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.

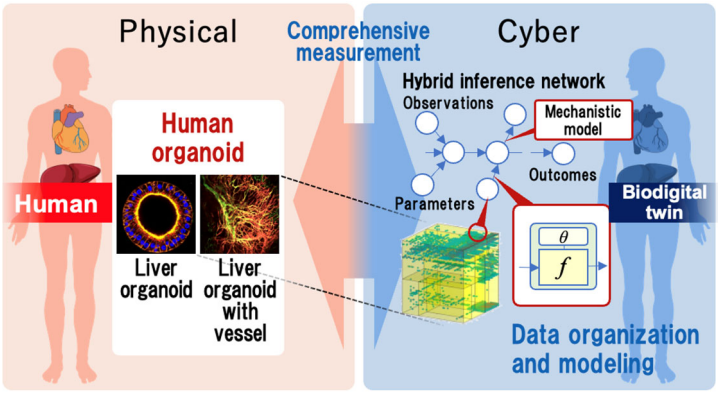

Figure 1: Development of Biodigital Twin

(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^2) to house PRIMe** within four years of this award. The newfacility will be a fully outfitted research environment. In the interim, Osaka University has secured approximately 2,000 m^2 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.

Research Center Project

* Compile in English within 25 A4 pages.

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Appendix 1: "Biographical Sketch of Prospective Center Director" (to be attached)

Appendix 2: "Reference (recommendation) for prospective center director by world's distinguished researcher(s) in the center's target field" (to be attached)

Administrative director: Takefumi Doi, Specially Appointed Professor

Appendix 3: "Biographical Sketch of Prospective Administrative Director" (to be attached)

1) Overall Framework of the Center Project

* Cleary and concisely describe your center's mission statement as a WPI center, its identity, and its goals toward achieving the objectives of the WPI program.

1) -1 Mission Statement

The Osaka University **"Premium Research Institute for Human Metaverse Medicine (PRIMe)"** will promote research that **integrates human organoid-based biomedical science with information and mathematical sciences**, including artificial intelligence (AI), mathematical modeling, and simulations (**Fig. 1**). PRIMe will **construct "digital twins" of the human body (referred to here as "biodigital twins")** that are capable of precisely replicating biological phenomena and pathological processes that occur in human organs. A digital twin is a technical concept that involves the reproduction and simulation of an environment-gene-organ network in digital space based on data obtained in the real world. This virtual platform will generate **a new scientific field-human metaverse medicine-**focused on **elucidating mechanisms underlying human diseases** and **predicting disease onset, progression**, and **response to treatments**, with the ultimate goal of **developing individualized prevention and treatment methods**. Through PRIMe, we aim to **launch the "human metaverse",** a new concept that we define in this proposal as an information space platform for sharing and utilizing

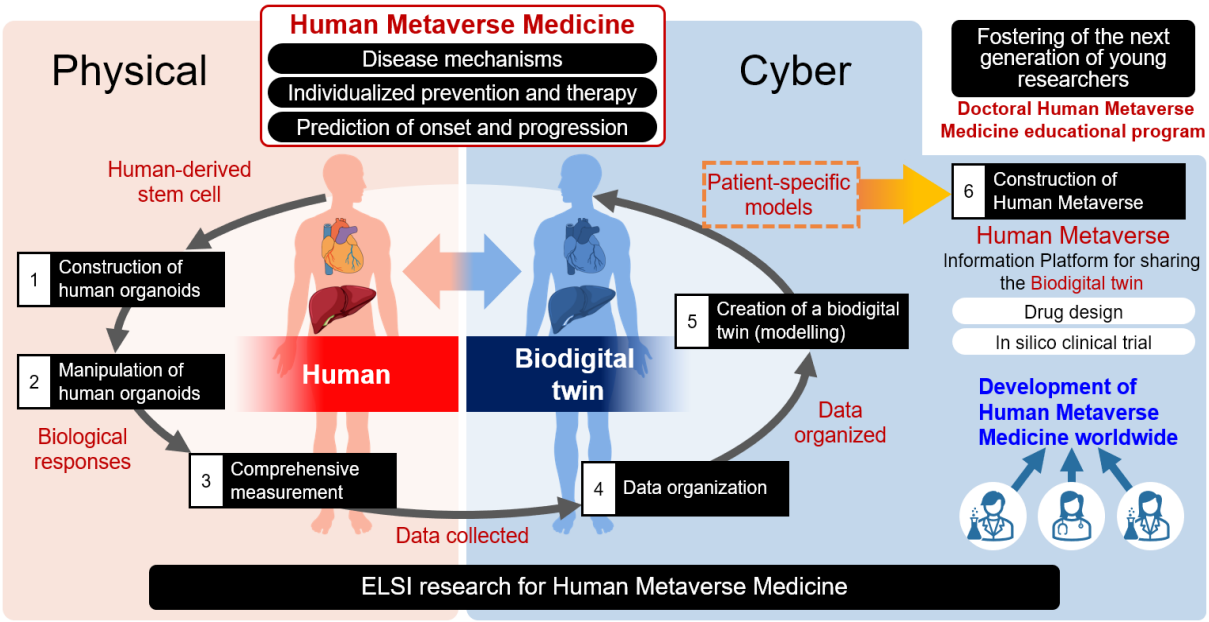


Figure 1: Outline of Osaka University PRIMe

the power of biodigital twins with researchers and medical professionals worldwide. We aim to popularize and establish the field of human metaverse medicine, while simultaneously fostering a research environment in which researchers from diverse fields of study, nationalities, and backgrounds can mingle and interact "under-one-roof" to conduct interdisciplinary and integrative research. The PRIMe environment and approach will also be used to **educate and train the next generation of leaders in human metaverse medicine**. Our goal is to deliver solutions to diseases of currently unknown pathology that are influenced by the deterioration of homeostasis brought on by aging, as well by interactions between human genetics and environmental factors encountered through life. In this way, PRIMe will **contribute to the attainment of a healthy and sustainable society for all humankind**.

1) -2 Center Identity

Through PRIMe, **two advanced fields will be fully integrated for the first time: human organoid-based biomedical science and information/mathematical science** (AI, mathematical modeling, computer simulations, etc.). Both research areas are globally recognized strengths at Osaka University. PRIMe will also integrate expertise from the Center for Quantum Information and Quantum Biology, (established by Osaka University as the International Advanced Research Institute, IARI) and the humanities, social sciences and clinical medicine. This synergistic integration will form a new biomedical science, human metaverse medicine. Coordinated research involving bidirectional sharing of physical and cyber spaces will allow **exploration of mechanisms by which genetic and environmental factors affect human organs and patient outcomes**. Collectively, we will form a unique global base to elucidate onset mechanisms and pre-disease states and to develop individualized disease prevention and treatment regimes. Furthermore, PRIMe will aim to **become the world's leading center for fostering young researchers who understand biomedical science and information/mathematical science from a bird's eye view**.

1) -3 Goals

The goals of the Institute are as follows:

1. To establish the technologies needed to **build and apply biodigital twins for the new scientific field of human metaverse medicine**. We will model the continuum from homeostatic disruption to phenotypic manifestation of disease, with the aim of elucidating human disease mechanisms, predicting the onset and progression of diseases and their treatment responses, and ultimately developing individualized plans for prevention and therapy.
2. To **develop the information space platform (human metaverse)** for storage and distribution of biodigital twin information. Biodigital twin data will be shared worldwide with professionals from areas including the life sciences, medicine/medical science, and pharmaceutical sciences, to develop human metaverse medicine internationally. We anticipate that human metaverse medicine will be applicable to the resolution of many unsolved diseases.
3. To **educate and train the next generation of leaders and researchers** by fostering organic collaboration and mentorship, framed around the concept of human metaverse medicine.

2) World-Leading Scientific Excellence and Recognition

2) -1 Research fields

* Write in your target research field(s)
* Describe the importance of the target research field(s), including the domestic and international R&D trends in that research domain and neighboring field(s), and describe the scientific and/or social significance of the field(s).
* Describe the value of carrying out research in the field(s) as a WPI center (e.g., Japan's advantages in the subject fields, the project's international appeal as an initiative that challenges world-level science issues, and the future prospects of the research)
* List up to 5 centers either in Japan or overseas that are advancing research in fields similar to the center's field(s), and evaluate research levels between your center and those centers.

* Appendix 4: "Up to 10 English-written papers (review papers are also acceptable) closely related to the center's project and their list" (to be attached)

2) -1-1 Target research field

The target research field of PRIMe will be **the new medical field of human metaverse medicine**, which includes the causes, onset, and progression of human diseases, treatment methods and the prediction of treatment responses, and disease prevention efforts. The complex manner in which genetic and environmental factors interact over the course of an individual's life can result in disease development. Corresponding research in both physical and cyber spaces will be the basis for construction of biodigital twins, which will enable **new avenues of scientific disease-focused research that traditional medical approaches have failed to provide**. We will begin our studies with diseases such as non-alcoholic fatty liver disease (NAFLD), obesity, dementia, retinal and optic nerve degeneration, heart failure, osteoarthritis, and developmental disorders (achondroplasia and idiopathic short stature).

2) -1-2 Importance of the target research field

Domestic and international R&D trends and scientific and social significance

Despite much effort, **many diseases with complex pathologies still lack individual preventive or curative treatments**. In addition, the incidence of common diseases caused by aging, such as NAFLD, metabolic diseases (e.g., obesity and diabetes), neurodegenerative diseases (e.g., dementia, retinal and optic nerve degeneration), heart failure, and osteoarthritis is growing. To study mechanisms underlying such conditions, a new academic system dedicated to understanding complex interactions between genetic and environmental factors that can cause failure of homeostasis in humans will be essential.

Complex interactions between genetic and environmental factors are difficult to decipher using the traditional and current biomedical science approach: reductive animal model-based studies. No model animal can faithfully mimic human disease and **laboratory-based analyses alone do not evaluate environmental exposures humans encounter throughout life.** Individual human characteristics are influenced by inputs from a wide variety of superimposable factors, from genes and genomes to the environment, thus complicating any full understanding or resolution. Moreover, our ability to temporally capture reactions and changes to natural stimuli in humans is limited. Thus, due to the high dimensionality, non-uniformity, and discreteness of biometric data, it has been **difficult to construct a biodigital twin based on currently available signals and information from human real world studies alone**.

Recent research initiatives have been undertaken to analyze pathophysiological phenomena typical of human life through the analysis of large real-world data (biological signals and biological information) obtained from individual humans (patients, disease specimens, etc.), using information and mathematical science methods such as AI and mathematical modeling. Nippon Telegraph and Telephone Corporation (NTT) established Bio-Medical Informatics Research Center (BMC) in NTT Basic Research Laboratories in 2019. It has initiated research to precisely map biological signals and mathematical or functional models, with the ultimate goal to create biodigital twins. The BMC will be a satellite of our proposed PRIMe.

Recently, **organoid research has attracted worldwide attention**, and it has become possible to establish human organoids (i.e., miniature three-dimensional tissues that imitate human organs) for almost all organs of the human body. A key advantage of organoids is that they can be used to create models that reflect patient-specific disease-causing features. In addition, genetic and/or environmental perturbations can be introduced and manipulated, and the response they elicit can be continuously monitored. Hence, organoid research allows us to analyze human diseases in multiple dimensions; from molecular and cellular, to the level of the organ. The systematic science required to connect the enormous amounts of data to be obtained from organoids to advance the elucidation of diseases, however, remains to be developed.

PRIMe will utilize human organoids as a living library for reproducing both the pathological condition

and the *in vivo* information network, all in an *in vitro* setting. The structures will be digitized, and the interface between the expressive power of the biodigital twin and reality will evolve through continual exchange and feedback between the two systems. Through this mechanism, we will aim to accelerate our multidimensional understanding of the individuality of living organisms and complex pathological conditions. **The biodigital twin platform will aid in untangling complex interactions between genetic and environmental factors occurring in humans and enable pathogenic mechanisms of unresolved human diseases to be elucidated and personalized disease prevention and curative treatments to be developed.** Furthermore, by constructing a human metaverse containing biodigital twins and global implementation, we will **contribute to the development of science and medicine, improve health, and further a sustainable society for all humankind**.

2) -1-3 The value of PRIMe as a WPI center

Value of carrying out research in the field as a WPI center

The potential of biodigital twins to reveal new mechanisms to address currently unsolved diseases is profound. This work will require **novel interdisciplinary inputs, combining organoid-based biomedical science with information from disparate fields of mathematical sciences and quantum science**. Clinical medicine and the involvement of **the humanities and social sciences** will be required as well. We envision bidirectional development of biomedical science experiments in physical space, with information and mathematical science research in cyber space, as indispensable to our success. Hence, it will be essential to form an institute of world-class minds who have achieved success in individual research fields and interdisciplinary research endeavors, who can gather under-one-roof in PRIMe to share their expertise to develop a new integrated research area.

Superiority of Japan

In the worldwide field of human organoid-based biomedical research, significant contributions have been made by Japanese researchers. Especially, Takebe, deputy director of PRIMe, is a driving force in the development of this science [see *2) -2-2 Research plans*]. Highly functional liver organoid has been generated by Takebe during past ten years, and being developed for manipulatable system toward human metaverse study (**Fig. 2**). Moreover, Nishida, Hayashi, Tsumaki, Miyagawa, and others, who will participate as PRIMe principal investigators (PIs), have produced highly recognized achievements [also see *2) -2-2 Research plans*].

To implement the new concept of human metaverse medicine, quantum sensing will be necessary for the measurement of metabolism, temperature, active enzymes, pressure, and other parameters at the cell and organelle level. These technological achievements were not possible until recently. **The Osaka University Center for Quantum Information and Quantum Biology, (established as the International Advanced Research Institute) is the largest research center for quantum-related research in Japan** and among the first organizations in the world to begin working on the fusion of quantum mechanics with biomedical science.

