World Premier International Research Center Initiative (WPI)
FY2022 WPI Project Progress Report

Host Institution	Osaka University	Host Institution Head	Shojiro Nishio
Research Center	Premium Research Institute for Human Metaverse Medicine		
Center Director	Kohji Nishida	Administrative Director	Takefumi Doi

Common instructions:
* Unless otherwise specified, prepare this report based on the current (31 March 2023) situation of your WPI center.
* So as to execute this fiscal year's follow-up review on the "last" center project plan, prepare this report based on it.
* Use yen (¥) when writing monetary amounts in the report. If an exchange rate is used to calculate the yen amount, give the rate.

- Prepare this report within 10-20 pages (excluding the appendices and including Summary of State of WPI Center Project Progress (within 2 pages)).
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Summary of State of WPI Center Project Progress (write within **2 pages**)

1. World-Leading Scientific Excellence and Recognition

Advancing Research of the Highest Global Level

Premium Research Institute for Human Metaverse Medicine (PRIMe) which was launched officially on November 11, 2022, with the appointment of Kohji Nishida as Director strives to create digital twins of humans that will replicate biological phenomena and pathological processes in human organs in cyberspace through the advanced integration of human organoid-based biomedical science and information and mathematical sciences.

To achieve PRIMe's goal described above, we have currently recruited outstanding 19 PIs to PRIMe, among them five female (26%) and two come from overseas (11%). Our final goal of researcher composition is six female and four overseas PIs. The PRIMe PIs have initiated their projects relevant to PRIMe's activities. Two papers were published in this initial period as follows, "Engraftment of allogeneic iPS cell-derived cartilage organoid in a primate model of articular cartilage defect" (*Nat. Commun.* 14, 804, 2023) (Tsumaki's group) and "Generation of functional oocytes from male mice in vitro" (*Nature* 615, 900-906, 2023) (Hayashi's group).

Generating Fused Disciplines

To enhance and advance the integration of organoid biomedical science and information and mathematical science, the first PI meeting was held in December 2022. As a result, four projects described below are particularly noteworthy in this initial period, highlighting disciplinary research opportunities and future general versatility.

1) Informatics pipelines aggregating PoP (Population Organoid Panel) and GWAS datasets. (Takebe and Nemoto)
2) High-resolution intracellular temperature measurements in oocyte. (Hayashi and Harada)
3) Measurement and visualization of human body vibrations in 3D space. (Tsukada, Kashino, and Cybermedia Center at Osaka Univ.)
4) Visualization of metabolic process in organoid with hyperpolarized NMR/MRI. (Negoro and Takebe)

PRIMe also provides opportunities for interdisciplinary exchange for young researchers. For example, we plan to create bottom-up joint research through monthly exchange meetings between young and senior researchers of all fields, a series of lectures beyond their expertise, and to have a retreat camp in September 2023.

2. Global Research Environment and System Reform

Realizing an International Research Environment

1. Establishment of PRIMe's research space

To achieve "under-one-roof", PRIMe set up new research building (a whole floor of 20,000 m^2) and

iPSC core facilities, and also renovated CoMIT and TA-AB buildings on Suita campus.
Moreover, PRIMe built an original collaboration system that provides a virtual under-one-roof environment connected by network regardless of limitations on meeting in person.

2. Establishment of worldwide researcher networking

PRIMe has appointed two distinguished overseas PIs (Hwa and Domínguez-Hüttinger). We are still making great efforts to search and hire early-career researchers with extraordinary abilities from overseas. For this purpose, we are creating easy-to-understand administration guidelines to fully support overseas PIs and will introduce original plan for recruitment (Diversity Enhancement Plan) to attract excellent researchers from all around the world.
Two overseas PIs will frequently visit PRIMe and perform their research at PRIMe. They also have close discussions with the Director and other PIs and their close cooperation with PRIMe substantially helps to raise the level of the center's international recognition.
PRIMe international satellites are set up at the University of British Columbia and National Autonomous University of Mexico. We also explore research in Human Metaverse Medicine, internationally in cooperation with additional four overseas research institutes: the Cincinnati Children's Hospital Medical Center, Stanford University, Systems Biology Ireland at University College Dublin, and Institut Curie. This cooperative framework can contribute to not only scientific interaction but also to recruitment of overseas researchers.
To further enhance the visibility of the center, PRIMe contributed to the Nature Index Japan special issue published on March 8, 2023, held the kick-off symposium on March 14, 2023 at Osaka in person and online, and started PRIMe's website in both English and Japanese from March 2023 to attract people all over the world.

Making Organizational Reforms

PRIMe is positioned in the International Advanced Research Institute, headed by the President of Osaka University. PRIMe is 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.
The center is managed and operated by the center director independently of other departments within Osaka University. The center director has the same authority as a department director regarding personnel affairs, such as recruitment of researchers and budget execution within PRIMe. Recruitment of Administrative and Research Support staffs were already completed and their roles were assigned to support foreign researchers and to create an environment where PIs can concentrate on their own researches.

3. Values for the Future

PRIMe is taking efforts to foster the next generation researchers with advanced expertise in "Human Metaverse Medicine" as well as bird's eye view of entire field. In preparation for establishing the degree program, we have determined a schedule to build the program step by step while addressing institutional issues in collaboration with the university administrative office. We are preparing to open the "Human Metaverse Medicine" subject (lecture series) in graduate school in October 2023 and launch Human Metaverse Medicine graduate course in April 2024. We are also working to create the Human Metaverse Medicine Ph.D. program (degree program) and double degree program in October 2025.
PRIMe identifies 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. Kishimoto, one of the PIs of PRIMe, is the working in this field.

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

1. World-Leading Scientific Excellence and Recognition

1-1. Advancing Research of the Highest Global Level

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

The Premium Research Institute for Human Metaverse Medicine (PRIMe) officially launched on November 11, 2022, with the appointment of Kohji Nishida as Director. PRIMe challenges to create digital twins of humans ["biodigital twins"] which will replicate biological phenomena and pathological processes in human organs in cyberspace. This section describes key research achievements in FY2022, and future direction of the PRIMe PIs, irrespective of their appointment dates.

Nishida's group has been working on elucidating the mechanisms of inherited dystrophy and age-related macular degeneration. The macula, being a crucial region in human visual function found in human retinal tissue, is a prime target for diseases that cause blindness, including inherited retinal diseases, age-related macular degeneration, and diabetic retinopathy. However, rodents such as mice, which are commonly used as experimental animals, lack the macula. To address this, they have been developing the world's first human macular organoid by utilizing their original technology, the ocular organoid (SEAM; *Nature*, 531, 376–380, 2016). As a result of this year, they successfully developed the first generation of macular organoids (patent pending 2023), confirming the existence of a CYP26A1-positive region specifically expressed in the macula and in reproducing the structure of retinal pigment epithelial cells lining the neural retina in a sheet-like form. Further studies will be conducted to develop macular organoids.

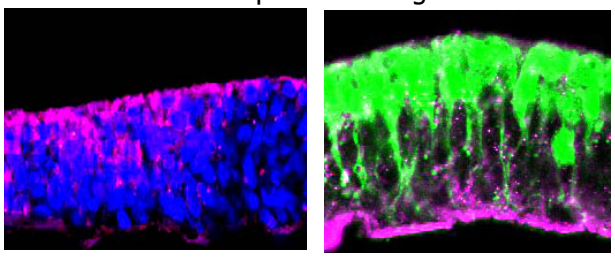


Figure 1. Immunofluorescence image of retinal organoid prepared by SEAM method. Confirmation of the presence of a macula-specific CYP26A1-positive region (left). Successfully reproduced the structure of retinal pigment epithelial cells lining the neural retina in sheet form (right).

Takebe's group has developed a new technology to create liver organoids from human stem cells at a population scale *(Cell,* 2022 App1:22). Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease and can develop into non-alcoholic steatohepatitis (NASH), which involves fat accumulation, damage, and inflammation in the liver. However, known genetic variants explain only a small fraction of the risk of developing NAFLD/NASH, and researchers disagree on the importance of certain mutations. Using a population organoid panel, the team conducted a genotype-phenotype associated study at the organoid level and resolved the puzzling role of genetics in NASH associated with type 2 diabetes. With NAFLD affecting nearly one billion people globally, early identification of patients who require different types of care may improve NASH prevention and treatment. Our research findings highlight the complexity of identifying genetic risk factors for disease in different contexts and the power of cutting-edge in vitro organoid models to assist in disentangling these factors. More broadly, this study represents one of the earliest applications of the novel population organoid creation technique to study the causes of human disease at the individual and population levels, paving a way for highly personalized metabolic digital twin applications in WPI program.

Hayashi's group has succeeded in the reconstitution of primordial germ cell (PGC) specification in various species, including mice, common marmosets, and endangered animals (as reported in *Sci. Adv.* 8: eabp9683. 2022 App1:11); *Sci. Rep*. 12:3100 2022 (App1:75); *Development* 149 2022 App1:87). The team has successfully recapitulated the gene expression profile and epigenetic reprogramming of these primordial germ cells in culture. By comparing the gene expression profiles

of species such as mice, rats, monkeys, humans, cows, and rhinoceroses, the group has identified a conserved gene expression program (shown in Fig. 2). These studies pave the way for understanding the molecular mechanisms underlying germ cell development in various species, including humans.

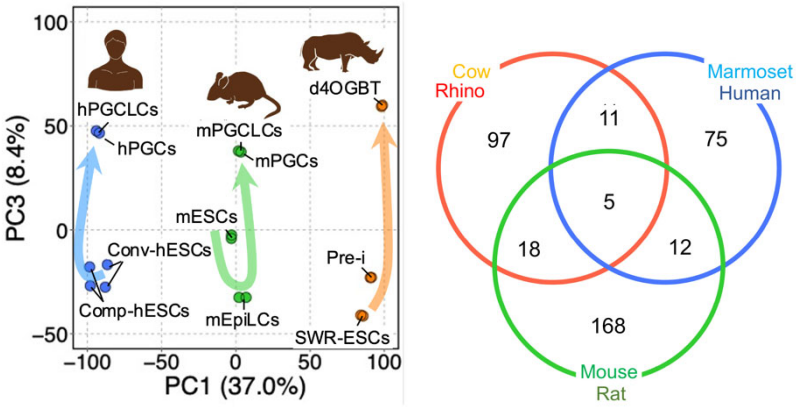


Figure 2. Reconstitution of primordial germ cell-like cell (PGCLC) development in various species. PGC differentiation process have a similarity among humans, mice, and rhinoceros (left). A set of genes conserved among various species are identified (right).

