveal the details of this complex interplay. In particular, mechanisms underlying the signal conversion of external to internal biological information, as well as the intricate network connecting the immune, neural, and metabolic systems, are difficult to decipher by conventional analyses. Invention of new methodologies are required to elucidate the extremely complex and dynamic interactions within the multiorgan network by a reductionist yet integrated approach. Recent technological innovations promise to help solve this predicament. Metabolomics can now characterize metabolite diversity and dynamics, and organoid technology ensures the semi-permanent culture of human tissue stem cells, leading to major breakthroughs in human biology research. Furthermore, epigenetic analyses targeting transposons and connectomics analyses of neural circuits are both powerful tools for elucidating multiorgan homeodynamics. In addition, artificial intelligence (AI), represented by deep learning, is becoming a cutting-edge tool in biological science. In particular, quantum

computing is a new technology that uses quantum bits, which can achieve the superposition of the 0 and 1 states and thus has a far higher representational power than traditional computers. Therefore, by combining quantum computing together with AI and by projecting super multiomics data onto high dimensional quantum Hilbert spaces, we expect to solve more complex tasks and discover hidden features of complex multiorgan network structures. Furthermore, quantum computing can be powerful to accelerate research through the rapid generation of highly valid hypotheses. The cooperation of experts in various fields and the integration of AI and quantum computing will thus enable discovering, inferring, and verifying novel causal relationships between the microbiome and multiorgan networks. We firmly believe that by harnessing this kind of integrated research, it will be possible to elucidate the mechanisms underlying the conversion of external environmental changes (including the microbiome) into internal signals, and examine the associated multiorgan regulatory networks (the gut-brain axis in particular) at a greater resolution than currently prevalent.

To this aim, we will establish a research center that can integrate all the above-mentioned technologies. We propose the **Human Biology-Microbiome-Quantum Research Center (Bio2Q)** as a new WPI center that aims to decipher human multiorgan homeodynamics by collecting multiomics and microbiome data associated with various human diseases, development, and aging, and by combining quantum computing technology and AI. Pioneers in the fields of Biology, Microbiome, and Quantum will collaborate to address the problem of biological signal conversion and to forge a new life science field based on the elucidation of the mechanisms of organ homeodynamics. The Bio2Q Center will comprise three research core units: **Bio-1: Multidimensional Data Analysis Core, Bio-2: Homeodynamics Mechanistic Analysis Core, and Q: Quantum Computing Core**. The three cores will function cooperatively to overcome the bottlenecks of current research and to establish a new methodology in human biology and microbiome research. The new methodology will not only become a gateway to exploring various biological phenomena but will also have a significant impact on the health and medical industry.

Keio University is already bringing together researchers with world-class expertise in microbiome, organoid, metabolome, transcriptome, and connectome technologies. We aim to make our organization highly attractive to top-class international students and postdocs and a starting point for the transformation into a globally competitive center. In line with the aim of Bio2Q, I have selected a core of 14 top-class scientists. I have enlisted the help of the Central Institute for Experimental Animals and RIKEN, which function as domestic satellites. In addition to 3 international PIs, our proposal has attracted the participation of 10 international outstanding collaborators in the fields of immunology, microbiology, neuroscience, informatics, biochemistry, metabolism, stem cell biology, and structural biology. Their home institutes (Harvard, NTU, MRC-LMB, Rockefeller, MIT, Yale, NYU, Broad Institute, and Stanford) will function as overseas satellites.

Furthermore, we believe that the establishment of the WPI Center is an excellent opportunity to promote innovation within Keio University as well. By crossing department barriers and working closely with international centers, the WPI Center will accelerate the university's globalization. In conjunction with the ongoing digital transformation (DX), we will significantly improve old-fashioned administrative and meeting systems. By enhancing researcher support such as intellectual property acquisition and contracts, support for writing papers in English, and public relations, we will create an environment where researchers can focus more on their own research. At the same time, we will review the progress of each core unit and projects and reflect the results in the evaluation of researchers and budget. We will also flexibly adjust the system by incorporating new themes and consolidating or eliminating research teams. We are confident that this center will establish itself as a true "world-class research center" and serve as a platform for fostering the next generation of domestic and international researchers.