PRIMe will offer an unparalleled global advantage, in that researchers with the highest level of technological expertise will collaborate under-one-roof to develop integrated biomedical science data, mathematical modeling, biodigital twin construction, and creation of the metaverse space. M. Okada, also a deputy director of PRIMe, is a leading researcher in data-driven mathematical modeling. Y. Okada is a renowned bioinformatics scientist who is at the forefront of disease genome research aimed at personalized medicine. Nagahara, who developed

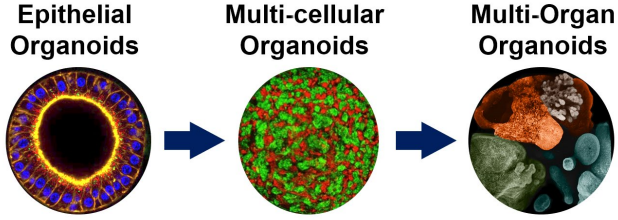


Figure 2: Evolution of Human organoids

state-of-the-art eXplainable AI, is a researcher whose work involves "whitening" (increasing the transparency of) the black box of AI, which is a significant AI drawback. Yachie, Nemoto, Fey, Shinobu, and others are young researchers who have made remarkable achievements in the fields of AI and drug design. In NTT, the PRIMe satellite center, Tsukada and Kashino are developing original data science algorithm and technology and **ahead of the world to advance the new concept of the biodigital twin for human diseases**. Through PRIMe, it will be possible to build, disseminate, and utilize a world-wide human metaverse space.

PRIMe will address outstanding challenges, garner international attention, and establish a future academic field

As the global population ages, **much focus and priority has been given to extend healthy life expectancy** to ensure both a good quality of life and an effective social security system. However, **many common diseases (diabetes, dementia, heart failure, etc.)** influenced by factors such as aging are increasing exponentially, threatening modern society and hindering the extension of healthy life expectancy. Many of these diseases develop through complex interactions between genetic and environmental factors over the time course of an individual's life. It is extremely difficult to pin-point the onset of these conditions or to comprehensively understand their pathological mechanisms through conventional experimental approaches using animal models. Even with state-of-the-art bioinformatics using real-world data (biological signals or biometric information) from individuals, the high dimensionality, non-uniformity, and discreteness of the biometric data present huge barriers to medical breakthroughs. Here, **we propose to establish a new technology that could accelerate our understanding of the human body and revolutionize medical research—building human biodigital twins**.

Construction of biodigital twins by PRIMe is an original concept that is unique in the world and likely to attract a great deal of international attention. Biodigital twin constructs could be a medical turning point that could open the way to resolve numerous poorly understood diseases. Our intent is to develop a human metaverse of stored human biodigital twins as an information space platform, to be utilized by the world's greatest minds. This effort could lead to the globalization of **human metaverse medicine**, which would be beneficial for all. Importantly, the novel science developed through PRIMe will be highly utilized to **study many unsolved diseases, broadly furthering research in the life sciences, medicine/medical science, and pharmaceutical sciences**.

In order to create a new academic field of human metaverse medicine, it is necessary to truly integrate the research fields of biomedical and information and mathematical sciences. To this end, we will establish **a higher education program for undergraduate students, such as human metaverse medicine educational programs and other research/education programs, disseminating these concepts and outcomes to wide field of scientific community outside PRIMe**.

2) -1-4 Five centers in fields similar to those of PRIMe

Hubrecht Institute

Led by Hans Clevers and his group, the Hubrecht Institute is a mecca for organoid research using somatic stem cells and has succeeded in establishing various organoids from cancerous and diseased biopsy specimens. There is also active research in the prediction of clinical pharmacological effects. However, because most of the organoids developed by the Hubrecht Institute are limited to the epithelium, interactions between tissues, organs, and lineages are lacking. PRIMe's goal to generate multi-organ organoid systems that permit the evaluation of interactions between various bodily systems (e.g., immune, blood, and endocrine systems) will have a distinct advantage in handling complex biological phenomena. Of note, with the announcement of Clevers' recruitment by Roche, the Hubrecht Institute has lost its iconic world leader.

Cincinnati Children's Hospital Center for Stem Cell & Organoid Medicine (CuSTOM)

CuSTOM is a top research institute in the field of developmental biology and has strengths in areas such as disease modeling for rare intractable diseases. In recent years, it has been a site for creating embryonic stem (ES) cell- or induced pluripotent stem (iPS) cell-derived organoids with tissue-to-tissue interactions. Recently, the CURE program for realizing the world's first organoid transplantation was announced, as was a policy of focusing on the transplantation field (budget: $20 million or 2 billion yen, for the next 10 years). PRIMe possesses a real advantage over CuSTOM, however, because of its plans to incorporate AI and data analysis to unravel common life phenomena. Collaborative cooperation of PRIMe with CuSTOM is possible, given Takebe (a PRIMe deputy director) is a deputy director of CuSTOM as well.

The German Cancer Research Center

The Deutsches Krebsforschungszentrum (DKFZ, aka The German Cancer Research Center) has many computational scientists and was the earliest to engage in research on mathematical modeling and clinical application to human diseases at the national level. The center conducts research on cancer, immune diseases, and neurological diseases, among others, with a focus on mathematical modeling. In 2014, it launched the systems medicine program, e:Med, for accelerating interdisciplinary fusion research. However, because the DKFZ approach is mainly centered on classical biochemical methods using cells, the PRIMe, using human organoids, has an overwhelmingly superior research advantage.

Luxembourg Centre for Systems Biomedicine (LCSB)

Established in 2009 for the purpose of personalizing medical care, the LCSB focuses on research integrating mathematical modeling and omics, with a particular emphasis on personalized medicine for Parkinson's disease. Although it is strong in the comprehensive analysis of omics, the introduction of mathematical modeling and AI has been delayed, giving PRIMe's objective to build a biodigital twin an enormous advantage.

Whole-Cell Modeling Consortium

This virtual research organization focuses mainly on young computational scientists who perform whole-cell modeling. The theme of the organization is "predicting phenotypes from genotypes for science, medicine, and engineering." Markus Covert (Stanford U), a member of the consortium, specializes in mathematical modeling (whole-genome modeling, systems of 1000 or more genes) and the large-scale simulation of microorganisms and cultured cells. The consortium has a strong publication record and strong computing power, but its work is quite distant from disease research. In that respect, PRIMe has a clear advantage in its chosen field.

2) -1-5 Ten Papers Closely Related to the Center's Project

See Appendix 4.

2) -2 Research objectives and plans

* Describe in a clear and easy-to-understand manner by the general public the research objectives that your project seeks to achieve by the end of its grant period (in 10 years). In that process, describe what world-level scientific and/or technological issues are you seeking to solve, and what will be the expected impact of the scientific advances you aim to achieve on society in the future.
* Describe concretely your research plan to achieve these objectives and any past achievements related to your application.

2) -2-1 Research objectives

To date, achievements in the biomedical sciences have made it possible to identify many diseases with clear causes and effects, and to greatly extend the human life span to the point that some individuals can live over 100 years or more. However, despite much effort, there are still **large numbers of diseases whose pathology is complicated and for which there are no preventive or curative strategies**. Incidence of these common diseases is influenced by aging and is rising (e.g., diabetes, obesity, dementia, heart failure, etc.), threatening modern society and hindering the extension of healthy life expectancy.

Many of these diseases develop over the course of one's life, via complex interactions between genetic and environmental factors over time, making it extremely difficult to comprehensively understand pathogenic mechanisms by conventional approaches.

To overcome these challenges, **PRIMe will create a new scientific field that would bring medicine fully into the digital age, human metaverse medicine**. Specifically, we will integrate experimental data from human organoids (which imitate human organs in a culture system) with real-world data (biological signals or biological information) and existing public data obtained from human individuals. These repositories will be used to develop original information and mathematical science methods, which will then be used to develop technologies for **the construction of biodigital twins that are able to reproduce the biological phenomena and pathological processes occurring in human organs in cyber space**. By utilizing this technology, we aim to **clarify the mechanisms of many unresolved diseases**, such as NAFLD, obesity, infertility, dementia, retina and optic nerve degeneration, heart failure, osteoarthritis, and developmental abnormalities (achondroplasia and idiopathic low stature). At the same time, we will work on **predicting the onset and progression of diseases and the response of individuals to treatment,** as well as **developing optimized preventive and curative treatment methods**. PRIMe will **educate and train the next generation of leaders in human metaverse medicine**; that is, researchers capable grasping the entirety of the field and developing it on the global stage. We aim to **launch the human metaverse**—a new concept that we define in this proposal as an information space platform for sharing and utilizing the aforementioned biodigital twins—to be shared by researchers and medical professionals world-wide.

Through the human metaverse, the results of PRIMe will be spread to a wide range of human-oriented resources throughout the world, such as those in the life sciences, medicine/clinical science, and pharmaceutical sciences. At the same time, by applying our achievements to many unsolved diseases, **we will contribute to the realization of a healthy and sustainable society for humankind**.

2) -2-2 Research plans

PRIMe will create **organoids from humans** in healthy, pre-symptomatic, and diseased states, manipulate the condition and artificially control the transition process from normal physiology to homeostatic failure. We will accumulate high-quality biological data through **advanced measurement** technologies, such as genomics, multiomics, imaging, quantum sensing, photonics and electronics, which enable multidimensional and multilayered measurements at the cell, tissue, organ, multi-organ, and multisystem levels to acquire responses of organoids to genetic and environmental perturbations. The data obtained from each organoid system, individual human data, public data (published in the literature), and other pertinent data will be integrated, organized and analyzed using AI and mathematical modeling. In this way, we will **model the continuous process from homeostatic breakdown in the body's metabolism and physiology to the phenotypic manifestation of disease**. The model created will be refined through repeated verification and model reconstruction, and finally reproduced as a **biodigital twin in the cyber space**. By advancing research in the physical and cyber spaces in a bidirectional manner, we will create "**Human Metaverse Medicine"** to **elucidate disease mechanisms and pre-symptomatic states, predict individual disease-onset processes**, and develop **personalized prevention and treatment methods**. In addition, we will construct a digital platform **"human metaverse" for storing biodigital twins to popularize and establish the field of human metaverse medicine worldwide**.

<u>Contents of interdisciplinary fusion research</u>

The following is a description of "Contents of the interdisciplinary fusion research" and "Development of key technology: creation of biodigital twins", "Development of key technologies in physical space", and

"Research on ethical, legal, and social issues (ELSI)" to realize the fusion research. (**Fig. 3**)

We will focus on biological responses and disease onset in important life events, *i.e.* development, reproduction, and aging throughout the lifespan, including growth, adulthood, and old age. In particular, we will target the following internal systems for which the PIs at PRIMe have amassed outstanding results worldwide (**Table 1**) : the hepatobiliary and pancreatic systems (Takebe: Nature, 2013, Cell Stem Cell 2013, Nature, 2017, Cell Metab 2019, Nature, 2019), reproductive system (Hayashi: Cell 2011, Science 2012, Nature 2016, Nature 2021, Science 2021), central nervous system (Pasca: Neuron 2017, Nature 2017, Nature Neuroscience 2019, Nature Medicine 2019, Cell 2020, Nature Medicine 2020, Science 2020, Nature Neuroscience 2021, Nature 2021, Cell Stem Cell 2022), sensory organ system (Nishida: NEJM 2006, Nature 2016, Nature Protoc 2017, Cell Rep 2018, Cell Rep 2021, Nature 2022), bone and cartilage system (Tsumaki: Nature 2014, Nature Commun 2016, Biomaterials 2022), and cardiovascular system (Miyakawa: J American Heart Association 2017, Molecular Therapy 2021).

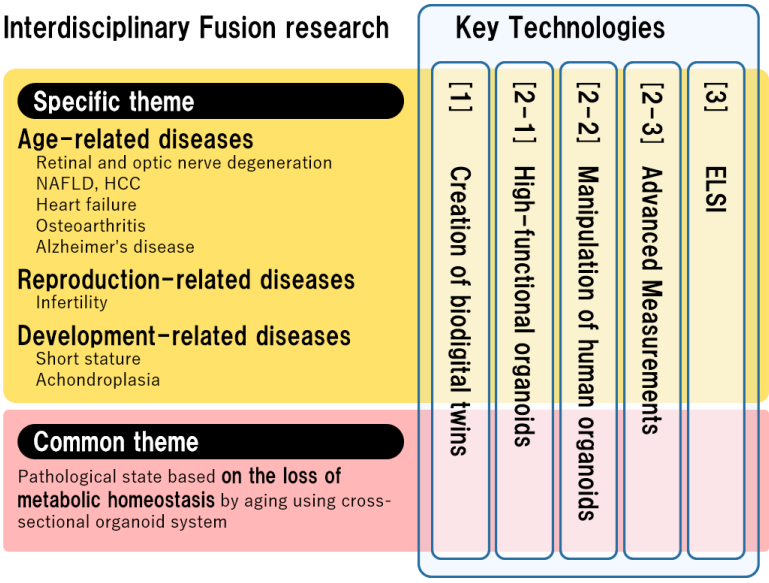


Figure 3: Contents of the interdisciplinary research

Among these, joint research by Takebe, M. Okada, and Tsukada has begun for NAFLD. Multiple genes affecting disease severity were identified using data of the steatosis phenotype of 25 organoids combined with data from the corresponding single nucleotide polymorphism array, scRNA-seq data of organoids, and public RNA-seq data. By combining identification via the Super Bayes method, ODE model construction of the network, and simulation analysis, we have been working to **construct a biodigital twin of NAFLD**

Table 1: Interdisciplinary fusion research

Internal systems	Target disease	PI			
		Biomedical	Measurement	Information	ELSI
Sensory organ system	Retinal and optic nerve degeneration	K. Nishida	M. Negoro Y. Harada H. Yokota	M. Okada H. Nagahara N. Yachie D. Fey Y. Okada T. Nemoto A. Shinobu K. Kashino S. Tsukada	A. Kishimoto
Hepato-biliary-pancreatic systems	Non-alcoholic fatty liver disease (NAFLD), Hepatocellular carcinoma(HCC)	T. Takebe			
Cardiovascular system	Heart failure	S. Miyakawa			
Reproductive system	Infertility	K. Hayashi			
Endocrine system	Growth failure Short stature	V. Hwa			
Bone and cartilage system	Chondrodysplasia Osteoarthritis	N. Tsumaki			
Central nervous system	Alzheimer's disease	S. Pasca			
Cross-sectional organoid system	Pathological state based on the loss of metabolic homeostasis with aging	K. Nishida T. Takebe S. Miyakawa K. Hayashi V. Hwa N. Tsumaki S. Pasca			