Additionally, Hayashi's group published a review article summarizing the reproductive organoid systems they have developed (published in *Curr. Opin. Genet. Dev.* 77:101982 2022 App1:102). The group has also successfully reconstituted the ovarian environment in mice, resulting in the production of fully potent oocytes. This discovery will serve as the basis for the construction of a human ovarian organoid.

Miyagawa's group previously published an article titled "Circulating Re-entrant Waves Promote Maturation of hiPSC-derived Cardiomyocytes in Self-organized Tissue Ring" (J. Li et al., *Communications Biology,* 2020). The study describes the development of a device that allows for the formation of three-dimensional self-organized tissue rings from iPSC-derived cardiomyocytes. Using calcium imaging, the researchers observed one or more traveling waves of action potential that originated spontaneously within the ring and ran robustly at a frequency of up to 4Hz. Subsequently, after two weeks, the tissue ring with these waves showed higher maturation, including improved structural organization, and increased cardiac-specific gene expression. This technology has the potential to be used for patient-derived disease model evaluation and drug screening purposes.

Tsumaki's group has published an article titled "Human iPS Cell-Derived Cartilaginous Tissue Spatially and Functionally Replaces Nucleus Pulposus" (*Biomaterials*, 284: p. 121491, 2022 App1:64). The objective of the study is to gain insights into the molecular mechanisms that regulate cartilage development and regeneration. Their study demonstrated that human iPS cell-derived cartilage cells

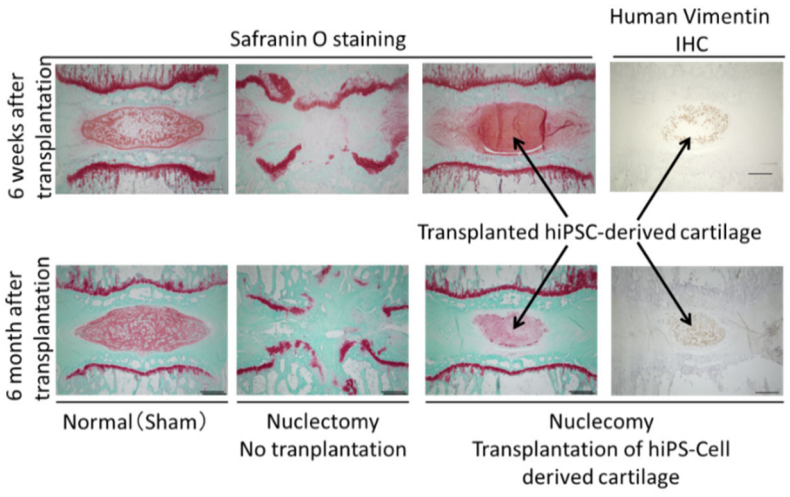


Figure 3. After removal of nucleus pulposus (nuclectomy) from an intervertebral disc of a nude-rat, human iPS cell-derived cartilage was transplanted into nuclecomized space. Transplanted sites were harvested and subjected to histological analysis 6 weeks or 6 months after transplantation.

have transcriptome profiles like those of the nucleus pulposus and that when transplanted, the iPS cell-derived cartilage regenerated the function of the nucleus pulposus. The transplanted iPS cell-derived cartilage was found to survive and prevent degeneration of the intervertebral disc (as illustrated in Fig. 3). These findings suggest that iPS cell-derived cartilage is functional in vivo and has the potential to be used for modeling not only joint diseases but also intervertebral disc diseases. This work is expected to contribute to the development of biodigital twins for cartilage diseases, where information collected from iPS cell-derived cartilage disease models can be applied.

Hwa's group, in collaboration with pulmonologists from Harvard and Cincinnati Children's Hospital Medical Center, has reported on a rare disease in the American Journal of Respiratory and Critical Care Medicine. The article, titled "Signal Transducer and Activator of Transcription 5B Deficiency-Associated Lung Disease," describes the clinical, radiological, and pathological manifestations, natural history, and therapy for lung disease in siblings with STAT5B deficiency (*J. Aller. Clin. Immunol,* 150, 931, 2022 App1:18). Using STAT5B deficient patient-derived induced pluripotent stem cells (iPSCs), differentiated to macrophage-like cells, they showed that the reduced STAT5 signaling response to GM-CSF correlates with a significantly impaired ability to clear surfactant. This indicates that the closely related functional STAT5A cannot compensate for the loss of STAT5B. These results recapitulated the clinical phenotype and highlighted not only the importance of STAT5B for GM-CSF actions in the lungs but also the potential explanation for the increased susceptibility to infections due to the vital role of GM-CSF signaling in host defense mediated by macrophages, neutrophils, natural killer cells, and T-helper cell type 17 cells.

Negoro's group has recently published an article titled "Prediction of 1H Singlet Relaxation via Intermolecular Dipolar Couplings Using the Molecular Dynamics Method" (*J. Phys. Chem. B* 126, 3530, 2022 App1:55). The spin relaxation time of hyperpolarized molecules is a key factor in various fields, including drug discovery and medical diagnosis. To extend the relaxation time, the quantum entangled state that is decoherence-free against dipolar relaxation between spin pairs has been studied both theoretically and experimentally. In this study, they used molecular dynamics and quantum chemistry simulations to predict the relaxation time of entangled states composed of proton spin pairs. The analysis considered intermolecular dipolar interactions between solvent and solute, chemical shift anisotropy, and spin-rotation interactions. The calculated values were of the same order of magnitude as experimental values. Their program provides valuable insights into the molecular design of various NMR applications, and in advance, they have reported the prediction of the nuclear spin relaxation time of synthetic molecules (DOI: 10.26434/chemrxiv-2022-tfkk1).

Harada's group previously demonstrated the robustness of fluorescent nano-diamonds (FNDs) as temperature sensors, capable of measuring temperature independently of intracellular pH, salt strength, viscosity, and molecular interactions. However, the effect of electron irradiation, required to introduce nitrogen vacancy centers into FNDs, on the coupling coefficient ($\Delta D/\Delta T$) of FND thermal measurements has not been investigated. This study revealed that excessive electron irradiation can influence the coupling coefficient, highlighting the necessity for caution when using the commonly used value of -70 kHz/°C for temperature measurements. In parallel, the group developed a highly dispersive FND that emits ODMR signals with an average particle size of 26 nm, enabling measurement of micro-regions at the organelle level in the future.

M. Okada's group has developed a computational framework called Pasmopy (Patient-Specific Modeling in Python), which has been published in the following papers (Imoto et al., *iScience* 2022, App1:83), STAR Protocols, 2022, App1:94). Patient heterogeneity brings about a challenge to cancer treatment and drug development, making it essential to develop methods for finding prognostic markers for individualized treatment. Pasmopy is a tool that can be used to stratify patients using in silico signaling dynamics. It also has a function to convert texts and sentences on biochemical systems into an executable mathematical model for any modeling purposes. Using this framework, the group built a model of a signaling network and performed in silico simulations of 377 breast

cancer patients using clinical transcriptome datasets. The temporal dynamics of kinases in each patient accurately predicted differences in prognosis and sensitivity to kinase inhibitors in triple-negative breast cancer (TNBC). Since its publication, the Pasmopy package has been downloaded 20,000 times as of March 2023.

Y. Okada's group has recently published a paper in the journal Nature on a large-scale genome-wide association analysis of human height in a multi-ancestral population of around 5.4 million individuals worldwide. The research was conducted through the GIANT Consortium, an international collaborative research group aiming to elucidate the genetic basis of individual variations in physical traits such as height and obesity (Yengo et al., *Nature* 2022, App1:101). The GIANT Consortium comprises genome cohorts from around the world, such as Biobank Japan in Japan and UK Biobank in the UK. This study is the largest genome-wide association analysis conducted to date, and the results revealed approximately 12,000 susceptibility gene regions that are associated with individual differences in height. According to the report, the current sample size of the study is almost sufficient to fully explain the genetic backgrounds of height.

Nagahara's group has published an article titled "Match them up: visually explainable few-shot image classification" *(Applied Intelligence,* pp. 1573-7497, 2022, App1:97), describing a visually explainable few-shot image classification method addressing the black-box nature of neural networks used in few-shot learning (FSL). FSL is an approach that transfers pre-trained knowledge from base classes to novel classes for image classification, though it is challenging to understand what is being transferred due to the black-box nature of neural networks. The proposed method utilizes a visual representation from the backbone model and patterns generated by a self-attention based explainable module. The representation, which is weighted by patterns, includes only a minimum number of distinguishable features, and the visualized patterns serve as an informative hint on the transferred knowledge. The results of experiments on three mainstream datasets prove that the proposed method enables satisfying explainability and achieves high classification results.

