

# Summary of Research Center Project

**Center name: Premium Research Institute for Human Metaverse Medicine (PRIME)**

**Host institution: Osaka University**

**Head of host institution: Shojiro Nishio, President**

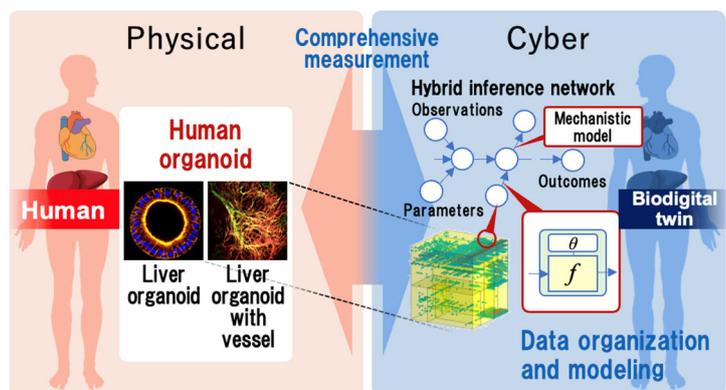
**Prospective Center director: Kohji Nishida, Professor, Graduate School of Medicine**

**Prospective Administrative director: Takefumi Doi, Specially Appointed Professor**

## (1) Overall Framework of the Center Project

We will create a World Premier International Research Center Initiative (WPI) "**Premium Research Institute for Human Metaverse Medicine (PRIME)**", with **the goal to revolutionize medical research aiming to overcome many unsolved diseases**. Diseases with complex pathologies (such as diabetes, obesity, dementia, and heart failure) remain resistant to traditional means of study, such as reductive animal model-based studies and human studies using data from the patients in the real world. Such conditions are rising, threatening modern society and hindering the extension of healthy life expectancy. The complex diseases are influenced by the deterioration of homeostasis brought on by aging as well as interactions between human genetics and environmental factors encountered through life. Therefore, the reductive notion of a simple dichotomy between health and disease is insufficient. We assert that to understand these conditions, it must be appreciated that a continuum between health and disease exists, and pre-symptomatic pathological states will be informative.

**PRIME will attack this important problem by integrating organoid-based biomedical disease research with information and mathematical sciences, quantum science, clinical medicine, and humanities and social sciences for the first time. This means creating a new scientific field—human metaverse medicine—that will bring a paradigm shift in both biomedical research and health care.** Specifically, we will integrate experimental data on human organoids, which imitate human organs in a culture system, and biological and clinical data obtained from human individuals using information and mathematical science methods, to develop technologies that reproduce the biological phenomena and pathological processes in human organs as **biodigital twins of human body in cyber space**. (Fig. 1). Using these technologies, we aim to **clarify the mechanisms underlying many unresolved diseases**, such as **retinal and optic nerve degeneration, non-alcoholic fatty liver disease, heart failure, infertility, central nerve degeneration**. We will **predict the onset and progression** of these conditions and the response of individuals to treatment, as well as to address **prevention and treatment strategies**. PRIME will also launch the **human metaverse—an information space platform** for researchers and physicians worldwide to share and utilize *in silico* patient-specific biodigital twins. As part of its mission, **PRIME will train the next generation of leaders in human metaverse medicine**; that is, innovative researchers capable grasping the entirety of the field and developing it on the global stage.



**Figure 1: Development of Biodigital Twin**

## (2) World-Leading Scientific Excellence and Recognition

**1) Research content.** This proposal will take a new approach to disease, by creating an academic system to comprehensively understand the disruption of individual human homeostasis caused by the disease

state. To accomplish this goal, we will create organoids from human-derived stem cells. Organoids reflect the individual human source and mimic human organs. Organoids derived from healthy, pre-symptomatic and diseased state will be used to measure responses to genetic and environmental factors at the molecular, cellular, organ, and multisystem levels, in multiple dimensions, by using advanced measurement techniques, such as genomics, multiomics, imaging, quantum sensing, photonics and electronics. By integrating, organizing and analyzing these data, along with published population health and disease datasets, using artificial intelligence (AI)-based machine learning and mathematical modeling, etc, we will model the continuum from homeostatic disruption to phenotypic manifestation of disease. The resulting model will, in essence, be a human biodigital twin, lodged in a cyber space. The construction of biodigital twins combines two approaches: Bayesian inference, which is a data-driven method of information dependency analysis and inferences, and the ordinary differential equation (ODE) model, which is constructed on the basis of prior biological knowledge. The expressive power of this digital technology will evolve through continual exchange and feedback. By advancing research in this bidirectional manner, we will elucidate disease mechanisms and pre-symptomatic states, predict individual disease-onset processes, and develop personalized prevention and treatment methods.

As our first content area, we will focus on **development (short stature, chondrodysplasia), reproduction (infertility), and aging (retinal and optic nerve degeneration, non-alcoholic fatty liver disease, heart failure, osteoarthritis, Alzheimer's disease)** aiming to discover common, as well as unique, principles that lead to the onset of disease at each time. Furthermore, a common research theme of PRIME focuses on **the pathological state caused by the loss of metabolic homeostasis** with aging. To accomplish these interdisciplinary fusion research, we will strategically **develop key technologies towards creation of human biodigital twins**, to recapitulate the physiological network of organ systems in human organoid culture, and to artificially control and evaluate the transition from normal physiology and metabolism to homeostatic failure. We will also work on ethical, legal, and social issues (ELSI).

PRIME will also **develop a digital platform, or human metaverse**, for storing the information produced that will be freely shared through a user-friendly web interface. Analysis tools will be distributed, and researchers will be able to search for relationships and latent factors using their own data.