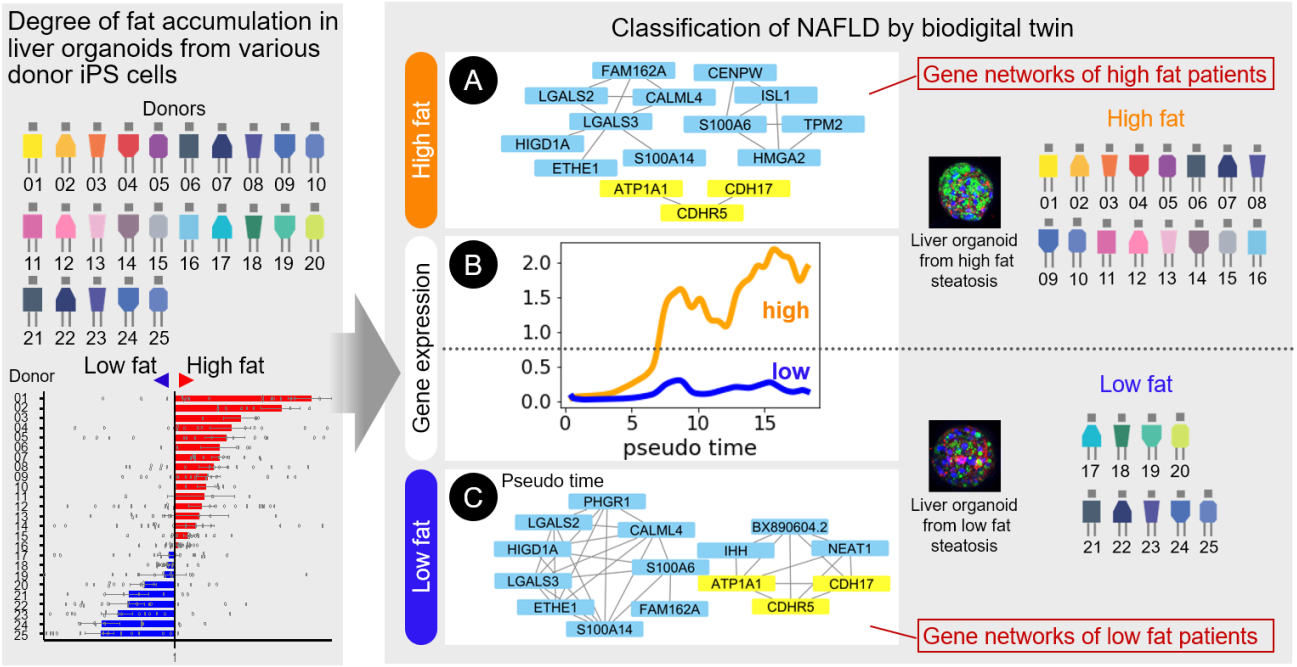


Figure 4: Feasibility study of construction of biodigital twin (*in silico* mathematical model) for classifying individual non-alcoholic fatty liver disease (NAFLD) patients (preliminary results by Okada (Mariko), Tsukada, Kano, Takebe)

We analyzed single-cell transcriptome data from high and low NAFLD human organoids and identified populations of hepatocytes and hepatocyte-specific common genes from many other cells. Pseudo-time analysis of hepatocytes was performed using information and mathematical science (**refer to Fig. 6**). Genes with high temporal correlation with other genes were identified, and a high-low gene network of NAFLD patients was constructed (at this point, the genes with low correlation have been deleted). A neural network model was used to confirm the reproducibility of the data and model, and the time course pattern of gene expression was predicted from this network. Finally, we focused on three major genes and predicted the time course of CDH17 expression from the ATP1A1 and CDHR5 genes in high and low NAFLD patients. In summary, single-cell data from organoids helps predict the temporal trajectory of each patient and build a gene regulation model for classifying patients based on gene expression dynamics. More mechanical models require high resolution time-course data.

that can be used to elucidate the disease mechanism and identify drug targets (**Fig. 4**). Our preliminary data shown here is considered as proof-of-concept which strengthen our research plan.

Joint research on infertility has also been begun by Hayashi and Harada, who are developing a technique to measure temperature and the activity of mitochondria inside oocytes. For developmental disorders, research is underway to construct a systemic growth prediction model to predict individual growth curves, using organoids derived from the three germ layers. We have conducted a proof-of-concept experiment using an iPS cell library from growth failure disease (an ultra-rare disease) banked by PI Hwa and her group; preliminary data support the feasibility of this method.

We hypothesize that the pathogenesis of many common diseases is based on the age-related loss of metabolic homeostasis maintained by inter-organ networks (**Fig.5**). To test this hypothesis, we will first conduct an integrated analysis in dry-lab research by linking the data obtained from individual organoids in cyber space. Next, we will draw hypothetical inferences about the network from analysis in wet-lab research, and then test the hypothetical inferences in an inter-organ organoid culture system. Through these processes, as well as using clinical data from human individuals and public knowledge base and dataset, we aim to discover new information on the inter-organ metabolism networks.

●Our hypothesis: the pathogenesis in common diseases based on the age-related loss of metabolic homeostasis maintained by inter-organ networks.

Challenge to model the inter-organ network

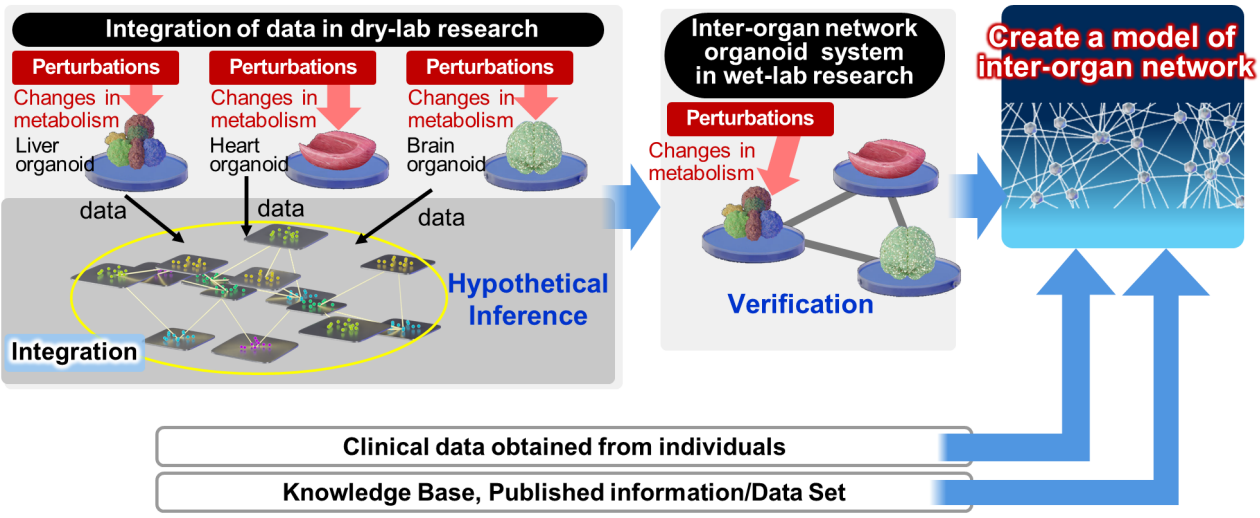


Figure 5: Common theme – inter-organ network associated with metabolism

[1] Development of key technology: creation of biodigital twins and construction of metaverse platform

This process consists of the following three steps (*Fig.1 the process 4, 5 and 6; Fig.6.*):

(1) From physical to cyber

Data collected by means of conventional biometrics has the following three characteristics:

・**High dimensionality**: It is a huge advantage to use organoids for experiment because we can acqure a vast number of different types of data, including phenotypic characterization, gene expression profiling, and quantum phenomena. Therefore, the dataset to be produced is highly multidimensional. The organization of these varied, large-scale datasets for maximal productivity will be optimized in PRIMe.

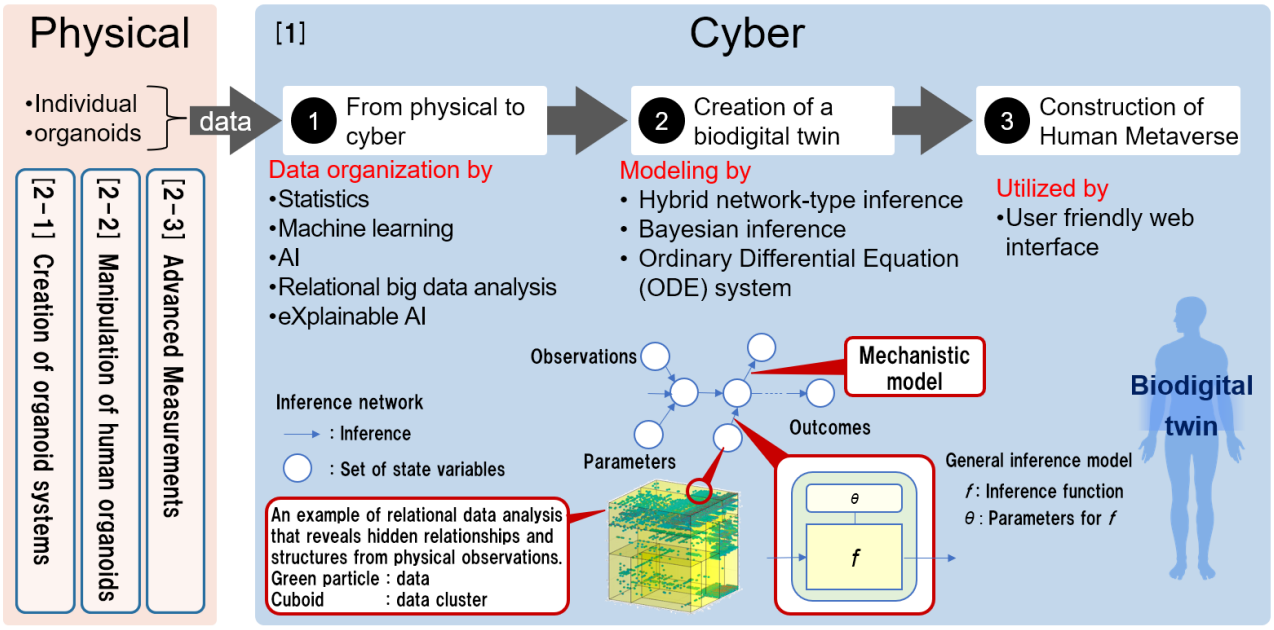


Figure 6: Development of biodigital twins and metaverse platform

・**Non-uniformity**: Most biological information, such as gene expression patterns, shows variability across individuals. Variability is also observed across different racial and ethnic populations. To ensure the validity of PRIMe results, a sufficient amount of data governing inter-individual and inter-group variability will be incorporated in the virtual metaverse. We will utilize the expertise of biostatisticians for these calculations.

・**Discreteness**: Some biometric information measurements require large-scale equipment and expensive materials. Thus, for these points, continuous, high-frequency measurements in humans may not be feasible and real-life data collection may be incomplete. As such, biodigital twins cannot be directly constructed from the sparse data currently obtained from human individuals.

The key advantage of using organoids is that they enable *in vitro* experimentation on organ-like cell clusters composed of cells genetically identical to those of human individuals. The number of measurements or time points can be increased using this system, resulting in a more complete capture of characteristics beyond that of *in vivo* biological data. By converting the data obtained from organoids into a mathematical model of a genetic network, it will be possible to capture continuous temporal changes, and hopefully predict the future development of disease.

Success will depend on closely interweaving **data science and mathematical modeling.** First, using data science, **statistics, machine learning, and AI**, we will develop technology that accurately extracts and classifies individual characteristics relevant to disease (e.g., gene mutations and epigenomic changes) from multidimensional data and information obtained from organoids. We (Y. Okada, Nagahara, Yachie, Nemoto) will independently develop data analysis methods that match the characteristics of organoid data, such as non-uniform data normalization methods, gene network estimation methods (M. Okada), and automatic 3D reconstruction of organoid images (Yokota). We will use these methods for feature extraction and dimensional reduction. We will also **identify factors that have a significant effect on classification, namely, disease markers and causative factors**. To that end, we will develop **the relational data analysis technology originally developed by NTT** (Tsukada, Kashino) and **eXplainable Artificial Intelligence (XAI)** (Nagahara) that demonstrate the reason of classification. Through such analyses, we will extract important factors from the organoid measurements and construct a mathematical model to reproduce the dynamics through which these important factors develop and

change over time.

(2) Creation of biodigital twin

The development of an analyzable machine learning framework for use in the creation of a biodigital twin will aim at modeling with sparse data, such as data from hundreds of organoids. However, the data uniformity perspective is still important. To achieve breakthroughs in this respect, we will create a specialized conference for cross-disciplinary discussions among the respective expert teams on specific experimental methods, quantity and quality of necessary/expected data, and specific mathematical models, and provide feedback to each of the experimental design, clinical data collection, and modeling as needed for overall optimization of each.

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. For the former, we developed a **novel nonparametric Bayesian method** with infinite resolution that is completely data-driven, allowing it to adjust its own complexity autonomously according to the quantity and quality of the target data (Tsukada, Kashino). For the ODE model, we will use the mathematical modeling platforms BioMASS and PasmoPy (M. Okada), which can identify the control mechanism of the network. To take advantage of these original cutting-edge methods, we will further **develop a hybrid network-type inference technique that can combine Bayesian methods and the ODE**, or mathematical/physical-based models. This learning inference machine will be able to search for latent factors hidden in biological information and signals; predict disease-onset processes; reflect physical, chemical, and biological mechanisms; and capture the effects of individual characteristics and the environment (Tsukada, Kashino). Through the combination of these techniques, it will become possible to predict the severity of disease in an individual and understand its cause due to environmental and genetic factors. Since most data are currently obtained at the hospital after the onset of disease, understanding and prediction of the pre-illness state is difficult. Conversely, exposing human organoids with a unique genetic background to various environmental factors might enable collection of informative data regarding the combined effects of genes and the environment. **By using Bayesian methods and ODE models, the information obtained from these measurements can be converted into a single mathematical model**, and **time-course changes can be captured by simulation of life-courses**. For example, it may be possible to identify environmental factors that affect the threshold for onset of certain diseases. A mathematical model of the gene network of each organoid generated by such a combination of environmental and genetic factors will be constructed as a biodigital twin in the metaverse space (M. Okada, Fey, Yokota, Tsukada, Kashino). Furthermore, with regard to the disease-causing genes identified from such analysis, drug design will be performed through molecular dynamics simulation based on the protein structure (Shinobu).