Yachie's group has published a paper entitled "Molecular recorders to track cellular events" (*Science*, 377, 469-470, 2022, App1:42) and outlined the key issues and perspectives in the field of DNA event recording and cell lineage tracing (Fig. 4). For the cell lineage tracing, the team has also recently developed a new deep distributed computing platform FRACTAL and succeeded in a precise lineage reconstruction of over 200 million mutated sequences generated by a simulator (*Nature*

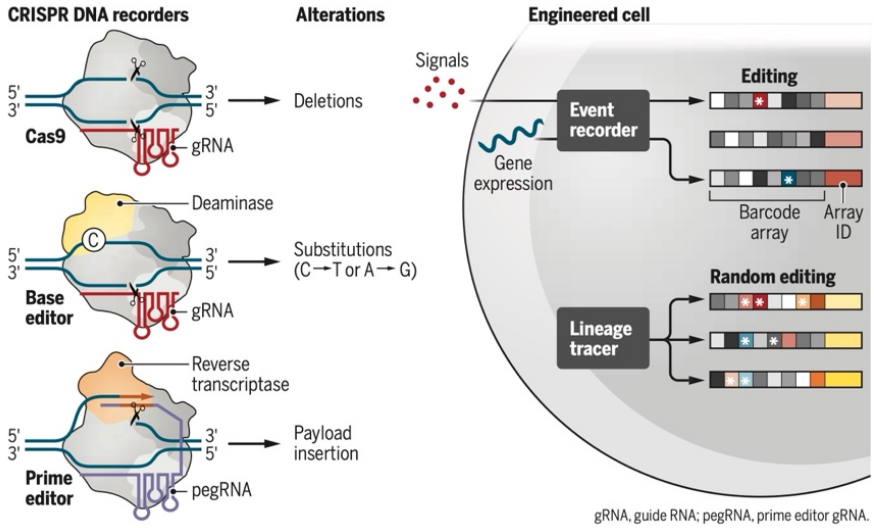


Figure 4. DNA Event Recording. Cell-embedded synthetic CRISPR-Cas information-writing enzymes can progressively record cellular events and lineage transitions into DNA tapes (or barcode arrays) by introducing various types of DNA alteration. DNA tapes are read out by single-cell sequencing, and the biological event histories are computationally reconstructed. Cell lineage can be recorded by continuous accumulation of random mutations into DNA tapes. Other event recording systems necessitate editing event-specific DNA tape positions or inserting specific DNA payloads into the DNA tape.

Biotechnology, 40, 566–575, 2022, App1:72). This work was featured on the cover of *Nature Biotechnology.* Yachie's group has also recently established a new semantic framework, QUEEN, to efficiently share reproducible DNA materials and construction protocols in the broad of life sciences community (*Nature Communications*, 13, 2894, 2022). Furthermore, another software platform, INTERSTELLAR, has been established by the team to interpret and translate high-throughput sequencing read structures to accelerate the development of new sequencing-based assays (*Science Advances*, 9, add2793, 2023). This work was also featured on the cover of *Science Advances*.

Nemoto's group has published an article titled "Reconstructing long-term dengue virus immunity in French Polynesia" in PLOS Neglected Tropical Diseases (16.10: e0010367, 2022, App1:19). Dengue viruses have four different serotypes, that can cause antibody-dependent enhancement. This means that if someone is infected twice with different serotypes, the antibodies from the first infection can facilitate the entry of the second virus into cells, causing severe symptoms. It is therefore important to estimate the percentage of the population that has already been infected once to anticipate how many of them may develop severe dengue. However, obtaining this number is not easy since patients with primary infections are less likely to be registered by surveillance systems due to their mild symptoms. To resolve this issue, Nemoto's group developed an algorithm that uses an age-stratified sero-catalytic model under the Bayesian inference framework to infer the number of unreported patients. A similar mathematical technique could be valuable in the analysis of age-structured data for constructing pipelines in bio-digital twins at PRIMe.

Shinobu's group has published a paper titled "Practical Protocols for Efficient Sampling of Kinase-Inhibitor Binding Pathways using Two-Dimensional Replica-Exchange Molecular Dynamics" (Frontiers in Molecular Biosciences 9, 2022 (App1:70)). The team focused on understanding the molecular mechanisms of drug molecules binding to their target proteins, a crucial aspect of designing new drugs. In this study, the team performed large-scale molecular dynamics simulations on the supercomputer Fugaku to simulate the binding of inhibitors (PP1, dasatinib, and imatinib) to the protein c-Src kinase. They simulated 240 replicas in parallel using a replica-exchange method, allowing the crossing of high-energy barriers. After carefully tuning the simulation parameters, the research team obtained a good sampling of the binding landscape. For two of the inhibitors (PP1 and dasatinib), they collected a total of 600 μs of simulation data from which they identified the binding pathway and multiple states along it. additionally, they analyzed the conformational dynamics of the inhibitors and found that the larger inhibitor (dasatinib) adopts bent conformations, which play a role during the binding process. These findings can be applied to establish a connection between a drug candidate's shape and binding mode, which can be used as a parameter for drug screening.

Yokota's group has been developing an image processing infrastructure for 3D image analysis of organoids. As the acquired images contain time-series 3D information, they have begun designing the extension of the image processing framework. In addition, they are designing the framework to be able to adapt to large-scale datasets. The team is also upgrading RICS, a spatio-temporal simulator of intracellular phenomena that was originally developed for the supercomputer K computer.

Domínguez-Hüttinger's group has constructed and analyzed mathematical models to understand the mechanisms and optimize treatment strategies for maintaining and recovering epithelial homeostasis. The research team integrates clinical and experimental data into bottom-up, mechanistic, and quantitative models encoded as coupled non-linear dynamical systems. Their mathematical models encompass different timescales simultaneously, allowing them to reproduce gradual pathogenic transitions as emerging properties of the dynamical coupling between biochemical-level regulatory networks and micro-environmental differentiations.

Tsukada's group has developed an analytical method called Tensor Electro Cardiography (TCG) that models the relation of ECG and collective myocardial action potential (AP) as the difference of cumulative density functions (CDFs). This method is used to estimate the variance of AP from the ECG, as myocardial AP and their variances are crucial information for understanding the state of ion channels directly related to cardiac pacing and contraction. At WPI PRIME, the research team is advancing research on applying TCG to estimate various pathological states of heart failure (HF) from ECG data. The ECG dataset of HF was simulated by modulating the function of INa, IK, ICa, and NCX, which are known as the major factors of HF, using cardiac simulation by finite element method. The group analyzed the ECG datasets of simulated combinations of the conditions using TCG. As a result, nonspecific ECG strains caused by the factor modulation were detected in specific metrics changes of TCG. The TCG analysis of ECG using the variance of collected AP transition is expected to be a new strategy for estimating cardiac pathophysiology in the bio-digital twin of the heart.

Kashino's group at NTT has been making quick progress with the administrative preparations to start full-scale research at PRIMe. They have assembled a team of five researchers, including two notable machine learning experts - Tomoharu Iwata, Senior Distinguished Researcher, and Masahiro Nakano, Distinguished Researcher at NTT. Additionally, the team consists of an expert in model estimation (Ryohei Shibue) and an expert in information transformation (Ryo Nishikimi).

Kishimoto's group has conducted a preliminary literature review of the ethical, legal, and social issues (ELSI) related to the Human Metaverse Medicine project. The review focused on two main areas: ELSIs in human organoid-based biomedical science and ELSIs in information and mathematical sciences. The former included issues such as informed consent and privacy of cell donors, the moral and legal status of organoids, the potential acquisition of human "characteristics or qualities," and potential misuse and dual-use issues. The latter included issues such as the treatment of patient privacy, ownership of personal data, accountability and transparency of algorithms, conceptual shifts in the distinction between health and disease, and the right not to know about unfavorable predictions. The group developed a methodology for identifying and addressing ELSIs, as shown in the figure below.

1-2. Generating Fused Disciplines

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

To accelerate interdisciplinary fusion research, the kick-off PI meeting was held on December 22nd, 2022, with both in-person and virtual attendance to promote collaborative research. After a fruitful discussion, a networking session was held by the onsite participants, which provided a great opportunity to meet in person and deepen exchanges. As a result,

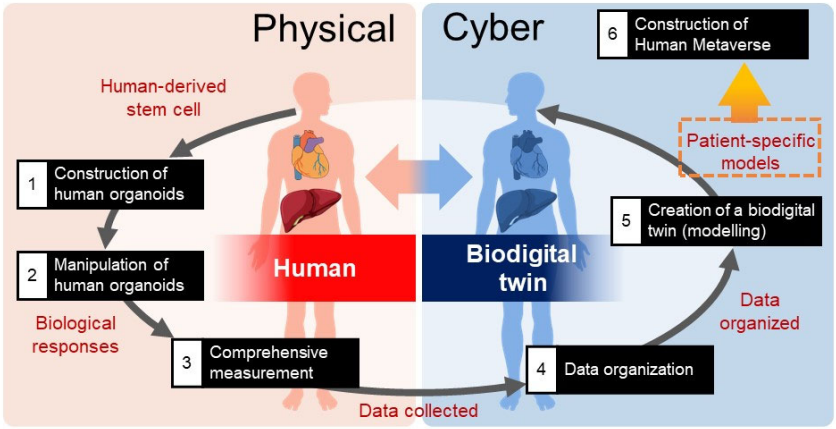


Figure 5. Research scheme for creating biodigital twins and Human metaverse.

interdisciplinary research projects have been initiated, which are described below.
To facilitate communication and collaboration, a Slack workspace was introduced in January 2023. This platform has enabled PRIMe PIs, research staff, and URAs to interact and exchange ideas using text, chat, and document sharing tools, among others. Using current online tools, PRIMe members can engage in continuous discussion and collaboration, regardless of place.
We are also planning for in-person events such as PRIMe Seminar Series, Happy Hour, and a retreat to spend a couple of days outside the campus, during which we expect further mutual exchange.