**2) Interdisciplinary research.** The potential of biodigital twins to reveal new mechanisms to address currently unsolved diseases is profound. This work will require the novel integration of a broad array of interdisciplinary inputs, **uniting world-class researchers from Osaka University, other institutions in Japan and overseas.** Principal investigators (PIs) of PRIME include: biomedical sciences (7), information and mathematical sciences (10), quantum science (2), humanities and social sciences (1) (total of 20 includes 4 female PIs). The Osaka University Center for Quantum Information and Quantum Biology will support PRIME research. In addition to our main center, PRIME satellite facilities in Japan will include **the Bio-Medical Informatics Research Center at NTT Basic Research Laboratories** and **the RIKEN Center for Advanced Photonics.** Four foreign institutions will partner with PRIME to create the metaverse space: **Stanford University (organoids), Cincinnati Children's Hospital Medical Center (organoids), University College Dublin Systems Biology Ireland (data science), and the Curie Institute (bioinformatics).**

### **(3) Global Research Environment and System Reform**

**1) International research environment.** Dr. Nishida, the PRIME Director, has the creativity and deep expertise needed to lead the PRIME enterprise. He will be assisted by Dr. Takebe, Deputy Director of the Organoid Center at Cincinnati Children's Hospital, and Dr. M. Okada, a leader in interdisciplinary fusion research in informatics and biology. Dr. Takebe will have been cross-appointed at Osaka University in January of next year. All three have "borderless" sensibilities and networks and will be very effective in these roles. In addition, foreign researchers will be recruited to PRIME, including Dr. Vivian Hwa (Cincinnati) and Dr. Sergiu P. Pasca (Stanford) and Dr. Dirk Fey (Dublin), and PRIME partner institutions in the USA and Europe will strengthen our work. Strategic international recruits whose interests match the theme of PRIME will be carefully selected and generously supported with startup funds, research funds, space, and faculty/researcher posts. **At least 30% of PRIME researchers and staff will be foreign.** Activities at

PRIME will be in English.

**2) Center management and system reform.** The center will be managed and operated by the PRIME director, Dr. Nishida. A **center steering committee** of the center director, deputy directors, administrative director, and PIs will support the director and contribute to PRIME's medium- to long-term planning. An evaluation meeting will be held every one or two years, assembling prominent researchers from Japan and overseas, business people, etc., to evaluate the progress of PRIME. The administrative director will be Dr. Doi, a past director and vice president of Osaka University. Excellent administrative staff will provide strong management support to all PRIME investigators to enable their continued research progress. High-quality bilingual staff will provide strong administrative support to foreign researchers.

At PRIME, in cooperation with the host institution, we will create a system and environment that reflects modern change and social conditions. The seniority-based system will be eliminated in favor of a culture where all researchers, from senior members to students, are encouraged to productively exchange information and ideas on an equal basis. Reflecting the modern, ground breaking nature of this proposal, the PRIME faculty is young, with **9 of 20 PIs in their 30s or 40s (including a deputy director)**. PRIME values the contributions of all researchers and will establish exemplary equity and diversity standards. When hiring young researchers, PRIME will actively seek female candidates. PRIME will develop systems to enable flexible employment to consider researchers varied needs, as well as Osaka University policies. In this way, the existing systems will be improved and revitalized, as befits a globally leading research center.

#### **(4) Values for the Future**

**1) Generating and disseminating the societal value of basic research.** The goals of PRIME are dedicated to creating a society where **well-being can be realized** through technological innovation. PRIME will practice the model of "Responsible Research and Innovation" (RRI) and identify **ethical, legal, and social issues (ELSI)** relevant to our work in parallel with our research. We will respond to these issues with the participation of various stakeholders, including citizens and patients, and communicate the content and significance of our basic science research to the general public. **The Osaka University ELSI Research Center** will aid in our public relations and outreach activities.

**2) Fostering next-generation human resources linked with higher education. PRIME is dedicated to the world-class education of graduate students** and recognizes the benefits that early-stage trainees accrue by their residence in a top research center during their career development. A **doctoral human metaverse medicine educational program will be established** at the Graduate School of Medicine. Furthermore, in collaboration with the Support for Pioneering Research Initiated by the Next Generation (SPRING) program of Osaka University, **PRIME will actively promote the involvement of its researchers in graduate school educational activities.** Postdoctoral researchers and young international researchers will also benefit from interdisciplinary seminar courses and grounded research activities. The Advanced Postdoc system [proven at Osaka University Immunology Frontier Research Center (IFReC), a former WPI center] will also be established.

**3) Self-sufficient and sustainable center development.** Osaka University is committed to the formation and establishment of PRIME as a strategic priority. PRIME will have the status of an independent department and receive **~2 billion yen annually in in-kind support from the University**, including research space and external funds. PRIME will seek large-scale support from multiple companies and foundations and will steadily advance these connections, with the goal to create a strongly supported research environment. As with IFReC, **Osaka University will make PRIME a permanent organization** after WPI support period ends. Osaka University is dedicated to the construction of a new, state-of-the-art **research building (20,000 m<sup>2</sup>) to house PRIME** within four years of this award. The new facility will be a fully outfitted research environment. In the interim, Osaka University has secured approximately 2,000 m<sup>2</sup> of additional space in the Graduate School of Medicine for PRIME. The new research building and other infrastructure will be **self-financed by the university through bonds**, budget requests to the Ministry of Education, Culture, Sports, Science, and Technology, indirect funds, and other sources.