(3) Construction of human metaverse.

The biodigital twin will **feed back useful information to the real world about disease mechanisms as well as personalized disease prediction, prevention and treatment**. Furthermore, PRIMe will **develop a digital platform, or human metaverse, for storing biodigital twins, to be shared by researchers and medical professionals around the world**. A user-friendly web interface will be implemented, analysis tools will be distributed, and PRIMe will cooperate with data analysis. Researchers will be able to search for relationships and latent factors using their own data, and we will create an environment where analytical results can be visualized graphically on a dashboard in a variety of modalities (Tsukada, Kashino). In addition, we will clarify the precise simulation of current and one-step-ahead states; visualization of the estimation basis of XAI; and prediction of the future, including

the turning point of disease progress and the main factors that determine that progress. In this way, we will enhance the utility of biodigital twins and build a computational framework that promotes their use (Okada, Nemoto, Tsukada, Kashino).

[2] Development of key technologies in physical world

[2-1] Creation of organoid systems *(Fig.1, the process 1; Fig.6.)*

To recapitulate the physiological network between organ systems in the human body, we propose an innovative technological advance-incorporating multi-system interaction *ex vivo* into human organoid culture. Past organoid research has focused on single organs, and therefore failed to capture essential system-level crosstalk across organ systems (e.g., circulatory-endocrine-digestive). To achieve this goal, we will assemble **cross-sectional organoid systems** and take a research and development approach to promote their integrated development by building a highly functional culture system that can evaluate the physiological and homeostatic response across the multi-organ systems.

The PIs of PRIMe have an outstanding track record that is recognized worldwide in human iPS cell-derived organoid research. Here, we will establish a model that can acquire organ responses generated by the endocrine, immune, reproductive skeletal and nervous organoids that we have pioneered (Nishida, Takebe, Tsumaki, Miyagawa, Hayashi, Hwa, Pasca). As described in "2) -2-2 Research plans", an overarching theme, we would target mitochondrial metabolic response, as this is increasingly recognized to be an upstream factor in governing individual development and aging at a systemic level. Our objective is to assess the variables that define human metabolism, because growing evidence shows variation of individual metabolic level throughout life course. To this end, we will target not only single organoid systems (hepatobiliary, cardiovascular, bone and cartilage, and cranial nervous systems), but also cross-sectional organoid systems. In addition, it will be essential to incorporate gender differences in the construction of highly accurate inter-organ system networks (e.g., postmenopausal women show many signs of disease in these organs). The cross-sectional organoid systems will be poised to capture and interrogate metabolic differences in endocrine function between males and females, which are partly driven by reproductive organs and reflect sex-dependent differences in development and disease. This will be achieved by incorporating reproductive organs into the cross-organ culture system.

The abundant data possessed by the PRIMe clinical group, which is the strength of this institute (Nishida, Tsumaki, Miyagawa), will be interfaced with results from the cross-sectional organoid systems, to assess changes in metabolic response caused by aging and disease and be sensitive to gender differences. In addition, we will construct an innovative organoid system that can reproduce and track characteristics that reflect the transition from normal health to disease state in the same individual, something that is currently difficult to evaluate clinically (Yachie).

[2-2] Manipulation of human organoids *(Fig.1, the process 2; Fig.6.)*

We will build a cell manipulation technique to model the life-course response at an accelerated speed. By leveraging several advantages of iPS cell technology, we will **introduce cell intrinsic and extrinsic regulatory factors into bio-banked human iPS cell libraries**, including factors relevant to (1) synthetic biology (Yachie, Nemoto), (2) genome biology (Y. Okada), (3) mathematical modeling (M. Okada), and (4) endocrine/metabolic nutrition (Hwa, Takebe). Using these, we will introduce mutations and perturbations to the genomic and epigenomic states, propelling the deterioration of metabolic homeostasis within an observable window. Starting from healthy human- and patient-derived organoid panels that have already being constructed, an *ex vivo* human cohort model for tracking the metabolic life course at the population level will be established. Ultimately, these studies to comprehensively screen manipulable factors will delineate key genetic and environmental elements that are instrumental in the development of metabolic disorders.

[2-3] Advanced Measurements *(Fig.1, the process 3; Fig.6.)*

We will **introduce novel quantum technologies to measure physiological and pathological changes at the organellar, cellular and organoid levels**. To achieve this, PRIMe has welcomed members of the Osaka University's International Advanced Research Institute (IARI), Quantum Information and Quantum Biology as PIs. Using **quantum sensing** technology at the sub-cellular levels, we will be able to capture organellar and intracellular molecular dynamics that were previously impossible to elucidate. Through measurement of parameters such as metabolism, temperature, active enzyme, and pressure, we will mechanistically explore the normal maintenance of homeostasis and its breakdown (Negoro, Harada). Specifically, Osaka University has recently conducted research on a quantum sensing method called **hyperpolarized NMR/MRI**, which aligns the spin states in a molecule at ambient temperature. By controlling the quantum state of the sensor molecule, it is possible to detect ligand–receptor interactions, clarifying activation processes and level of metabolism. In the PRIMe project, we will perform high-speed automatic measurement of a significant number of organoids using a large number of room temperature hyperpolarizers. Then, we will attempt to understand disease models at the quantum mechanical level by using supercomputers to compare the results of sensor molecular states and proteins obtained with quantum chemical calculations and molecular dynamics calculations. Our goal is to acquire sufficient quantum mechanical-level data from organoids to establish a foundation for a quantum biomedical science that enables diagnoses based on knowledge about various diseases at the quantum mechanical level (Negoro). In addition, **fluorescent nanodiamonds** have recently attracted attention as quantum sensors capable of measuring the local environment inside cells. Nanodiamond fluorescence is derived from the internal nitrogen-vacancy center (NVC). By combining NVC and magnetic resonance technology, technology development is underway to acquire and image physical parameters such as electric field, magnetic field, and temperature of intracellular nanospace, which was not possible with conventional fluorescent probes. Fluorescent nanodiamonds will be used in this project, and we will analyze cellular states (Harada). In the conventional method of measuring living cells, the limit of measurement is the resolution of a microscope, but in our research, we have succeeded in developing a quantum sensor with a spatial resolution of 4 nm, which is much higher than the resolution of a microscope. The advantage of fluorescent nanodiamond quantum sensor measurements is that only one particle can precisely and quantitatively measure physical information inside the cell. Another advantage of quantum sensors is their high measurement accuracy. Quantum sensors can measure temperature with an accuracy of 1 milli-degree. This makes it possible to verify the possibility that minute temperature fluctuations within a cell may be involved in biochemical reactions.

We will also **develop image processing technology for capturing various images—from cells to the human body.** This will be indispensable for constructing morphological models of organoids and human bodies and organs (Yokota). Yokota has developed an observation device that automatically repeats the cutting of biological samples and the acquisition of cross-sectional images. Additionally, he has developed a multidimensional image processing method for the acquisition of voxel information to extract and visualize regions of organelles and organs and to perform numerical analysis by quantifying the extracted regions and processing their geometry. Utilizing these achievements, we aim to quantitatively analyze phenomena through image processing to extract information from organelles, cells, organoids, tissues, organs, and the human body. Furthermore, we will systematize these technologies and **establish an image processing platform for human biodigital twins** using image-based modeling technology. Using these systems, we will construct spatiotemporal simulations.

[3] Research on ethical, legal, and social issues (ELSI)

Both the entirety of the research conducted at this center as well as the nature of the research subjects

and fields themselves are cutting-edge. It is therefore expected that ethical, legal, and social issues (ELSI) will arise in the process of our research and development, as well as societal implementation. PRIMe PI Kishimoto (Osaka University ELSI Center), a noted researcher in Humanities and Social Sciences, is focused on these studies. In PRIMe, **ELSI will be addressed in advance with the participation of various stakeholders, including citizens and patients**. By proactively dealing with ELSI academically and practically, we will link our research results to proposals for governance and ethical guidelines. In organoid research, for example, informed consent and cell donor privacy, moral and legal positioning of created organoids, and rules for using organoids for regenerative medicine and organ transplantation, etc. are pertinent issues for discussion. Regarding the construction of biodigital twins, the legal position of data, secondary usage rules, treatment of patient privacy, potential bias of algorithms, explanation/verifiability, etc. are, similarly, important ELSI to address. By responsibly applying and developing research results in the fields of biotechnology and information technology, we will support innovations necessary for the societal implementation of this research.

2) -3 System for advancing the research

* Describe the center's research organization (including its research, support and administrative components) and your concept for building and staffing the organization.
* Describe your concrete plan for achieving the center's final staffing goal, including steps and timetables.
* Describe your concrete plans (steps and timetables) for achieving the center's gender-balance plan. The plans should be divided into the following two categories, describing each:
  a. plans at the executive level including the center director and administrative director
  b. plans among principal investigators (professors, associate professors) and other researchers
* If the center will form linkage with other institutions, domestic and/or foreign, *by establishing satellite functions*, provide the name(s) of the partner institution(s), and describe their roles, personnel composition and structure, and the collaborative framework with the center project (e.g., contracts to be concluded, schemes for resource transfer).
* If the center will form linkage with other institutions, domestic and/or foreign, *without establishing satellite functions*, provide the names of the partner institutions and describe their roles and linkages within the center project.
* Appendix 5: "List of Principal Investigators" (If there are changes from the PI list in the first screening application documents, describe the points changed and reasons.) (to be attached)
* Appendix 6: "Biographical sketch of principal investigator" (to be attached)
* Appendix 7: "Composition of personnel in center" (to be attached)
* Appendix 8: "Letters from researchers invited from abroad or other Japanese institutions expressing their intent to participate in the center project" (to be attached)

2) -3-1 The center's research organization, concept for building and staffing the organization

In order to realize our vision, we will unite world-class researchers from Osaka University, Japan and overseas to create an interdisciplinary, integrated, and diverse faculty. **The PIs have the following research specialties: Biomedical Sciences** (7), **Information and Mathematical Sciences** (7 local, 3 from satellite institutes), **Quantum Science** (2), **Humanities and Social Sciences** (1) (total of 20, including 4 female PIs) (**Fig. 7**). Reflecting the groundbreaking and modern nature of the science proposed, the PRIMe faculty is composed largely of young researchers: three of the 20 PIs at PRIMe are in their 30s (including one deputy director), and six are in their 40s. As such, the PRIMe project can drive new academic research 20 years or more after its inception. **PRIMe satellite centers** will include: the **Bio-Medical Informatics Research Center at NTT Basic Research Laboratories** and **the RIKEN Center for Advanced Photonics**. **Overseas partner institutions of PRIME** will include: **Cincinnati Children's Hospital Medical Center** (organoids), **Stanford University** (organoids), **University College Dublin Systems Biology Ireland** (data science), and **the Curie Institute** (bioinformatics). We will welcome PIs or visiting professors to PRIMe to create an international, collaborative research environment for the development of human metaverse medicine.

Full-time University Research Administrators (URAs) will be hired to staff the PRIMe administrative

department. These URAs will benefit from the know-how of the Immunology Frontier Center (IFReC), which is a WPI Academy center, and cooperate with the URAs of the Office of Management and Planning, which is a university-wide Osaka University office. The URAs will provide information for external grant funding opportunities that PI can apply for, and support planning research collaborations. In addition, they will proactively, support grant writing, formulate research plans, accommodate site visits, and prepare various reports. In addition, they will work with the Co-Creation Bureau, which is an university-wide industry-academia collaborative organization of Osaka University, to foster joint research projects with companies and manage intellectual property. A URA will be assigned to each PI individually, who will provide pre- and post-award support, creating an environment in which PIs can focus on research progress.

In addition, **a dedicated administrative department will be set up at PRIMe**, and excellent administrative staff will be selected and assigned from within Osaka University. By doing so, research work and office work can be separated, and researchers can concentrate on their research.

2) -3-2 Concrete plan to achieve the final staffing goal

Of the PIs participating from outside the host organization, three will transfer to Osaka University immediately if PRIMe is selected, and the other will transfer to Osaka University in the second year. We made an offer to one of the deputy director, Takebe as a faculty of Osaka University in January of next year. Two PIs will participate in PRIMe through means such as a cross-appointment. **We plan to complete recruitment of PRIMe researchers about two years after being selected as a WPI center.** New PIs will be carefully selected by international recruitment, utilizing the excellent human resources support of the four overseas PRIMe partner institutions, Cincinnati Children's Hospital Medical Center and Stanford University (USA), University College Dublin Systems Biology Ireland, and Curie Institute (France).