Figure 5 shows the steps involved in constructing a biodigital twin from human-derived stem cells. Each step requires interdisciplinary joint research, such as creating banks of organoids from human-derived barcoded iPS cells (1), manipulating organoids (2), and measuring their biological responses at high spatio-temporal resolution using advanced measurement techniques (3). Through data organization and analysis, biological models will be created (4&5), followed by the development of a visualization process for creating a metaverse platform (6).
Thus far, collaborations between PRIMe members have been initiated as follows:

■ **Informatics pipelines aggregating PoP and GWAS datasets** (Takebe and Nemoto)
This collaborative unit is related to the process in 1,2,3 and 4 in Fig. 5
A collaboration between the Takebe and Nemoto groups will explore the best informatics pipeline to harness massively mosaic donors-derived organoid phenotype data with available and relevant Genome Wide Associations Studies (GWAS) datasets. The NAFLD study will be the first application of fusion research under PRIMe. The groups have already shared the data and begun their analysis. Modern diseases, such as Type 2 diabetes and non-alcoholic fatty liver disease (NAFLD), can be triggered not only by genetic factors but also by environmental ones such as an unhealthy diet and a sedentary lifestyle. These environmental factors are difficult to control and quantify, making GWAS more challenging. Human organoids are considered as models that allow the study of genotype-phenotype associations under a controlled environment without major confounding factors. The Takebe and Hwa groups in PRIMe devised a pooled human population organoid panel (PoP) with multiple liver organoids from various donors (refer to Fig.6). By exposing PoP to a controlled fatty

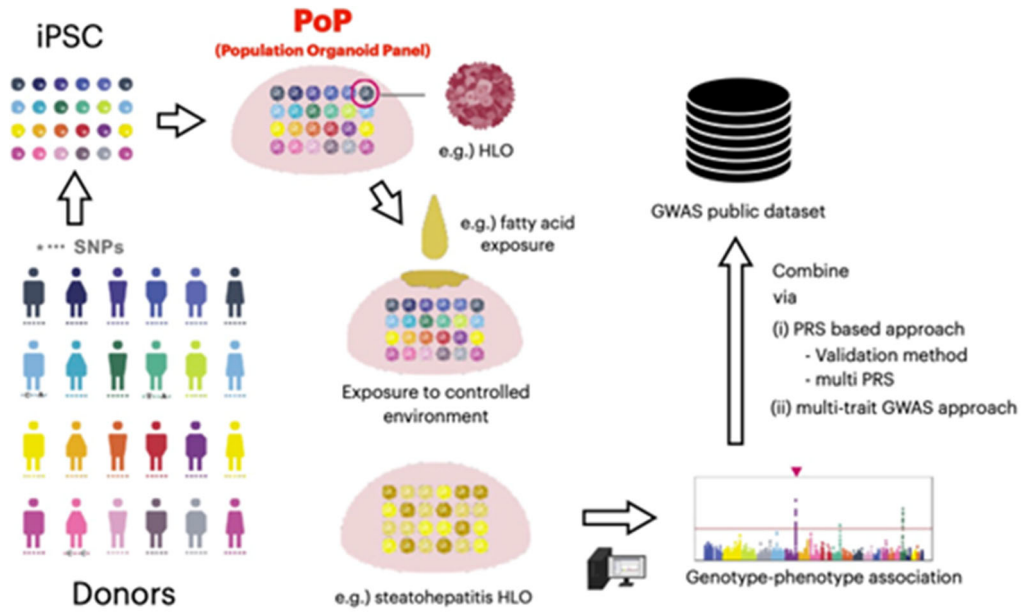


Figure 6. Population organoid panel (PoP) exposed to a control environment (Kimura et al., Cell, 2022). Obtained data is combined with GWAS public dataset using a variety of algorithms.

cid environment and hyperinsulinemic conditions, steatohepatitis-like pathologies were induced into the PoP. This enabled efficient evaluation of NAFLD related genotype-phenotype association studies, successfully disentangling the opposing roles of the glucokinase regulatory protein (GCKR) SNP on

non-alcoholic steatohepatitis (NASH) (Kimura et al., *Cell,* 2022, App1:22).
To generate and analyze diverse PoP type datasets at PRIMe, a possible obstacle involves modest donor sample sizes. This is because, compared with standard GWAS, increasing the sample size requires the time- and cost-prohibitive process of making human induced pluripotent stem cells (iPSC) and organoids from each participant of the study. This problem will naturally resolve itself in the course of time as PRIMe prepares systematic pipelines for creating larger PoP datasets. However, we could tackle this issue in a faster and more efficient way from an informatics/mathematical perspective by combining the PoP data with currently available GWAS/patient datasets. As more PoP data with varying sample sizes becomes available, we will gradually shift towards relying more on PoP data, while continuing to use the same informatics pipelines with only minor modifications.

- **High-resolution intracellular temperature measurements in oocyte** (Hayashi and Harada)

This collaborative unit is related to the process in 2,3 in Fig. 5
PRIMe will develop and apply cutting-edge technologies in human organoids derived from healthy and diseased patients of various organs. We have been applying this to the oocyte organoid for the first place.
Harada and Hayashi's group collaborated in obtaining metabolic and physiological data using oocytes, specifically, focused on temperature measurement at subcellular level. High-resolution intracellular temperature measurements have revealed that temperature changes are the driving force behind important biological phenomena such as stress responses, cellular divisions, and cellular differentiation. Mammalian oocytes are formed during the fetal period and are stored as dormant oocytes in the ovary for years or decades. While a small number of dormant oocytes are activated per month to initiate oocyte growth for ovulation, the mechanisms underlying it remain elusive. We hypothesize that the change of intracellular temperature triggers activation in dormant oocytes. By combining the expertise of the Harada's group in mapping high-resolution intracellular temperature with the Hayashi's group being a world leader in female germ cell research, we aim to identify the thermal signaling that induces activation of dormant oocytes in mammalian ovaries. This is a world-leading study that combines the cutting-edge technology of intracellular temperature mapping in the Harada Lab with the manipulating skills and in-depth knowledge of the mammalian female germ cells in the Hayashi Lab.
Initially, the possibility of mapping intracellular temperature in oocytes was investigated using

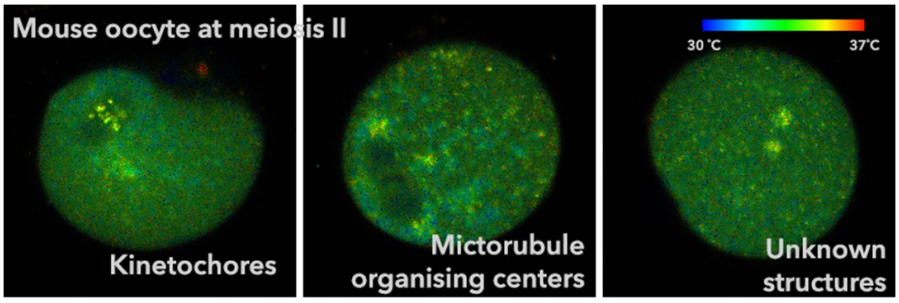


Figure 7. Temperature distribution in mouse mature oocytes. The regions close to kinetochores (left), microtubule organizing centers (middle) and unknown structures were warmer than cytoplasm.

mature mouse eggs, fluorescent polymeric thermometer (FPT) and fluorescence lifetime imaging microscopy (FLIM). By microinjection of FPT to mouse mature oocytes, we successfully observed the temperature gap between kinetochores/microtubule organizing centers/unknown structures and cytoplasm in mouse oocytes, demonstrating the feasibility of intracellular thermometry using mouse oocytes. Based on recent promising results, we are planning to induce *in vitro* activation of dormant oocytes microinjected with FPT while observing them with FLIM to investigate how temperature changes in the oocyte are related to the activation from dormancy.

- **Visualization of metabolic process in organoid with hyperpolarized NMR/MRI.** (Negoro and Takebe)

This collaborative unit is related to the process in 2,3, and 4 in Fig. 5

Hyperpolarized NMR/MRI can extract a wealth of information at the quantum mechanical level, including structural information of molecules, intermolecular interactions, and reaction intermediates, making it useful for deep inside the human body. Therefore, the same principle of measurement can be used to compare the metabolism of mice, human body, proteins, cells, and organoids. By comparing the metabolic measurements of organoids, we will be able to gain a better understanding of the inside of the human body at the quantum mechanical level.

Negoro's group has demonstrated metabolic processes of LDH (Lactate DeHydrogenase) in vitro using novel hyperpolarized NMR. With collaboration with Takebe's group, they will achieve hyperpolarized NMR of metabolic processes in organoids derived from healthy and diseased patients, and implanted organoids in mice in vivo. This method can be expanded to other samples and organoids to measure and compare metabolic processes among various environmental conditions. Furthermore, the metabolism measured in vivo will be visualized for the basis of metaverse platform.

- **Measurement and visualization of human body vibrations in 3D space** (Tsukada, Kashino and Cybermedia Center at Osaka University)

This collaborative unit is related to the process in 6 in Fig. 5

Among the human metaverse disease studies that encompass a broad range of concepts, our group is particularly responsible for information processing aspects for the construction and visualization of biodigital twins. One of the fundamental questions we aim to answer is what kind of "space" would be valuable and useful to create as a metaverse in the first place. To answer this question, it is essential to consider it not only on paper but while creating prototype environments that actually appeal to the five senses. Recognizing this, our group, in collaboration with the Cybermedia Center of Osaka University (hereafter CMC), attempted to visualize a 3D model, using heart function as an example. During initial stages of experimentation, we captured chest sounds on the body's surface using a specially designed hand-held device, called a telestethoscope. It can capture four channels of audio signals and an ECG signal simultaneously in a synchronous manner. Based on those signals, an estimation algorithm (developed by NTT) inversely estimates the vibration at an arbitrary point on the three-dimensional lattice within the body, in a region near the heart. A program (developed by CMC) then visualizes the vibrations. The user can change the viewpoint and zoom in and out. In the near future, the user will even be able to hear the vibrations at each grid point as sound.

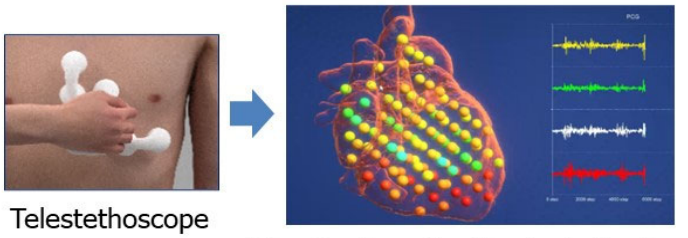


Figure 8. 3D visualization of biological data from human heart.

Visualizing vibrations in 3D space is crucial in practice because heart disorders, such as heart failure, often manifest as heart murmurs at an early stage. We plan to develop a general-purpose architecture that connects various computational models and visualization techniques. This is a significant step towards building a human metaverse that can enhance biological and medical research as well as medical practice.

2. Global Research Environment and System Reform

2-1. Realizing an International Research Environment

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

Currently, 19 PRIMe PIs are located in different places in Suita or Toyonaka campuses of Osaka University (Figure 9 and Appendix 3-1 Campus Map). To achieve the "under-one-roof" environment and strengthen the "international research network", following measures have been taken in this period.

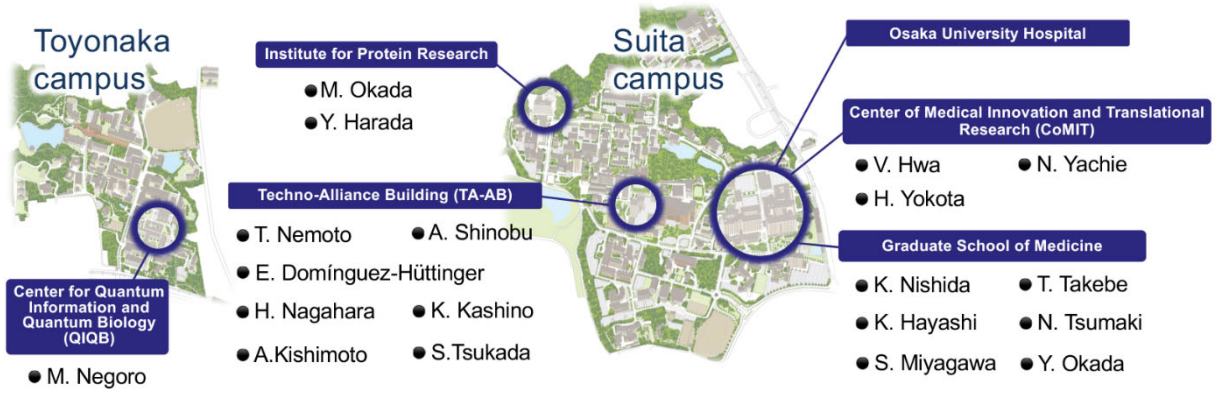


Figure 9. Location of PRIMe PIs on Osaka University

1. Establishment of PRIMe's research space

1) Setting up PRIMe's main building

A whole floor of 20,000 m^2 in a new, state-of-the-art research building on Suita Campus will house PRIMe in 2026. The new facility will provide a fully outfitted research environment in which all the PIs will conduct fusion researches under-one-roof. The building will include an open collaborative space where center members can interact, discuss, and meet new people in a relaxed atmosphere. The facility will be attuned to the needs of male and female researchers who are carrying out research and raising children at the same time. It will also support the development of well-accomplished researchers who will lead the next generation. In addition, to increase efficiency during this setting-up-period of PRIMe's main building, PRIMe built an original collaboration system that provides a virtual under-one-roof environment connected by network regardless of limitations on meeting in person (slack, zoom, etc. see also 1-2).

2) Renovation of CoMIT building

To enable PRIMe members to work in the same place, we firstly renovated the 3rd Floor of Center of Medical Innovation and Translational Research (CoMIT) building on the Suita Campus. The location of the CoMIT building conveniently allows quick access to most research spaces related to PRIMe such as Osaka University Hospital, which will be a source of cells for organoid construction and patient data and Graduate School of Medicine, which will connect the real world to biodigital twin information world using mathematical modeling. This 3rd Floor will be used as laboratory spaces of PIs (Hwa and Yachie), Jr. PI (Mori), and Guest professor (Yokota), an interaction space seminar room which is especially designed for active interaction among researchers, meeting spaces, and the offices for administrative team (Research Planning and Management) and the Director. By having all members and teams working on the same floor, it helps to facilitate work flow and team chemistry of PRIMe (Figure 10).

3) Renovation of Techno-Alliance building

Moreover, we create another temporary scientific cohort space on the 5th Floor (rental space) of Techno-Alliance Building (TA-AB) which is located close to CoMIT building. This floor will be used as

laboratory spaces of PIs (Shinobu, Nemoto, and Domínguez-Hüttinger) and Guest professors (Kashino and Tsukada), and seminar/meeting rooms to establish an active interdisciplinary exchange with CoMIT team (Figure 11).

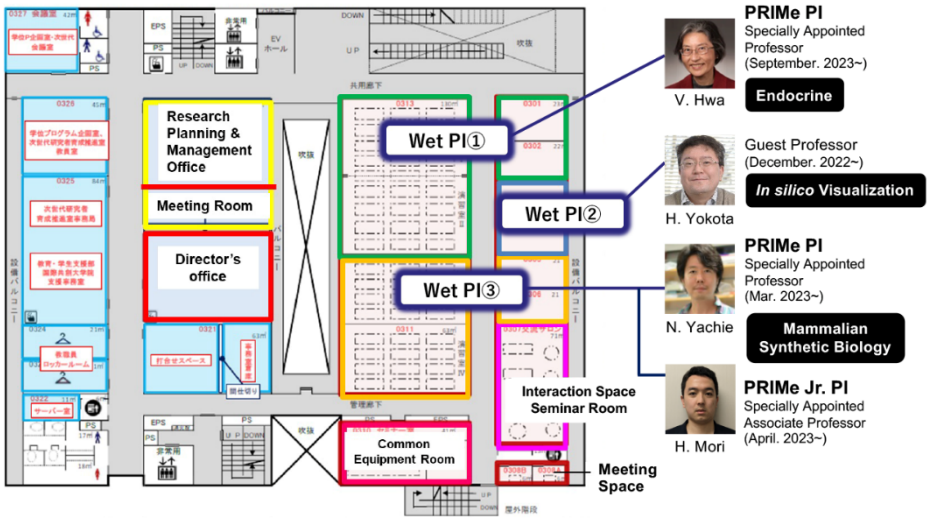


Figure 10. 3rd Floor of CoMIT building

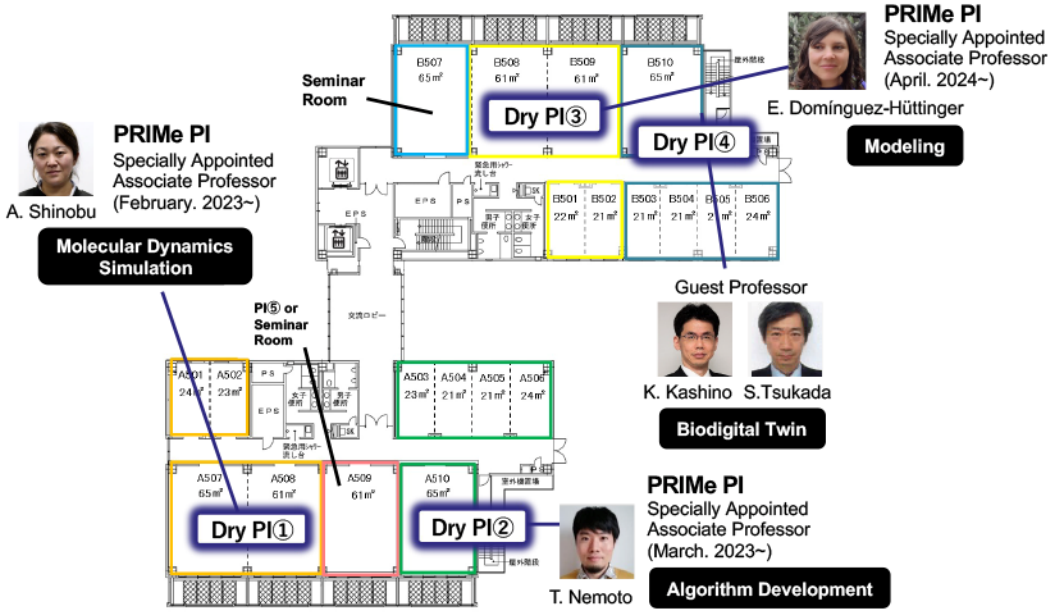


Figure 11. 5th Floor of TA-AB building

4) Setting up iPSC core facility in the Graduate School of Medicine

To establish, maintain, and store human iPS cells, PRIMe plans to implement special iPSC core facility including common equipment units in the Graduate School of Medicine of Suita Campus. We have secured enough space (about 400 m^2) and have already selected and purchased several equipment and apparatuses for this facility.

2. Establishment of worldwide researcher networking

To enhance the research activities and expand international networking of the center, we have hired two distinguished overseas PIs (Hwa and Domínguez-Hüttinger). For a smooth startup of their researches at PRIMe, we provide sufficient research space (about 500 m^2), start-up funding (up to 50 million JPY), and budget support for personnel costs (one or two associate/assistant professor and/or postdoctoral fellow) for each individual overseas PI. To efficiently support foreign researchers, the administrative staffing comprises bilingual employees. Paperwork, e-mail exchanges, and other

international communications are performed in both English and Japanese.
At this moment, PRIMe has recruited 19 PIs, among them five are female (26%) and two come from overseas (11%). Because our final goal of PI composition aims at six female and four overseas researchers, we are continuing making great efforts to find and hire early-career researchers with extraordinary abilities from overseas. To attract excellent researchers from all around the world, PRIMe will implement an original plan for recruitment (Diversity Enhancement Plan). For example, 1) When PRIMe hires extraordinarily talented researchers, it will also take care of the employment of their spouses. 2) Female and overseas researchers have priority access to day-care centers or receive subsidies for babysitting. 3) PRIMe allows PIs to conduct research at convenient locations (satellite sites), and so on. PRIMe international satellite sites are also able to contribute to the recruitment of overseas researchers. As a result, PRIMe plans to recruit two foreign researchers (Shakiba and Schiebinger) from University of British Columbia.
In addition, for recruitment of foreign researchers in a timely way, we offered well-rounded package that considers both the research environment and living quality and needs, in addition to the regular treatment of individual researchers. In fact, it is difficult for foreign PIs to understand the University's recruitment procedures or to start their own research groups in Japan, even if those procedures are written in English. Also, foreign researchers have troubles in getting used to lives in Japan and logistic works in laboratory (e.g., ordering procedure). To effectively resolve these issues, we will hire several special bilingual secretaries for foreign PIs to minimalize the problems.
Two overseas PIs (Hwa and Domínguez-Hüttinger) will frequently visit PRIMe and have close discussions with the Director and other PIs and will attend to Center Steering Committee of PRIMe via zoom every two months. Their close relationship with PRIMe substantially helps to raise the level of the center's international recognition. To further enhance the visibility of the center, PRIMe implemented the following activities in this initial period (see 3-1 and Appendix 6 in detail).