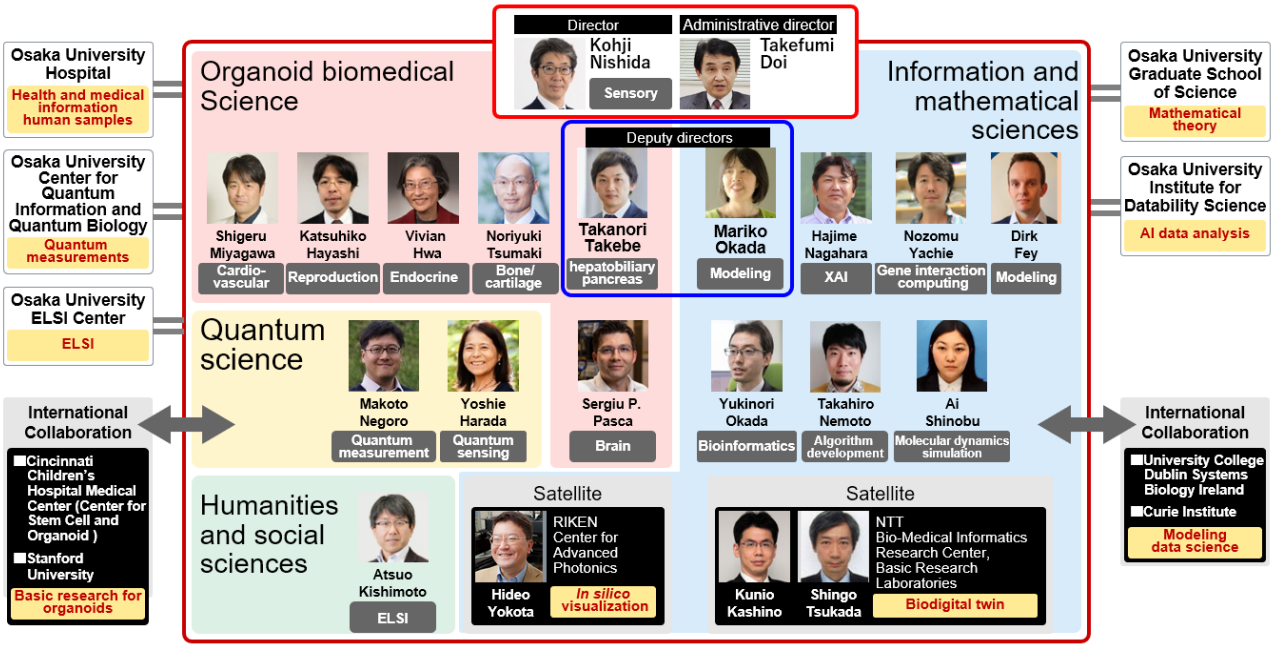


Fig. 7: PRIMe Researchers

In particular, when hiring young researchers, **we will actively seek female research candidates**. **PRIMe values the contributions of world-class researchers from diverse backgrounds, including PIs of both male and female gender**. In cooperation with the host institution, we will create a system and environment that reflects modern change and social conditions. These efforts will make PRIMe a center with exemplary equity, diversity, and inclusion standards, which can overcome current problems regarding gender balance and diversity.

We will establish the EDI (Equity, Diversity and Inclusion) Committee to raise awareness about the importance of achieving **gender balance** among our members and to propose specific improvements.

Our concrete measures to achieve gender balance in our research organization are as follows. As of June 2024, **8 out of 10 URAs in the Planning Office are women.** We will continue to prioritize gender balance in our administrative departments. For PIs and other researchers, we will promote **flexible working conditions**, provide **childcare support**, and advocate for work styles that consider work-life balance. We will also enhance the environment by including childcare facilities. Additionally, the number of female researchers will be increased through **open recruitment specifically for female researchers.**

2) -3-3 PRIMe satellites

In addition to the main center of Osaka University, PRIMe satellites will be set up at **RIKEN** and **NTT Basic Research Laboratories**. The roles of the satellites will respectively be: (1) the development of image processing technology and (2) aiding in the construction of biodigital twins and the human metaverse. Each satellite will have one or two PIs and additional researchers, including postdocs. Agreements addressing collaboration have been signed between each of the two satellite institutions and Osaka University and discussions among researchers have already begun. In the future, PRIMe will establish individual contracts addressing the specific content and method of joint research for each satellite.

2) -3-4 Linkage with other institutions

Cincinnati Children's Hospital Medical Center (CCHMC), **Stanford University**, **University College Dublin Systems Biology Ireland (UCD)**, and **the Curie Institute** have been designated as overseas partner institutions. The roles of each institution are as follows: CCHMC includes the new center for Stem Cell and Organoids Medicine (CuSTOM), that can share resources such as iPSC (induced Pluripotent Stem Cells) panels from patients and a state-of-art robotic organoid manufacturing facility. Specifically, we plan to collaborate with CCHMC in organoid research for studies of the gastrointestinal and respiratory systems, which are not the target disease themes of PRIMe. Stanford University hosts the Neurosciences Institute Stem Cell Core, which will provide cutting-edge brain organoid systems from healthy and diseased patients with psychiatric diseases to the PRIMe team. We will collaborate with Stanford University on research on Alzheimer's disease and inter-organ linkage research mediated by the cranial nervous system. UCD will develop mathematical models and algorithms for biodigital twin construction and apply these methodologies to the analysis of data at PRIMe. The Curie Institute will conduct bioinformatics analysis of clinical data and software development. PRIMe will actively exchange post-doctoral fellows and young researchers with these overseas partners, to ensure that the latest mathematical and computational methodologies are reflected in PRIMe research and that our junior colleagues receive state-of-the-art educational opportunities. MoUs and student exchange agreements have been already completed with UCD and will be addressed for the other satellites.

To facilitate interaction, for example, overseas research institutions where PRIMe PIs are assigned (Stanford University, University of British Colombia) will place deputy PIs at Osaka University, while Osaka University will establish custom laboratories at these institutions, to create an environment where relevant researchers can come and go freely. In addition, we will develop virtual under-one-roof environment for them to constantly interact with each other in a daily basis.

Furthermore, **Osaka University Hospital**, which is closely related to the research field of PRIMe, will be a source of cells for organoid construction and patient data (biological signals / biological information). **The Center for Quantum Information and Quantum Biology of Osaka University** will develop measurement technology using quantum science, and **the Graduate School of Science of Osaka University** will connect the real world to biodigital twin information world using mathematical modeling.

The Osaka University Institute for Datability Science will collaborate with PRIMe from the perspective of XAI (Explainable AI) development.

The following tables provide details regarding planned PIs and support members.

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

* Paste onto table a) in Appendix 7.

	At beginning of project	At end of FY 2022	Final goal (Date:November, 2027)
Researchers from within the host institution	11	11	13
Foreign researchers invited from abroad	4	3	4
Researchers invited from other Japanese institutions	5	5	3
Total principal investigators	20	19	20

b) Total number of members

* Paste onto table b) in Appendix 7.

	At beginning of project		At end of FY 2022		Final goal (Date:November, 2027)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	20		21		61	
Overseas researchers	3	15.0	2	9.5	19	31.1
Female researchers	5	25.0	5	23.8	18	29.5
Principal Investigators	20		19		20	
Overseas PIs	3	15.0	2	10.5	4	20.0
Female PIs	5	25.0	5	26.3	6	30.0
Other researchers	0		2		41	
Overseas researchers	0	0.0	0	0.0	15	36.6
Female researchers	0	0.0	0	0.0	12	29.3
Research support staff	7		8		9	
Administrative staff	3		6		17	
Total number of people	30		35		87	

	At beginning of project		At end of FY 2022		Final goal (Date:November, 2027)	
	Number of persons	%	Number of persons	%	Number of persons	%
Doctoral students	0		2		21	
Expected employment	0	0.0	0	0.0	5	23.8

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

2) -4 Securing research funding

2) -4-1 Past record

* Give the total amount of research funding (e.g., competitive funding) secured by the principal investigators who will join the center

project. Itemize by fiscal year (FY2017-2021).

The total annual amount of competitive and other funds obtained by the prospective PIs of PRIMe from 2017 to 2021 is shown below.

Year (FY)	2017	2018	2019	2020	2021
External Research Funds(unit: million yen)	1,092	1,310	1,163	1,228	1,260

2)-4-2 Funding prospects after the establishment of the center

* Based on the past record, describe your concrete prospects for securing resources that match or exceed the WPI grant (FY2022-2026).
* Calculate the total amount of research funding (e.g., competitive funding) based on the amount of funding that the researchers will allocate to the center project. Be sure that the funding prospects are realistically based on the past record.

Osaka University actively supports cross-departmental fusion research activities and prioritizes research dedicated to solving social issues. The PRIMe will secure about 2 billion yen annually (including the amount allocated by this subsidy), in in-kind support from Osaka University, including research space and external funds. In addition, Osaka University has traditionally had strong ties with industry and was established with donations from the private sector in Osaka. Following the lead of IFReC, the leading WPI Academy center, PRIMe plans to seek large-scale comprehensive cooperation to support PRIMe from multiple companies and foundations. We will steadily advance these connections, with the goal to create a strongly supported research environment where PIs can devote themselves wholly to research.

The contents of this WPI application are also positioned as a medium- to long-term strategic plan for Osaka University. The establishment of a new research building where the researchers of PRIMe will be assembled, and the development of other infrastructure, will be self-financed by the university. This financing will derive from university bonds, budget requests to the Ministry of Education, Culture, Sports, Science, and Technology, indirect expenses from joint research, and other sources. On April 28, 2022, Osaka University issued the 1st National University Corporation Osaka University Bond (issued at 30 billion yen). Funds raised through this bond will be implemented under the "OU (Osaka University) Master Plan 2027" formulated in January 2022 with the aim: "Creating a Society where Each Member Leads a Meaningful and Fulfilling Life." The new research building, where PRIMe researchers will gather under-one-roof, will be constructed utilizing funds procured from this bond.

From 2022 to 2026, the total annual amount of external research funds, etc., acquired by the PI of PRIMe is expected to be as follows.

Year (FY)	2022	2023	2024	2025	2026
External Research Funds (unit: million yen)	600	600	650	700	750

2) -5 Interdisciplinary research

* Describe the fused research domains, why interdisciplinary research is necessary and important in the target field(s), and what new field(s) can be expected to be created by way of this project. Describe your concrete strategy for fusing different research domains and creating new field(s) by the fusion.

2) -5-1 Critical need for proposed interdisciplinary projects and creation of new research fields

For the first time in the world, PRIMe will fully fuse the two fields of human/organic biomedical science and information/mathematical science (artificial intelligence, or AI, mathematical modeling, simulation). In addition, we will integrate these pursuits with **the Center for Quantum Information and Quantum biology** established by Osaka University as an International Advanced Research Institute, as well as with **humanities and social sciences** and **clinical medicine**. Through this unique fusion, for the first time, we will establish an innovative technology to construct a biodigital twin that precisely reproduces the biological phenomena and pathological processes occurring

in human internal organs in cyber space. **Biodigital twins will be indispensable in the bidirectional development of biomedical science experiments in physical space and information / mathematical science research in cyber space**.

Using biodigital twins created by this fusion research, PRIMe aims to predict the causes, onset, progression, and patient treatment response to disease, including diseases that have been resistant to biomedical research to date. Further, we aim to **create a new medical field: human metaverse medicine**, which will apply our discoveries for the development of preventive and therapeutic methods.

2) -5-2 Specific strategies for interdisciplinary collaboration

As shown in Fig. 1, PRIMe is engaged in (1) construction of human organoids, (2) manipulation of human organoids, (3) comprehensive measurement, (4) data organization, (5) creation of a biodigital twin (modeling), and (6) construction of human metaverse. For each of the six processes, a research team consisting of a world leader and early-career researchers will be formed to carry out PRIMe fusion research. In addition, researchers in the humanities and social sciences, including ELSI, will participate in research teams, as appropriate, to ensure that our fusion research is realized with a higher societal perspective and viewpoint.

The host institution, Osaka University, plans to construct a research building (20,000 m^2 of space) on Suita Campus, where PRIMe will be established. Osaka University will give PRIMe priority to use this building to promote its fusion research by realizing the "under-one-roof" environment. **The building architecture is intentionally open, so that researchers from different PRIMe research teams and disciplines will naturally mix and interact with each other.**

3) Global Research Environment and System Reform

3) -1 System for advancing international research

* Describe your concrete plan for building an international research center including the makeup of its foreign researchers, establishment of oversea satellites, or similar functions. Include a time schedule for the plan.
* Describe concretely your strategy for staffing foreign researchers (e.g., postdoc positions) through open international solicitations. Describe the procedures you will use to do so.
* Describe measures to help foreign researchers sustain and strengthen their activities under conditions when international exchange is limited.

3) -1-1 Specific plan for the establishment of an international research center

Nishida, the center director, has the creativity to yield new value through the fusion of disciplines and the international human resource network. He will be assisted by Takebe, who is the deputy director of the Organoid Center at Cincinnati Children's Hospital, and M. Okada, who has led interdisciplinary fusion research in informatics and biology. Both the center director and deputy directors have "borderless" sensibilities and networks, and will make full use of these to welcome **Vivian Hwa** of Cincinnati Children's Hospital Medical Center, **Sergiu P. Pasca** of Stanford University and **Dirk Fey** of University College Dublin as PRIMe PIs. In addition, an international research environment will be fostered through collaboration and regular communication with researchers of **Cincinnati Children's Hospital Medical Center** (organoids), **Stanford University** (organoids), **University College Dublin Systems Biology** (data science), and **the Curie Institute** (bioinformatics). Thus, we will develop a productive, active research environment and pursue our goal of expanding human metaverse medicine globally through these institutions. In addition, after the establishment of PRIMe, we will further expand domestic and international collaborations through our network of international research connections.

3) -1-2 International recruitment of researchers at PRIMe

International recruitment of researchers such as postdocs will be carried out at both the main center, Osaka University, and through our overseas partner institutions. Researchers with an international sense

whose interests match the theme of PRIMe will be carefully selected. In particular, in the hiring of researchers at the main center, we will benefit from **the successful experience of IFReC, an WPI Academy center**. In addition to the usual recruitment practices, an **Advanced Postdoc system** will be introduced. Here, we will exhibit PRIMe research and achievements in booths at overseas academic societies / events and meet with young researchers directly to confirm their abilities and qualities and encourage applications to PRIMe. Those hired will be paid a standard international salary and provided with research funds to conduct their studies. Human resources support at PRIMe overseas partner institutions will be leveraged to conduct surveys and carry out recruitment. We will encourage active recruitment of researchers that we are seeking to add to PRIMe.

3) -1-3 Efforts related to foreign researchers and the research environment in circumstances where personal interactions are restricted

PRIMe will be established as a place where researchers can gather and carry out collaborative, synergistic research activities under-one-roof. However, human interactions may continue to be restricted by COVID-19, or by similar situations, in the future. To continue to circulate international ideas, even when international exchange is limited, we will build **a virtual under-one-roof environment**, with a sense of presence to connect our members in domestic and overseas centers online. We will create an environment where new ideas and joint research can be easily initiated through frequent meetings across national borders through online conference systems. We will also develop shared online "private" rooms that researchers can freely use regardless of their actual surroundings. The deputy director of PRIMe, Takebe, currently operates laboratories at two institutions through cross-appointment. As he has already generated a virtual under-one-roof environment for his two laboratories, we will utilize his know-how to accomplish this goal.