1) PRIMe contributed to the Nature Index Japan special issue published on March 8, 2023, focused on the research strength of Japan, rising research stars in Japan, and latest research projects running in Japan.
2) PRIMe held the kick-off symposium on March 14, 2023 in Osaka in person and online.
3) PRIMe recently started its own Website from March 2023 written in both English and Japanese. The website will attract more and more people from all over the world.

2-2. Making Organizational Reforms

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

Decision-making mechanism/research support departments at PRIMe

In the first place, we try to reform the system based on seniority and create a culture for senior researchers and postdocs/students to productively exchange scientific information and ideas in an open, transparent and equal environment.
Next, to strengthen governance in PRIMe, the Center is managed and operated by the Center Director independently of other departments within Osaka University. The Center Director has the same authority as a department director regarding personnel affairs, such as recruitment of researchers and budget execution within PRIMe. Excellent administrative staff can provide strong management support to the Center Director, to enable the Center Director's research activities to proceed smoothly.
The 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. We will establish an External Evaluation Committee consist of prominent researchers from Japan and overseas, as well as individuals in business and other fields, to evaluate the progress of PRIMe. Based on these reports, 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 every two months. If the report shows problems, Center Director will assume full responsibility and take actions to solve the problem, along with the Center Steering Committee.
Under the Center Director and the Administrative Director of PRIMe, excellent bilingual staff has been providing strong administrative support to foreign researchers in general matters, accounting, and other logistic works. Recruitment of six administrative (management) and eight research support (URAs who have research experience and doctorate degrees) staffs was completed and their roles were assigned to support foreign researchers and to create an environment where PIs can concentrate on their own researches. The executive Board of Osaka University as well as university-wide URAs will also support PRIMe management (Figure 12 and Appendix 3-1 in detail). This strong support will enable foreign researchers to obtain external funds without much more difficulties, compared to Japanese researchers.

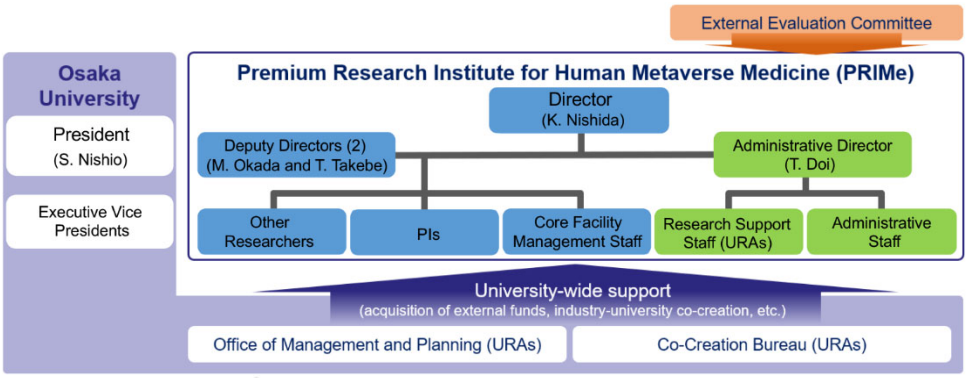


Figure 12. Center Management/Support System

Host institution's commitment to the system reforms
Osaka University will provide full support to PRIMe to implement various systemic reforms that are necessary for its development. 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, another new organization will be considered to realize the mission of PRIMe by reorganizing the existing organizations within Osaka University.

3. Values for the Future

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

* Describe the content of measures taken by the center to widely disseminate the results of its basic research to the general public.
* Describe what was accomplished in the center's outreach and other activities last year and how they have contributed to creating the Societal Value of Basic Research. In Appendix 6, describe concretely the contents of these outreach activities. In Appendix 7, describe media reports or coverage, if any, of the activities.

Since the inauguration announcement at the press conference on October 14th, 2022, **PRIMe has promoted its presence by several approaches** (for details, see Appendix 6). At first, we created the promotional film, viewed over 3,400 times in total in 6.5 months. Secondly, we launched the PRIMe website to widely promote the Center this March; we will improve this website in FY2023 and settle it as the hub of enhancing our Center's presence. Third, we published a Japanese pamphlet to increase PRIMe's recognition.
Further, in order to realize and expand the societal value of PRIMe, we contributed an article to **the Nature Index Japan special issue** published on March 8, 2023. In this article, Director Nishida clarified the purpose and vision of PRIMe in the advertising feature section of the magazine.
To demonstrate our efforts in creating societal values, we also would like to refer to **the PRIMe**

Kick-off Symposium, held on March 14, 2023. This event was attended and viewed by approximately 580 people (130 on-site and 450 on the web) from all over the world.
In addition, for young researchers, we co-hosted the **Joint Lab Tour** with WPI-IFReC (Osaka University). This tour, organized annually by the University of Tokyo, Kyoto University, Nagoya University and Osaka University, provides opportunities to first to third grades medical students to visit outstanding research institutes settled in the host university, and to build networks with other university students.
In addition to raising its presence in domestic and international societies, PRIMe identifies **ethical, legal, and social issues (ELSI)** relevant to its work and respond to them in parallel with our research and development in science and technology. Kishimoto, one of the PIs of PRIMe, is working in this field.

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

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

PRIMe is taking efforts to foster the next generation researchers with advanced expertise in "Human Metaverse Medicine" as well as a bird's-eye view of the entire field. In addition, it is necessary to build the foundation of ”Human Metaverse Medicine" to create broader impacts in various academic fields and to develop interdisciplinary collaboration. To this end, we have created the following educational programs.

Collaborative department of the Graduate School

PRIMe has completed the internal procedures necessary to participate as a collaborative department in the Graduate School of Medicine, Osaka University, starting April 1, 2023. As a result, faculty members belonging to PRIMe will be able to accept, supervise, and examine graduate students from April 1, 2023.

Ph.D. programs

In preparation for establishing the degree program, we have determined a schedule to build the program step by step while addressing center issues in collaboration with the university administrative office (Figure 12). We are preparing to open the "Human Metaverse Medicine" subject (lecture series) in graduate school (2 credits) in October 2023 and launch Human Metaverse Medicine graduate course (> 6 credits) in April 2024. We are also working to create the Human Metaverse Medicine Ph.D. program (degree program) and double degree program in October 2025. Currently, we have started creating the lecture series to be offered from October 2023, and the syllabuses will also cover cyber, physical, ethical, and social perspectives. Further, we plan to open the lecture series to graduate students and young researchers outside the Center, including graduate students of the World-leading Innovative & Smart Education program (WISE) and Leading Graduate programs.

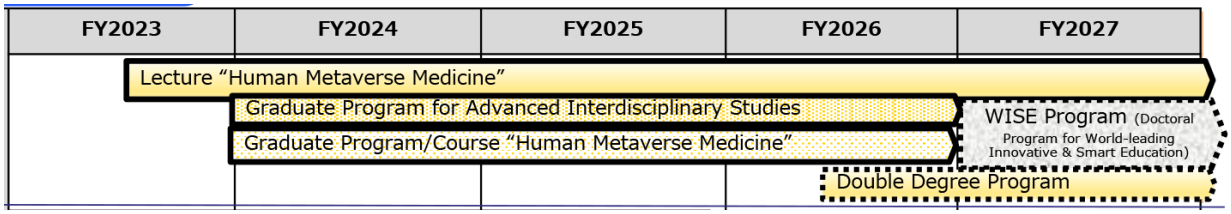


Figure 13. Time schedule of establishing the degree program

Seminar series

We have planned the Interdisciplinary Human Metaverse Medicine seminars and webinars for 2023 fiscal year. They will also be open to graduate students and young researchers outside the Center.

Postdoctoral training
We have designed and created postdoctoral and advanced postdoctoral programs to train young researchers for PRIMe. Funding basis will be guaranteed in collaboration with the Support for Pioneering Research Initiated by the Next Generation (SPRING) program of Osaka University.

Students, young researchers, PI gathering
We have planned to hold regular informal meetings to facilitate students, young researchers, and PIs to communicate and exchange ideas and experience, which will be helpful for young researchers to take advantage of the interdisciplinary research environment at PRIMe.

3-3. Self-sufficient and Sustainable Center Development

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

In present, as stated in the "OU Master Plan 2027", the University's mid-to-long-term management vision, as the world's most innovative university aiming to create "a society where each member leads a meaningful and fulfilling life", Osaka University is currently developing the OU (Osaka University) Ecosystem, which embodies a systematic co-creation with society to solve social issues. The world that PRIMe aims to create, "a world where all diseases are overcome and everyone can live a long and healthy life," concurs with "a society where each member leads a meaningful and fulfilling life".
PRIMe was established as the World Premier International Research Center to foster the university's mid-term goals, mid-term plan, and the OU Master Plan 2027. 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.

Facility Support
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") (bond 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 located. These funds will also be used to provide an environment where Center's researchers can gather to carry out research activities under-one-roof, and to secure sufficient space for the steady implementation of research activities at this Center. In the interim, Osaka University has secured approximately 1,500 m^2 of space in the Graduate School of Medicine for the researchers from outside the host institution, who will arrive immediately after the designation of PRIMe.

Personnel Support
One tenured faculty post has been secured. In the future, we will increase university support for up to ten faculty positions.