3) -2 Establishment of international research environment

* Describe your concrete strategy for establishing an international research environment, administration system, and support system (e.g., appointment of staff who can facilitate the use of English in the work process and provision of startup funding) to accommodate researchers from overseas.
* Concretely describe how the center will provide an environment in which researchers can work comfortably on their research by being exempted from duties other than research and related educational activities (e.g., allocation of adequate staff support to handle paperwork and other administrative functions) including your procedure and time schedule.
* Describe your strategy, procedure and timing for periodically holding international research conferences or symposiums (as a rule, at least once a year).

3) -2-1 Setting up research environments with international standards

To make PRIMe a truly international research center, we will provide up to **50 million yen as startup funds for PIs welcomed from overseas**. In addition, we will provide **research funds** for laboratory management for about three years until research funds in Japan can be stably obtained. The **Co-PI (Young Leader Researcher) system**, used with great success at IFReC, will be introduced at PRIMe. We will make it possible for a senior researcher welcomed from overseas to appoint a young leader researcher and make them resident at PRIMe as a close associate, so that the young leader can play an active role in joint research. In addition, a **research space (about 300 m^2)** and **faculty/researcher posts (10 people in total)** will be provided to enable early startup of research activities in Japan. In particular, the administrative department dedicated to PRIMe and the support offices of Osaka University will provide intensive assistance to foreign researchers. We will also provide full support in terms of life, including for family members, so that research can be conducted in the same way as Japanese researchers. "Kasugaoka House", an accommodation facility exclusively for foreigners at Osaka University, will give priority to foreign researchers staying for a short period of time.

All researchers employed at PRIMe will be hired through international recruitment; **at least 30% will**

always be foreign researchers. English-speaking staff and URAs will be assigned to the administrative department to provide an international standard for both the research and living environments of foreign researchers. It is desirable that the PIs welcomed from overseas stay at PRIMe for as long as possible. The center director will manage this effort with the goal to create such opportunities.

3) -2-2 Reducing or waiving of duties except education and research

For researchers to be able to concentrate on their activities comfortably, PRIMe will utilize the funds of PRIMe. In principle, work other than education and research will not be allocated. As a work environment with free and regular communication will maximize our productivity as a network of researchers, daily communication will be encouraged, especially for foreign researchers visiting Japan. At the same time, we will establish a vibrant online communication environment that transcends time, space, and culture with PRIMe researchers in remote areas.

3) -2-3 International workshops with world-class researchers

A face-to-face symposium will be held about once a year to disseminate the research results of PRIMe and to hold discussions with the world's top researchers. At an open symposium, published research results will be presented. A closed session will be held where researchers who have exchanged NDAs can bring unpublished research results for discussion. The symposium will invite researchers in ELSI and humanities and social sciences to discuss issues relevant to PRIMe and to deepen our members' understanding of the social significance and value of basic research. In addition, small-scale, thematic international workshops will be held several times a year.

3) -3 Center management and system reform

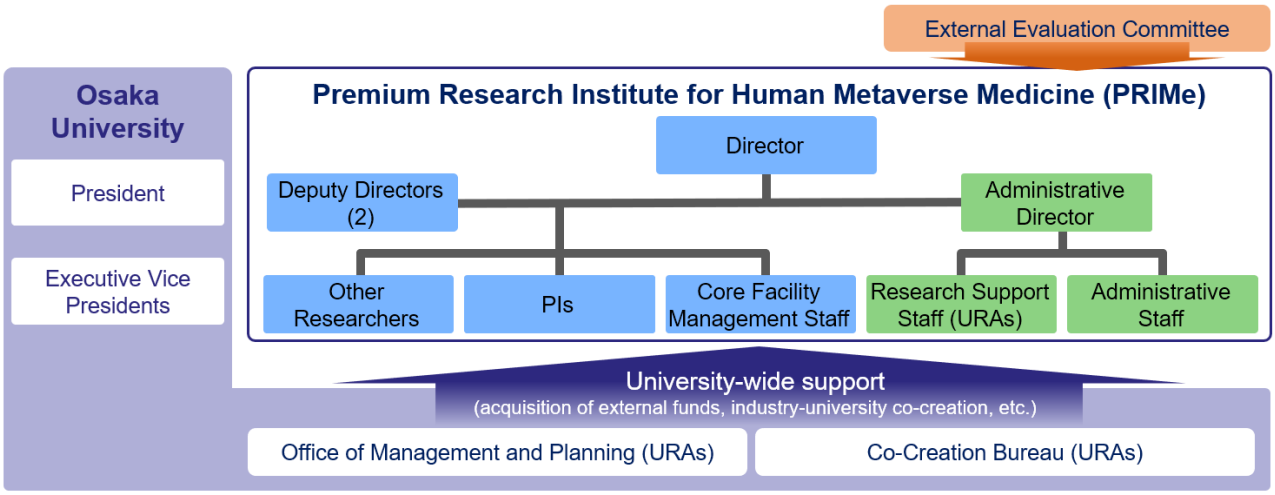
* Describe the role of the center director and the administrative director.
* Concretely describe your concept for establishing the center's administrative organization, the center's decision-making system and how authority will be allocated between the center director and the host institution. (Describe concretely the mechanism for decision making when the person in charge of management and the person in charge of research and education in the center are different, and describe the responsibility relationship between the two.)
* Concretely describe how the center will adopt a rigorous system for evaluating research and will introduce a system for merit-based compensation (e.g., annual salary scheme). Describe your procedures and timing for operationalizing these systems.

3) -3-1 Decision-making mechanism/research support departments at PRIMe

The center will be managed and operated by the center director independently of other departments within Osaka University. The center director will have the same authority as a department director regarding personnel affairs, such as recruitment of researchers and budget execution within PRIMe. Excellent administrative staff will provide strong management support to the center director, to enable the center director's research activities to proceed unencumbered.

A center steering committee consisting of **the center director**, **deputy directors**, **administrative director**, and PIs will be established to support the decision-making of the center director and to decide the medium- to long-term plan for PRIMe. 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. Based on these results, the center director will revise the medium- to long-term plan, determine the annual salary of full-time researchers, and decide whether non-tenured researchers will be continued. To ensure that research activities proceed in an integrated manner, we will hold progress report meetings once every two months. Then, if there are any problems, center director will take full responsibility to solve the problem, utilizing the steering committee. In addition, we will establish an external Evaluation Committee to find solutions.

Takefumi Doi, an emeritus professor at Osaka University, will be appointed as administrative director of the center. Doi has excellent research and management abilities, having served as the director of Graduate School of Pharmaceutical Science of Osaka University and Vice President of Osaka University.



Doi has experience in the practice of research management both at home and abroad, conducting international joint research on arteriosclerosis and serving as deputy director/department director of the Institute for Open and Transdisciplinary Research Initiatives of Osaka University. He is an expert in performance management and center management and has a bird's-eye view of various fields. He has excellent communication skills in English and is qualified as the administrative director of PRIMe.

Under the center director and the administrative director of PRIMe, excellent bilingual staff will provide strong administrative support to foreign researchers in general affairs, accounting, and so on. URAs who have research experience and a doctorate will be assigned to support foreign researchers, to create an environment where PIs can concentrate on their research. The executive Board of Osaka University as well as University-wide URAs will also support PRIMe management (**Fig. 8**). This strong support will enable foreign researchers to obtain external funds without disadvantage, compared to Japanese researchers.

3) -4 Research environment

* Concretely describe how equipment and facilities, including laboratory space, will be provided in a manner appropriate for a "world premier international research center." Include your procedure and timing.
* Describe measures taken with regard to the research environment to sustain and strengthen research activities under conditions when international exchange is limited.
* Concretely describe how the center will consider arranging for its researchers to participate in the education of graduate students.
* Describe new measures to improve or abolish existing systems and practices in the host institution toward optimizing the center's research environment.
* Concretely describe the plans by the host institution to provide a support system and to work toward improving the environment for achieving gender balance.
* Describe your measures other than those described above for ensuring that world's top researchers from around the world can comfortably devote themselves to their research within an international and competitive environment at the center.

3) -4-1 Equipment, facilities, and laboratory space appropriate for a WPI

Figure.8 Center Management/Support System

Osaka University is dedicated to **the construction of a new, state-of-the-art research building (20,000 m^2) to house the PRIMe** on the Suita Campus within approximately four years of the award of this proposal. The new facility will provide a fully outfitted research environment in which all the PIs will conduct fusion research under-one-roof. In the interim, Osaka University has secured approximately 2,000

m^2 of space in the Graduate School of Medicine for the four researchers who will arrive from outside the host institution immediately after designation of PRIMe. **The built environment will include an open collaborative space** where center members can interact, have discussions in a relaxed atmosphere, and meet new people. The facility will be attuned to the needs of men and women who are both carrying out research and raising children, which will support the development of fulfilled researchers who will lead the next generation.

As mentioned above, **all research, education, and operation of PRIMe will be conducted in English** so that the foreign researchers will not feel alienated. The administrative department will provide staff who are fluent in English from within Osaka University, and create an environment that is **rich in diversity**, to allow all researchers to concentrate on their research comfortably.

3) -4-2 Research environment for maintaining and strengthening research activities

PRIMe will build an original collaboration system that will create a virtual under-one-roof environment connected by a network. This environment is intended as more than an alternative measure for situations where human interaction may be restricted, but rather an effort to add value to PRIMe daily research activities regardless of limitations on meeting in person.

3) -4-3 Consideration for participation in graduate school 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. PRIMe will actively promote the involvement of its researchers in graduate school education, to the extent that these education and research activities are based on the mission of PRIMe. Work not directly related to PRIMe goals will be exempt. The host institution will allocate necessary personnel for education and research activities in the departments from which PRIMe researchers derive. For researchers who concurrently hold positions with other departments within the university, support will be provided in the form of reduced teaching activities in the departments.

3) -4-4 Improvement of existing systems and elimination of outdated traditions

We will abolish the seniority-based system and create a culture in which senior researchers and postdocs/students can productively exchange scientific information and ideas on an equal basis.

Securing strategic human resources to carry out the mission of PRIMe will be essential to our success. In addition to hiring full-time researchers, we will develop systems to enable flexible employment contracts that consider both researchers intentions and needs and the policies of Osaka University. Through this systems and by prompt response to requests, various situations, such as cross-appointment, acceptance of dispatched researchers, and recruitment of foreign researchers can be completed in a timely way. In addition, when hiring outstanding researchers, we will implement a packaged offer system that covers the research environment and living considerations, not just the treatment of individual researchers. This system will be expanded and introduced not only at PRIMe, but also in other research areas within Osaka University. In this way, we will improve the inadequate existing system and revitalize it, creating a system suitable for a globally leading research center.

3) -4-5 Plans by Osaka University to provide a support system for achieving gender balance

In September 2021, Osaka University released the **"Declaration for the Promotion of Diversity and Inclusion"** followed by the **"Proposal for the Realization of Diversity and Inclusion"** in March 2022. The university aims to achieve a female researcher ratio of 30% by FY2031 and 40% or more by 2049.

Osaka University has implemented a system to **support the activities of female researchers** by employing graduate students as **"research assistants"**. Additionally, the university has established an

operational system that allows the allocation of substitute faculty members for female faculty members who plan to give birth.

As measures to foster the next generation, Osaka University has established a network of female students in the natural sciences, implemented a festival for women in science and engineering, and hold consultation meetings on higher education. Additionally, the University has created an **"Entrance Support Fund System"** that awards 200,000 yen to some female students enrolled in the Faculty of Science and Engineering to support their development.

Further, Osaka University supports newly hired post-doctoral fellows by providing start-up research expenses up of 300,000 yen for male researchers and 500,000 yen for female researchers.

Furthermore, as a measure to support the balance between childcare and work, the university has established **on-campus nursery schools (three with a total capacity of 185 children) and a "collaborative space" that can be used for temporary childcare, lactation rooms, and rest rooms to provide a better environment for working women.**

Osaka university has established slots for WPI centers to receive these programs.

4) Values for the Future

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

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

* Describe your plans for fostering researchers with a view to achieving gender plans, and your plans for conducting domestic and international promotion activities to attract female researchers to the center.

At PRIMe, we aim to create a society in which each of us can realize well-being through technological innovation and societal implementation. To this end, PRIMe will **identify ethical, legal, and social issues (ELSI) relevant to our work and respond to them in parallel with our research and development in science and technology**. That is, we will practice the model of "Responsible Research and Innovation" (RRI). We will widely convey the content and significance of our basic science research efforts, including to the general public, and conduct two-way dialogue and cooperation to extract expectations, as well as concerns and anxieties. Through these efforts, we will **strive to share the social value of our achievements**. Osaka University was the first in Japan to derive the concept of "industry-academia collaboration" more than 10 years ago. In 2020, **the Research Center on Ethical, Legal, and Social Issues (ELSI Center)** was established to hold public participation workshops on new science and technology developments. PRIMe will utilize this knowledge and this facility to systematically engage in public relations and outreach activities. Kishimoto of the ELSI Center will lead these efforts as a PI.

We will **share the research results of PRIMe with many people across national borders** and promote their understanding of our efforts. We will participate in international scientific events, such as the annual meeting of the American Association for the Advancement of Science (AAAS), employ science press release distribution platforms such as EurekAlert, and develop educational material through massive open online courses (MOOCs) at Osaka University. In addition, for the research community, a face-to-face international symposium will be held once a year, and online international workshops with focused themes will be held several times a year. In this way, the concepts at the heart of PRIMe will be widely extended to the world, and further development of fusion research will be promoted.

In Japan, we will hold research results report meetings and science cafes in Japanese for the general public. Furthermore, in the creation of the human metaverse, one of the goals of PRIMe, we will try to form a new model of citizen science that involves the participation of the general public and acquisition of data on healthy people. There, participating citizens will be positioned not only as data providers, but also as actors in discussions to **build relationships between science and society, ultimately creating the next generation of science**.

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

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

We aim to realize the creation of a new academic field, human metaverse medicine, by truly fusing the research areas of biomedical science and information / mathematical science. For this purpose, it will be necessary to build a higher education program that transcends the boundaries of these fields and to improve the environment for the development of these next generation researchers. PRIMe will promote human resources development from the following **two perspectives**.