Financial Support
More than 700 million yen (about 7 million in US dollars) will be provided each year to reinforce the management.

4. Others

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

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

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

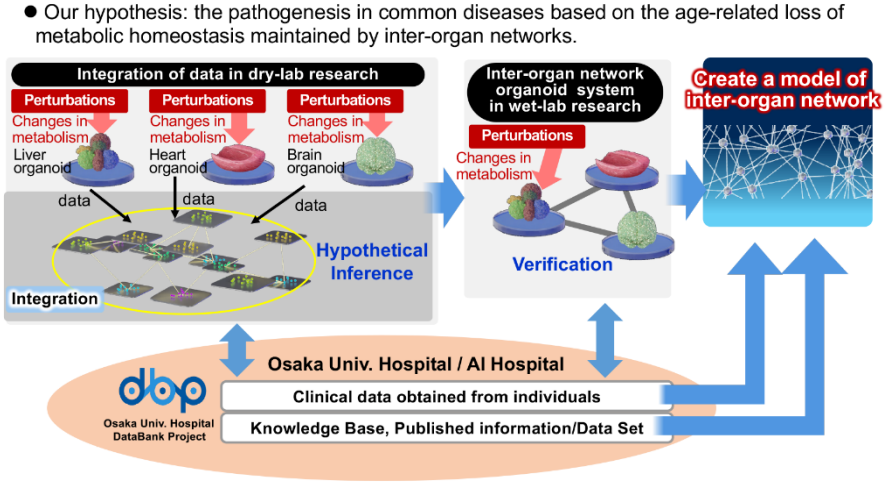
Our responses to the pointed items (1-5) in "Major points that need to be improved" are as follows.

1. As there is some lack of coherence in the project's overall plan, a risk exists that the research activities on digitization of life and medical phenomena will be disjointed given the center's diverse research themes. The center should strategically coordinate the research activities of the PIs toward building the biodigital twin, giving weight to Osaka University's strengths such as its organoid research on retina and liver and its mathematical modeling.

Response to 1. As shown in 2-2, PRIMe reformed management/support system to strengthen its governance. To ensure that research activities proceed in an integrated manner, we will hold progress report meetings every two months. If problems are identified, the Center Director will take full responsibility and steps to solve the problem along with the Center Steering Committee consisting of the Center Director, Deputy Directors, Administrative Director, and PIs. In addition, we will establish an External Evaluation Committee to come up with solutions.

2. It is unclear what strategy will be used to identify inter-organic linkages from organoid studies. The center needs to formulate a concrete and convincing strategy in this regard.

Response to 2. We hypothesize that the pathogenesis of many common diseases is based on the age-related loss of metabolic homeostasis maintained by inter-organ networks (see attached Figure below). 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 (cooperate with Osaka Univ. Hospital and AI hospital), we aim to discover new information on the inter-organ metabolism networks. We currently plan to investigate insulin resistance utilizing inter-organ organoids (hepato-biliary-pancreas).



Challenge to model the inter-organ network

3. Creating the biodigital twin will necessitate obtaining as much uniform data as possible from organoid studies and clinical data. Basic researchers, clinical researchers and data scientists should thoroughly discuss and plan ways of doing this.

Response to 3. The development of an analyzable machine learning framework to create biodigital twin will aim at modeling with sparse data, such as data from hundreds of organoids. However, the data uniformity perspective is also important. To achieve breakthroughs in this respect, first PI meeting was held on December 22nd, 2022 to provide opportunities for research presentations and active exchange of ideas to facilitate research collaboration, especially between wet- and dry-labs. In addition, PRIMe built an original collaboration system that provides a virtual under-one-roof environment connected by network (slack, zoom, etc.). To provide more opportunities for interdisciplinary exchange between researchers, PRIMe plans to create a bottom-up joint research through monthly exchange meeting between young and senior researchers of all fields (Happy hour), a series of lectures beyond their expertise, and to have a retreat camp in September 2023.

4. The highlighted use of "advanced measurement technology" under the heading "new quantum technology" looks artificial. For example, there are many ways to do temperature and pH measurements. The center should articulate a clear and concrete research plan for quantum sensing measurement of organoids in this project.

Response to 4. 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.

5. The contributions from foreign "partner institutions" are not clearly defined. The center should clarify the roles of overseas research facilities.

Response to 5. PRIMe international satellites are set up at the University of British Columbia (UBC, Synthetic Biology) and National Autonomous University of Mexico (Modeling). We also explore researches in Human Metaverse Medicine internationally and cooperate with additional four overseas research institutes: the Cincinnati Children's Hospital Medical Center (Organoids), Stanford University (Brain Organoids and Assembloids), Systems Biology Ireland at University College Dublin (Mathematics), and Institut Curie (Data Science).
For example, in order to facilitate interaction, UBC, as one of the overseas research institutions where PRIMe PIs are assigned, will place deputy PIs at Osaka University, while Osaka University will establish a custom laboratory at this institution, to create an environment where relevant researchers can have greater freedom in mobility. Moreover, these overseas PRIMe partner institutions provide strong supports in searching and hiring early-career researchers with extraordinary abilities from overseas through excellent human resources support. For the present, PRIMe plans to recruit two foreign researchers from UBC.

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

1. Refereed Papers

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

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

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

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

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

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

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

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

A. WPI papers

[Original articles]

none

[Review articles]

none

[Proceedings]

none

[Other English articles]

none

B. WPI-related papers

[Original articles]

1. Miyagawa, S., Kainuma, S., Imanishi, Y., Shimamoto, T., Nitta, Y., Matsuo, C., Sakata, Y., Takeuchi, M., and Sawa, Y. (2023). Prognosis of Patients With Heart Failure Receiving Autologous Myoblast Patches - Comparison of Single-Arm Trial Data to Registry Data. ***Circulation Journal : Official Journal of the Japanese Circulation Society*** *87*, 481–486. 10.1253/circj.CJ-22-0319.

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[Other English articles]
none

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

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

Date(s)	Lecturer/Presenter's name	Presentation title	Conference name
Dec. 12, 2022	Hajime Nagahara	Deep sensing - Jointly optimize imaging and processing -	International Workshop on Image Sensors and Imaging Systems
Nov. 3, 2022	Takanori Takebe	Human Organoids Toward Precision Hepatology	American Association for Study of Liver Disease (AASLD) Annual meeting, DC
Oct 11, 2022	Mariko Okada	Gene expression heterogeneity arises from signaling networks	International Conference for Systems Biology (ICSB) 2022, Berlin
Oct. 6, 2022	Katsuhiko Hayashi	Reconstitution of gametogenesis using pluripotent stem cells	Cold Spring Harbor Meeting
Aug. 26, 2022	Yoshie Harada	Intracellular thermometry with fluorescent polymer sensor and nanodiamond	The 15th Asia Pacific Physics Conference (APPC15)
Aug. 15, 2022	Katsuhiko Hayashi	Reconstitution of Gametogenesis using Pluripotent Stem Cells	Gordon Research Conference, Mammalian Reproduction
Aug. 9, 2022	Takanori Takebe	Modeling Steatohepatitis in Humans with Liver Organoids	Inter Organ Crosstalk in Non-Alcoholic Steatohepatitis (NASH), Whistler, Canada
May 17, 2022	Mariko Okada	Pasmopy – Patient-Specific Modeling in Python for Classification of Cancers	The 8th Conference on Systems Biology of Mammalian cells, Heidelberg
May 3, 2022	Katsuhiko Hayashi	Reconstitution of gametogenesis using pluripotent stem cells	14th Annual Conference of The Oncofertility Consortium
Apr. 15, 2022	Takanori Takebe	Engineering Multi-Organs in a Dish	The 126th Annual Meeting of the Japanese Ophthalmological Society, Osaka, Japan

3. Major Awards

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

Date	Recipient's name	Name of award
Mar. 10, 2023	Kohji Nishida	2022 2nd Tai Morishita Memorial Award, Terumo Life Science Foundation
Feb. 9, 2023	Takanori Takebe	ISSCR Outstanding Young Investigator Award, International Society for Stem Cell Research (ISSCR)
Dec. 15, 2022	Takanori Takebe	Inoue Prize for Science, Inoue Foundation for Science
Nov. 11, 2022	Yukinori Okada	Academic Award 2022, Japan Society of Human Genetics

Nov. 3, 2022	Shigeru Miyagawa	Journal of Artificial Organs Award 2022
Sep. 21, 2022	Yukinori Okada	Osaka Science Prize 2022, Osaka Prefecture, Osaka City, and Osaka Science and Technology Center (OSTEC)

Appendix 2　FY 2022 List of Principal Investigators

NOTE:

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

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

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

<Results at the end of FY2022> **Principal Investigators Total: 19**

Name	Age	Affiliation (Position title, department, organization)	Academic degree, specialty	Effort (%)*	Starting date of project participation	Status of project participation (Describe in concrete terms)	Contributions by PIs from overseas research institutions
Center director Kohji Nishida	60	Professor, Graduate School of Medicine, Osaka University	MD, PhD Stem cell biology, Regenerative medicine, Ophthalmology	90	Nov.11,2022	usually stays at the center	
Deputy-director Takanori Takebe	36	Professor, Center for Stem Cell and Organoid Research and Medicine, Director for Commercial Innovation, Cincinnati Children's Hospital Medical Center, Graduate School of Medicine, Osaka University	MD, PhD Organoid medicine, Organ development, Regeneration	30	Nov.11,2022	stays at the center about 7 times a month	
Deputy-director Mariko Okada	60	Professor, Institute for Protein Research, Osaka Univeristy	PhD Systems biology	45	Nov.11,2022	stays at the center about 10 times a month	
Katsuhiko Hayashi	51	Professor, Graduate School of Medicine, Osaka University	PhD Reproductive genetics, Ovarian organoids	70	Nov.11,2022	stays at the center about 15 times a month	
Shigeru Miyagawa	55	Professor, Graduate School of Medicine, Osaka University	MD, PhD Cardiovascular surgery, Regenerative medicine, Medical AI	80	Nov.11,2022	usually stays at the center	
Noriyuki Tsumaki	58	Professor, Graduate School of Medicine, Osaka University	MD, PhD cartilage, Regenerative medicine	70	Nov.11,2022	stays at the center about 15 times a month	
Vivian Hwa	64	Basic Research Director, Cincinnati Center for Growth Disorders/Cincinnati Children's Hospital Medical Center	PhD Growth deficiency disease, Genetics	75	Nov.11,2022	joins the event occasionally and a videoconference from another institution two times a month.	
Yukinori Okada	42	Professor, Graduate School of Medicine, Osaka University	MD, PhD Bioinformatics, Machine learning, Omics analysis	50	Nov.11,2022	stays at the center about 10 times a month	