First, **researchers will be trained in highly specialized human metaverse medicine.** PRIMe will be a collaborative department of the Graduate School of Medicine, and the faculty members belonging to PRIMe will be in charge of accepting, instructing, and examining graduate students. **A doctoral human metaverse medicine educational program will be established at the graduate school**, incorporating classroom lectures, exercises, and practical training from the perspectives of cyber, physical, ethical, and social issues. **In collaboration with the Support for Pioneering Research Initiated by the Next Generation (SPRING) program of Osaka University, approximately 20 students in each grade will be assigned to this course of study each year.** The human metaverse medicine graduate program will also be integrated with Osaka University's International Advanced Research Institute (IFReC and the Center for Quantum Information and Quantum Biology).

For postdoctoral researchers, we will establish a seminar course where researchers from different fields will meet together, study the recent literature, share their expertise, conduct brainstorming, and set up opportunities for collaboration. In addition, we will invite outstanding young researchers from all over the world to carry out grounded research activities for short periods while enjoying world-class treatment. To this end, we will introduce **the Advanced Postdoc system**, which has a proven track record in IFReC. Furthermore, by expanding **the tenure track system**, excellent young researchers will be able to concentrate on their research, and human metaverse medicine will be able to sustainably take root in Osaka University.

Second, we will develop **research and education programs for the dissemination of human metaverse medicine concepts and results** to those outside PRIMe. We will encourage **graduate students and young researchers outside PRIMe** to attend and earn credits. In addition, we will accept **students from the World-leading Innovative & Smart Education program (WISE) and Leading Graduate programs**. We will provide sub-specialization (minor) and advanced minor programs that make use of the concept of human metaverse medicine, and ensure that all doctoral students on campus will be able to take these courses. We will build a system to accept these students as PRIMe collaborators, as needed. In addition, we will hold regular research seminars that reflect the concept and research themes of human metaverse medicine and add them to the credit certification seminars required by the Graduate School of Medicine and the WISE program.

By addressing each stage of trainee career development in this way, PRIMe will foster young researchers in an international and interdisciplinary environment who will form the future generation of scientists.

To achieve gender balance, we will actively introduce successful cases of female researchers and provide role models for young researchers. Additionally, **female researchers will be prioritized in the selection process for adoption of the Osaka University Next Generation Researcher Development Project** under the SPRING Program.

Moreover, for young female researchers facing challenges in securing sufficient research time due to childbirth, childcare, infertility treatments and similar circumstances, the **"Research Support Staff System"** will be utilized to employ graduate students as "research support staff".

4) -3 Self-sufficient and sustainable center development

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

Osaka University has clearly positioned formation and establishment of PRIMe as a medium-term goal. In addition to implementing various systemic reforms that are necessary for its formation, Osaka University will provide full support to PRIMe. In addition, PRIMe will be positioned in the International Advanced Research Institute, headed by the President of Osaka University. PRIMe will be treated as an independent department and integrated into the departmental structure of Osaka University, which will **redistribute faculty posts from existing departments and provide space for PRIMe**, as needed. In addition, during the WPI support period, a new organization to realize the mission of PRIMe by reorganizing the existing organizations within Osaka University will be considered. As with IFReC, which was a WPI center (now a WPI Academy center), **Osaka University will make PRIMe a permanent organization after the WPI support period ends.**

Statement of Vision from the Center's Director
Professor Kohji Nishida, Osaka University

Conquering disease is an ambitious goal that has persisted throughout human history. To achieve this goal, we will establish a WPI center that will create a completely new scientific field, Human Metaverse Medicine, which will bring digital transformation to medicine.

Medical breakthroughs in the 20th century were largely achieved via animal experimentation. In the early 1970s, life sciences research blossomed, joining biology and medicine, and promising the means to conquer cancer and other diseases. A reductive approach, centered on the concept of a discrete dichotomy between health and disease has been routinely employed to study illness. Though many diseases with clear cause and effect have been defeated using this approach, and life expectancy has been significantly extended, other **diseases with complex pathologies remain resistant** to these efforts. For these, **no preventive or curative treatments exist**. In addition, an explosion in prevalence of common diseases has occurred, including diabetes, dementia, and heart failure. These are influenced by **the deterioration of homeostasis brought on by aging** (a process that varies greatly among individuals). **Interactions between genes and environmental factors** also compound metabolic differences and organ abnormalities. For these diseases, the conventional dichotomy between health and disease is lacking. In contrast, new medical research, based on the concept of a continuum between health and disease, as well as the notion of pre-symptomatic pathological states, or "Mibyo", has emerged. These efforts rely on mathematical methods, such as artificial intelligence (AI) and computer modeling, and real-world data and disease specimens from patients.

This proposal will take a new, nuanced approach to disease, by creating an academic system to comprehensively and continuously understand the process of homeostatic disruption that occurs in each individual human body. We will revolutionize this field by creating a World Premier International (WPI) Research Center, the **"Premium Research Institute for Human Metaverse Medicine (PRIMe)"**. PRIMe will promote a paradigm shift by integrating organoid-based biomedical science research with the information and mathematical sciences, quantum science, clinical medicine, and the humanities and social sciences. We define the "human metaverse" as an information space platform for sharing and utilizing ***in silico*** **patient-specific models constructed from human data, or "biodigital twins"**. Through our interdisciplinary research (**Fig. 1**), **we will create the scientific field of "human metaverse medicine,"** which will elucidate disease mechanisms and pre-disease pathological states. This new analytical platform will aid in development of personalized disease prevention methods and curative treatments and generate predictive methods for disease onset and drug response that are optimized to the individual. Furthermore, **we will construct an information space platform—the human metaverse** itself—to enable researchers and medical professionals around the world to share and utilize information in the form of human-biodigital twins. We will work with academics in the humanities and social sciences to interrogate relevant **ethical, legal, and social issues (ELSI)** throughout the process; any issues that arise will be collaboratively solved with key stakeholders.

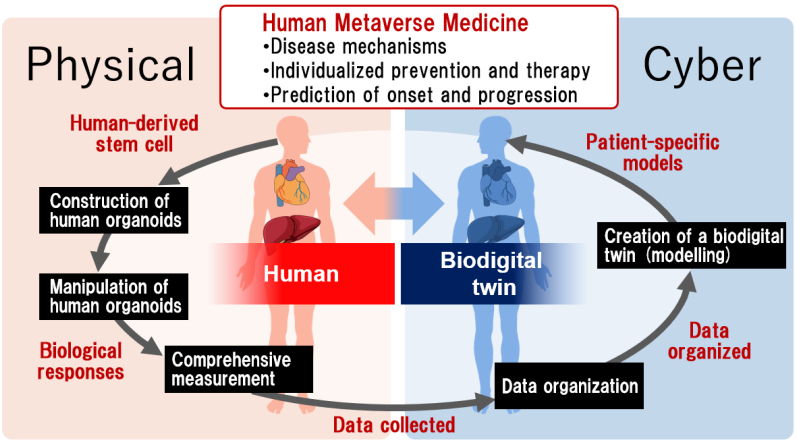


Figure 1: Creation of the "Human Metaverse Medicine"

To accomplish this goal, we will create **banks of organoids from human-derived stem cells**. Organoids are miniature three-dimensional tissue constructs that reflect the individual human source and

mimic human organs. Organoids, constructed from normal, pre-symptomatic or diseased patients, will be used to measure responses to perturbation by genetic and environmental factors at the molecular, cellular, tissue, organ, multiorgan, and multisystem levels, in multiple dimensions and layers, by using **advanced measurement techniques.** 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. As our first content area, we will focus on development, reproduction, and aging,** aiming to discover common, as well as unique, principles that lead to the onset of disease at each time.

The goals of this initiative are threefold: **1) creation of "human metaverse medicine"** to comprehensively understand disease, **2) construction and social implementation of a "human metaverse"** to prevent and treat disease, and **3) development of the next generation of researchers** trained in the new approaches we propose. In addition, we will foster early career researchers who can navigate "human metaverse medicine" as a whole and develop it widely on the international stage. To realize this goal, we will conduct interdisciplinary research "under-one-roof" in an interactive physical environment highly attuned to cooperation, collaboration, and collegiality. **A doctoral human metaverse medicine educational program will be established** at the graduate school. Human metaverse science will be included in the Cross-Disciplinary Graduate Programs and Challenging Research Programs for Next-Generation Researchers

We will assemble outstanding researchers from Osaka University to work with new recruits from overseas to establish a research system that fuses these diverse disciplines. Center Director, Kohji Nishida, has extensive experience leading large projects to success, and has published widely in the fields of fundamental stem cell science and organoid research (e.g., Nature 2016, 2022) and applied clinical research (e.g., New Engl J Med 2004). I will certainly draw on my vision to create exceptional value in the new WPI venture. PRIMe will have two Deputy Directors: Takanori Takebe, Deputy Director of the Organoid Center at Cincinnati Children's Hospital since 2017, a leading international institution for organoid research (e.g., Nature 2013, 2017, 2019, Nat Med 2020) and Mariko Okada (e.g., Cell 2010, Science 2014, 2021, Cell Rep 2020), a leader in the fusion of research between informatics and biology in Japan. PRIMe principal investigators (PIs) will be selected through interview, including seven experts in the field of organoid-based biomedical science, ten in information and mathematical sciences (including three at satellite institutes), two in quantum science, and one in ELSI (in total twenty PIs including four female PIs). Equity, diversity, and inclusion will be closely considered during recruitment. Satellite centers will be established at **the RIKEN Center for Advanced Photonics** and **the Bio-Medical Informatics Research Center at NTT Basic Research Laboratories**. In addition, **four overseas research institutes** renowned for their research in organoids and information and mathematical sciences will be invited as collaborating institutions. PIs or visiting professors will be invited to the new WPI Research Center to develop an international research environment and expand human metaverse disease science internationally through the collaborating institutions.

It is the shared dream of humankind to live a long and healthy life. PRIMe will contribute to the realization of this dream by achieving an unparalleled fusion of human biomedical sciences, information and mathematical sciences, quantum science, clinical medicine, and the humanities and social sciences. PRIMe will enable many unsolved diseases to be understood and fought in new ways. By spreading our results throughout the world, we will make new and unique contributions to a healthy and sustainable society for all people.

Host Institution's Commitment

To MEXT

Osaka University
Shojiro NISHIO, President

I confirm that the measures listed below will be carried out faithfully and concretely as follows regarding "Premium Research Institute for Human Metaverse Medicine (PRIMe)" if it is adopted under the World Premier International Research Center Initiative.

Concrete Measures

・Describe the concrete measures that the host institution will take to satisfy the following requirements.

1) For the center to become a truly "world premier international research center" and independent by the time WPI support ends, the host institution must clearly define the center's role within its own mid-to-long-term strategy and provide its comprehensive support from the time that the funded project starts, while showing that the center contributes to achieving the host institution's missions, etc.

※ Describe how the center will contribute to achieving the host institution's missions, enhance the founding spirit/philosophy of the host institution, and contribute to realizing the objectives of its operation, etc.

※Describe the center's role within host institution's own mid-to-long-term strategy.

Under the motto "Live Locally, Grow Globally," Osaka University has consistently pursued its educational and research activities in line with its "Osaka University Charter" to contribute to the well-being and welfare of society, world peace, and harmony between humankind and the natural environment. In particular, as stated in the "OU Master Plan 2027"[1] (established on January 19, 2022), the University's mid-to-long-term management vision, the University is currently developing the OU (Osaka University) Ecosystem, which embodies systematic co-creation with society, to solve social issues as a world's most innovative university aiming to create "a society where each member leads a meaningful and fulfilling life". The world that PRIMe aims to create, "a world that overcomes diseases and where everyone can live a long and healthy life," concurs with "a society where each member leads a meaningful and fulfilling life".

The center will be established as the world premier international research center that is promoted in accordance with the university's mid-term goals, mid-term plan, and the OU Master Plan 2027. Also, to achieve the above-mentioned mission, the OU Master Plan will be specifically positioned in the mid-to-long-term plan of the University when it is adopted. In addition, as one of the world's leading research centers in new academic fields, the University will provide full support for necessary institutional reforms and the development of research implementation systems to realize a world-class research environment and to ensure that such activities can be sustained even after this support ends.

2) Provide a mid-to-long-term policy on the direction of the host institution's operating organization, one that includes the reform of the institution's existing organization in ways that will achieve the center's independence and create a permanent place for it within the organization. A concrete plan must be established and a schedule set for carrying out the restructuring of the host institution's organization.

※Describe your mid-to-long-term policy on the direction of the host institution's operating organization and provide a concrete plan and schedule.

As described in 1) above, when the project is adopted, the University will position the center in a concrete manner in its mid-to-long-term plan and give a permanent position as one of the centers of the International Advanced Research Institute. By providing supports described below, the University will establish its position as an international research center and make the center permanent.

1. To ensure the implementation of the proposed research plan, the University will secure resources (including competitive research funds obtained by the center's researchers, in-kind contributions from the University (e.g., provision of research space), and donations from external sources) equal to or greater than the amount of support from the WPI Program from the first year.
2. Gradually increase the amount of external funds acquired from the third year onward to cope with the expansion of the research system and the reduction in the amount of support from the WPI program from the sixth year onward. In addition, this center will be treated as an internal organization with the same rights to request budget and personnel as existing departments, enabling the organization to become self-supporting.
3. In acquiring external funding, the URA at this center will support the application by research groups consisting mainly of researchers at the center for large-scale external fundings (such us large-scale projects under Grant-in-Aid for Scientific Research, AMED, JST, etc.), by quickly identifying information on external funding, organizing research projects, and providing support for their application. In addition, to enable foreign researchers to apply for external funding in Japan from the same starting point as Japanese researchers, information necessary for obtaining external funding will be provided in English. Furthermore, we will aim to obtain grants from overseas by foreign researchers in this center. This support will be ensured by utilizing the knowledge of the university's IR/URA organization, the Office of Management and Planning, and the URA of the Immunology Frontier Research Center (IFReC), the WPI Academy center.
4. Aim to stabilize the research system by carefully selecting excellent researchers at the center for tenure positions within a few years after the start of the program.
5. Secure the resources necessary for this center to become self-sustaining, by utilizing the knowledge of the Co-Creation Bureau, an industry-academia collaboration organization of the University, which has achieved large-scale industry-academia collaboration to make IFReC self-sustaining. (Reference: Industry-university collaboration-related income of IFReC in FY2020: 1.81 billion yen/61.8% of total project cost.) The Co-Creation Bureau will cooperate in the promotion of industry-academia collaboration at PRIMe from the first year, and strengthen it especially from the sixth year onward.

Through the above efforts, the ratio of support provided by this program will be gradually reduced, especially after the 6th year, and at the end of the 10th year of the support period, it will smoothly transition to a permanent organization within the University.

3) Describe the host institution's concept for allocating it's basic and other budgets and provide sufficient support for carrying out the center's operation and research activities, including necessary human, financial, and system support. In addition, when utilizing external funds other than the WPI grant for the center's operation and research activities toward realizing the missions of the host organization, show the relationship between the center and the other external funds.

* If a prospect exits for utilizing external funds other than the WPI grant for the center's operation and research activities, indicate the application/acquisition status of the relevant external funds and the relationship between them and the center. (If the following programs are included, be sure to describe them. Their relationship to the center can be illustrated if appropriate.)

・WISE Program(Doctoral Program for World-leading Innovative & Smart Education, ・Supereminent Program for Activating Regional Collaboration (SPARC), ・Open Innovation Platform for Industry-Academia Co-creation (COI-NEXT), ・Center of Innovation (COI) Program, ・Program for Promoting Regional Revitalization by universities as Center of Community (COC+ Program)

As the host institution of PRIMe, the University promises to preferentially allocate resources such as personnel and operating expenses that exceed the amount of support from the WPI program from other financial resources of the University to strengthen its operating base. The center director will be allocated at least 50 million yen per year as discretionary expenses, as well as reallocation of faculty and researcher positions (10 positions in total). The center's operations, especially research expenses, will be funded by external sources other than this program. The PIs of this center will receive about 1.2 billion yen in external funds per year. In addition to the URAs employed by the center, the URAs of the Office of Management and Planning, the University's URA organization, will provide strong support for the acquisition of external funds.

Regarding facilities, the University has already raised the same amount of funds through the 1st National University Corporation Bond (Sustainability Bon, nicknamed "Osaka University Social Creation Bonds that Foster a Purpose of Life") (issue amount: 30 billion yen) on April 28, 2022. The fund raised by the bond issue will be used to implement various projects under the "OU Master Plan 2027" with the aim of realizing "a society where each member leads a meaningful and fulfilling life". A new research building with a total floor area of 20,000m^2 is scheduled to be constructed in 2026 on the Suita Campus, where this center will be established, using these funds, to provide an environment where center researchers can gather to carry out research activities (under-one-roof), and to secure necessary and sufficient space for the steady implementation of research activities at this center.

4) Provide for the independent operation of the center including after the WPI grant period ends. Provide necessary support to include the long-term provision of human and financial resources, facilities, equipment and other elements needed to retain the center as a "World Premier International Research Center." Also, secure and provide from an early stage of the center's establishment the infrastructure needed for it to carry out its activities (e.g. land, research facilities and equipment, research space), and do so with a commitment to continually maintaining this infrastructure after the WPI grant period ends.

The University will continue to provide various resources necessary for the activities of the center to ensure that it continues to operate independently and remain the "world premier international research center"

even after the end of the support period. This will make the center a permanent organization. In addition, looking ahead to the end of the support period, the University will realize a virtuous cycle of co-creation with society by returning research results to society, and from the early stage of the support period, the University will provide support to enhance the financial base through industry-university co-creation. Specifically, the Co-Creation Bureau will provide strong support for the licensing of intellectual property, joint research contracts with companies, and support for venture startups, in addition to contracting procedures, management, and human resource development for handling such contracts.

Our university, especially Co-Creation Bureau, is leading Japanese universities in industry-academia collaboration, and has a track record of realizing a very large scale (10 billion yen per year x 10 years) "organization to organization" industry-academia collaboration for IFReC and having established an operational foundation after the WPI support ended. This knowledge will be utilized at the center.

Regarding facilities, it is as mentioned in 3), The necessary space will be systematically secured, and the necessary research environment will be secured and maintained after the support period ends.

5) Provide a system that will in practice allow the center director to make decisions in implementing the center project, including personnel and budgets, and that will secure the autonomy of the center's operation.

The host institution will be allowed to operate the center as an independent department of the International Advanced Research Institute (under the direct control of the President) as described above. In other words, the Center Director will have both management and research/education responsibilities, and will manage and operate the center and make decisions centrally within the center. The center director has the same authority as the department heads in terms of personnel matters such as hiring and promoting researchers within the center, and final decisions on budgeting and execution within the center. In addition, to support the decision-making of the center director, particularly excellent administrative staff and URAs will be assigned to provide strong support in terms of office management.

6) Provide support to the center director by coordinating with other departments regarding assigning researchers to the center and creating an effective environment for the center within the host institution. Needed adjustments to do so should be made proactively while giving consideration to their effect on the educational and research activities of those departments.

If the Center Director wishes to have a faculty member of the Graduate School or another research organization of the University participate in the research activities of the center, the Executive Vice President of Research will negotiate with the Dean of the Graduate School or the head of the research organization. At that time, considering the impact on education and research activities, the Executive Vice President of Research will coordinate the assignment of the necessary personnel for education and research activities at the home department of the on-campus researcher who has become full-time at the home institution. The University will also provide support to concurrently appointed intramural researchers to reduce the burden of their educational activities. The University will provide the necessary financial and personnel support for this purpose.

7) Offer cooperation in flexibly applying, revising, or supplementing the host institution's internal systems as needed for the center to effectively implement new management methods unfettered by conventional modes of operation (e.g. English-language environment, merit-based pay, top-down decision making, linkage to graduate school education).

IFReC has implemented many system reforms using non-traditional methods of operation. In addition, the University has promoted system reforms such as a performance-based annual salary system, rules on special measures related to the personnel affairs of world premier international research center departments, and an employment system based on a cross-appointment system. The University will take the lead in incorporating such best practices in the management of this center. Furthermore, in order to support the autonomous and advanced management of this center, the University will proactively consider the necessary environmental improvements, including making the existing system more flexible and revising them.

8) Provide other types of assistance to give the center maximum support in achieving its project and in becoming a world premier international research center in both name and deed.

In order to make PRIMe an international research center, we will provide approximately 50 million yen as start-up funds in the first year to PIs from overseas, and will also provide them with research funds to run their laboratories for about three years until they can obtain stable research funds in Japan. In addition, a research space (about 300 m^2) will be provided and a Co-PI with extensive experience in research and obtaining research funds in Japan can be appointed to facilitate research during the period of absence in Japan. Also, a total of 10 faculty and researcher positions will be allocated to enable the early launch of research activities in Japan. Furthermore, the Research Support Division for the center and the University-wide Support Office will provide intensive support to foreign researchers, including PIs, to enable them to conduct research efficiently in Japan and to provide them with full support for their daily lives; including their families, so that they can conduct research on a par with Japanese researchers. For foreign researchers on short-term stays, priority will be given to those staying at Kasugaoka House, the University's dedicated accommodation facility for foreign residents.

All researchers and research staffs hired at this center will be recruited internationally, and at least 30% of them will be non-Japanese. The administrative staff and URA of this center will be staffed with people who are fluent in English to provide a research and living environment of an international standard. The University will provide maximum support for the center to become a " world premier international research center " in both name and reality, including the points above.

9) The host institution is to self-evaluate the results of the system reforms achieved by the center and distribute the results that it evaluates highly to all of the departments throughout its organization.

The achievements of IFReC, specifically the globalization of education, improvement of the learning environment including campus life, promotion of international joint research through cross-appointments, and enhancement of URA, have progressed and spread throughout the University.

The University will also position this center as a leader in organizational reform at the University, and will conduct a self-evaluation of the center's performance, and establish an evaluation committee consisting of prominent researchers and businesspeople from Japan and abroad to evaluate the center every one or two years. The results of outstanding system reforms will be horizontally disseminated to

other departments within the university through its executive office.

10) (For host institutions that already have an existing WPI center and/or Academy center) Fully support and sustain the existing WPI and/or Academy center and advance its development as a world premier international research center, while being capable of fully supporting the new center at the same time.

Osaka University has been supporting IFReC, a WPI Academy center, to maintain and develop it as a world premier international research center. Specifically, the University has continued to allocate additional tenure posts (succession posts) to IFReC at the discretion of the President. Furthermore, after the WPI support ended, a new industry-university collaboration scheme was implemented with strong support from the Co-Creation Bureau, a university-wide organization, and comprehensive collaboration contracts totaling over 10 billion yen were initiated with private companies over a 10-year period.

For PRIMe, looking ahead to the end of the support period, a virtuous cycle of co-creation with society, such as returning research results to society, will be realized, and support will be provided from the early stage to enhance the financial base through industry-academia co-creation. In addition to contracting procedures, the Co-Creation Bureau will provide strong support for the management of intellectual property licensing, joint research contracts with companies, and support for venture startups, which are necessary for this purpose, as well as for the training of human resources to handle such contracts. By taking advantage of industry-university co-creation, which is one of the strengths of the University, the new center and the existing center will be fully supported and sustained at the same time.

The University is committed to both providing sufficient support for the new center (PRIMe) and continuing to support the existing center (IFReC).

11) (For host institutions that already have an existing WPI center and/or Academy center) Take the initiative to spread the existing centers' good system reform results to other departments throughout the host institution and apply them to implementing the host institution's own reforms.

Osaka University has so far voluntarily and proactively spread the excellent results of IFReC throughout the University, leading to the transformation of the institution itself. Specifically, the globalization of education, improvement of the learning environment including campus life, promotion of international joint research through cross-appointments, enhancement of URA, promotion of commercialization of translational research through the medical, dental and pharmaceutical networks in Osaka, promotion of outreach activities, establishment of one-stop acceptance, dispatch and exchange support system, and improvement of multicultural and multilingual global campus environment. As well as IFReC, the University will spread the best practices of PRIMe voluntarily and proactively to the entire University, leading to the transformation of the institution itself.

World Premier International Research Center Initiative (WPI)

List of Principal Investigators

・If the number of principal investigators exceeds 10, add columns as appropriate.
・Place an asterisk(*) by the name of the investigators who are considered to be ranked among the world's top researchers.
・Give age as of 1 April 2022.
・For investigators who cannot participate in the center project from its beginning, indicate the time that their participation will start in the "Notes" column.
・If there are changes from the PI list in the first screening application documents, describe the points changed and reasons in the "Notes" column.
・Include principal investigators affiliated with satellite institutions. Give the name of their satellite institutions in the "Notes" column.
・Fill in the achievements of each PI in the "Biographical Sketch of Principal Investigators."

	Name	Age	Current affiliation (Department/ School/Institution)・Title	Specialization	Effort * (%)	Notes
1	Kohji Nishida*	59	Graduate School of Medicine/Osaka University・Professor	Stem cell biology, Regenerative medicine, Ophthalmology	90	Director
2	Takanori Takebe*	35	Center for Stem Cell and Organoid Research and Medicine/Cincinnati Children's Hospital Medical Center・Director for Commercial Innovation	Organoid medicine, Organ development, Regeneration	70	Deputy-Director
3	Mariko Okada*	59	Institute for Protein Research/Osaka Univeristy・Professor	Systems biology	45	Deputy-Director
4	Katsuhiko Hayashi*	50	Graduate School of Medicine/Osaka University・Professor	Reproductive genetics, Ovarian organoids	70	
5	Shigeru Miyagawa*	54	Graduate School of Medicine/Osaka University・Professor	Cardiovascular surgery, Regenerative medicine, Medical AI	80	
6	Noriyuki Tsumaki	57	Graduate School of Medicine/Osaka University・Professor	cartilage, Regenerative medicine	70	
7	Vivian Hwa*	63	Cincinnati Center for Growth Disorders/Cincinnati Children's Hospital Medical Center・ Basic Science Director	Growth deficiency disease, Genetics	90	
8	Sergiu P. Pasca*	40	Psychiatry and Behavioral Sciences/Stanford University Medical School・Associate Professor	Central nervous system disease, Organoids	20	
9	Yukinori Okada*	41	Graduate School of Medicine/Osaka University・Professor	Bioinformatics, Machine learning, Omics analysis	70	
10	Hajime Nagahara	48	Institute for Datability Science/Osaka Univerisity・Professor	Computer vision, machine learning	70	

11	Nozomu Yachie*	41	School of Biomedical Engineering (SBME)/The University of British Columbia・Associate Professor	Synthetic biology, Information science	20	
12	Takahiro Nemoto*	35	Graduate School of Informatics/Kyoto University・Assistant Professor	Data science, Algorithm development	90	
13	Ai Shinobu	40	Center for Biosystems Dynamics Research/Riken・Research Scientist	Molecular dynamics simulation	90	
14	Makoto Negoro*	39	Center for Quantum Information and Quantum Biology/Osaka University・Associate Professor	Magnetic resonance, Quantum computer	35	
15	Yoshie Harada*	62	Institute for Protein Research/Osaka Univeristy・Professor	Quantum sensing, Live imaging	70	
16	Atsuo Kishimoto	51	ELSI Center/Osaka University・Director	ELSI, Risk assessment	30	
17	Hideo Yokota	53	Center for Advanced Photonics/Riken・Team Leader	Image Processing	50	**Satellite** Riken/Advanced Photonics Center
18	Shingo Tsukada	56	NTT Bio-Medical Informatics Research Center/NTT Basic Research Laboratories・NTT Fellow	Bio-digital twin, Bio-Medical Informatics&ICT	20	**Satellite** NTT Bio-Medical Informatics Research Center
19	Kunio Kashino	54	NTT Bio-Medical Informatics Research Center/NTT Basic Research Laboratories・Senior Distingished Researcher	Bio-digital twin, Bio-Medical Informatics&ICT	20	**Satellite** NTT Bio-Medical Informatics Research Center [Joining as expertise for construction of the biodigital twin]

* Percentage of time that the principal investigator will devote to working for the center vis-à-vis his/her total working hours. (Activities carried out using competitive funding can be included as effort as long as they correspond to the purpose of the WPI center and are conducted for the center.)