Hajime Nagahara	49	Professor, Institute for Datability Science, Osaka Univerisity	PhD Computer vision, machine learning	70	Nov.11,2022	stays at the center about 15 times a month	
Nozomu Yachie	42	Associate Professor, School of Biomedical Engineering (SBME), The University of British Columbia	PhD Synthetic biology, Information science	15	Nov.11,2022	working at home twice a month	
Takahiro Nemoto	36	Associate Professor, Premium Research Institute for Human Metaverse Medicine, Osaka University	PhD Data science, Algorithm v development	100	Nov.11,2022	usually stays at the center	
Ai Shinobu	41	Associate Professor, Premium Research Institute for Human Metaverse Medicine, Osaka University	PhD Molecular dynamics simulation	100	Nov.11,2022	usually stays at the center	
Makoto Negoro	40	Associate Professor, Center for Quantum Information and Quantum Biology/Osaka University	PhD Magnetic resonance, Quantum computer	35	Nov.11,2022	stays at the center about 7 times a month	
Yoshie Harada	63	Professor, Institute for Protein Research, Osaka Univeristy	PhD Quantum sensing, Live imaging	70	Nov.11,2022	stays at the center about 15 times a month	
Astuo Kishimoto	52	Director, ELSI Center, Osaka University	PhD ELSI, Risk assessment	30	Nov.11,2022	stays at the center about 7 times a month	
Elisa Domínguez Hüttinger	38	Research Associate, National Autonomous University of Mexico	PhD Bioengineering	8	Mar.1,2023	joins event or videoconference from another institution occasionally	
Hideo Yokota	54	Team Leader, Advanced Photonics Center, Riken	PhD Image Processing	20	Nov.11,2022	joins event or videoconference from another institution occasionally	
Shingo Tsukada	57	NTT Fellow, NTT Bio-Medical Informatics Research Center, NTT Basic Research Laboratories	PhD Bio-digital twin, Bio-Medical Informatics&ICT	20	Nov.11,2022	joins event or videoconference from another institution occasionally	
Kunio Kashino	55	Senior Distingished Researcher, NTT Bio-Medical Informatics Research Center, NTT Basic Research Laboratories	PhD Bio-digital twin, Bio-Medical Informatics&ICT	20	Nov.11,2022	joins event or videoconference from another institution occasionally	

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

Principal investigators unable to participate in project in FY 2022

Name	Affiliation (Position title, department, organization)	Starting date of project participation	Reasons	Measures taken
Sergiu P. Pasca	Psychiatry and Behavioral Sciences/Stanford University Medical School, Associate Professor	Nov.11,2022	Change participation status as a business consignment	Continued request for cooperation in center operations

Appendix 2a Biographical Sketch of a New Principal Investigator

(within 3 pages per person)

Name (Age): Elisa Domínguez-Hüttinger (38)

Affiliation and position:
Research Associate, Department for Molecular Biology and Biotechnology, Institute for Biomedical Research, National Autonomous University of Mexico (UNAM)

Academic degree and specialty:
2015, PhD in Bioengineering, Imperial College London, Specialty: Systems Biology

Timing of participation From March 2023
* If the PI will participate in the center project from its beginning, enter "from start."

Effort **8.3%**
* Percentage of time that the principal investigator devote to working for the center vis-à-vis his/her total working hours.

Research and education history

2020- Now: Research associate in systems biology, Institute for Biomedical Research, UNAM.
2021: College for Life Sciences Fellow at the Wissenschaftskolleg zu Berlin.
2018-2020: Research associate in Mathematical Biology, Centrer for Mathematical Sciences, UNAM
2019: Short term JSPS Postdoctoral research stay, Osaka University.
2016-2018: Postdoctoral Researcher, Ecology Institute, UNAM.
2015: Postdoctoral Researcher, Imperial College London.
2015: Postdoctoral research stay, RIKEN Center for Integrative Medical Sciences.
2011-2015: PhD in Bioengineering, Imperial College London
2014: Doctoral Research stay, Universidad de Buenos Aires.
2012-2014: Research technician in Biological Control & Systems, Imperial College London.
2009-2010 MRes in Systems and Synthetic Biology, , Imperial College London.
2004-2008 Bachelor in biology, UNAM
2007: Social service, Clinical Research Unit in Metabolic Diseases, Mexican Health Institute.

Achievements and highlights of past research activities

Elisa is a theoretical systems biologist passionate about developing and applying mathematical and computational tools to understand pathogenic mechanisms of complex diseases. Her focus is on uncovering mechanisms and early markers of gradual disease transitions. She constructs and analyses mathematical models that help to understand and prevent the development of severe forms of disease, and to design and optimize treatment strategies to revert to mild and asymptomatic stages. To achieve these goals, she integrates clinical and experimental data into bottom-up, mechanistic, and quantitative models encoded as coupled non-linear dynamical systems. Typically, her mathematical models encompass different timescales simultaneously, allowing me to reproduce gradual pathogenic transitions as emerging properties of the dynamical coupling between biochemical-level regulatory networks and micro-environmental changes**.**

She has successfully applied her integrative systems biology approach (explained in full depth in Ref. 13) to uncover pathological mechanisms and to design optimal treatment strategies of several

epithelial tissue diseases including Atopic dermatitis (Refs. 3,4,5,8, 9 and 10), tuberculosis (Ref. 1), upper airway infection by *Streptococcus pneumoniae* (Ref. 6), and carcinomas (Refs. 2 and 7).

Achievements

(1) International influence * Describe the kind of attributes listed below.

a) Recipient of international awards

1. Level II Member of the National System of Researchers, **2022-2027**
2. Scientist-in-Residence award, **2023**
3. College for Life Sciences Fellowship, Wissenschaftskolleg zu Berlin, **2021**.
4. Posdoctoral fellowship from the Japan Association for the Promotion of Science, **2019**
5. Sofía Kovalevskaia award from the Mexican Society for Mathematics, **2018**

b) Member of a scholarly academy in a major country: **NA**

c) Guest speaker or chair of related international conference and/or director or honorary member of a major international academic society in the subject field

Guest speaker:

1. New Voices in Infectious Biology, **2022**
2. World Conference on Natural Resource Modeling, **2020**
3. MexSiam *conference.* **2019**
4. 1st Latin American Workshop and Conference on Systems Biology. **2017**
5. First Colombian Biomathematics Symposium, **2015**
6. London Skin club, **2015**
7. International Summer Symposium on Systems Biology, **2014** and **2016**

Organizer:

8. ISCB-Latin America-SoIBio and BioNetMX International Conference **2022**, Mexico
9. Biomathematics session, Conference of the Mexican mathematical Society **2020**, Mexico
10. 3rd International Summer Symposium on Systems Biology (IS3B2019) **2019**, Mexico
11. Program Committee 1st Workshop Machine Learning for Health Care **2019**, Mexico

d) Editor of an international academic journal

12. Review editor for *Frontiers in Genomics – Section* Nutritional Genomics, **2023**

e) Peer reviewer for an overseas competitive research program (etc.)

13. Fanconi Anemia Research Fund Grant Reviewer, **2023**

(2) Receipt of major large-scale competitive funds (over the past 5 years)

1. Mexican Council for Research and Technology research grant, Project number 319600, **MXP 665,630.00**, Principal Investigator, 2022-2024.
2. Support Program for Research and Technological Innovation Projects (PAPIIT) grant for researchers, **MXP 190,000.00**, Principal Investigator, 2022-2024.
3. Support Program for Research and Technological Innovation Projects (PAPIIT) grant for researchers, **MXP 129,384.00**, Principal Investigator, **2019-2020**.

(3) Major publications (Titles of major publications, year of publication, journal name, number of citations)

1. Eliezer Flores-Garza, Mario A. Zetter, Rogelio Hernández-Pando, **Elisa Domínguez-Hüttinger***. 2022. Mathematical model of the immunopathological progression of tuberculosis, ***Frontiers in Systems Biology*** 2:912974, 10.3389/fsysb.2022.912974, **Citations: 0**
2. Shigeyuki Magi, Sewon Ki, Masao Ukai, **Elisa Domínguez- Hüttinger**, Atsuhiko T Naito, Yutaka Suzuki, Mariko Okada. 2021. A combination approach of pseudotime analysis and mathematical modeling for understanding the drug-resistant mechanism. ***Scientific reports*** 11:18511 https://doi.org/10.1038/s41598-021-97887-z, **Citations: 2**
3. Guillem Hurault, **E. Domínguez-Hüttinger**, Langan SM, Williams HC, Reiko J. Tanaka. 2020. Personalised prediction of daily eczema severity scores using a mechanistic machine learning model, ***Clinical and Experimental Allergy*** 00:1–9. https://doi.org/10.1111/cea.13717, **Citations: 8**
4. G. Tanaka, **E. Domínguez-Hüttinger**, P. Christodoulides, K. Aihara, and R. J. Tanaka. 2018. Bifurcation analysis of a mathematical model of atopic dermatitis to determine patient-specific effects of treatments on dynamic phenotypes", ***Journal of Theoretical Biology*** 448: 66-79, **Citations: 8**
5. P. Christodoulides, Y. Hirata, **E. Domínguez-Hüttinger**, S. G. Danby, M. J. Cork, K. Aihara, and R. J. Tanaka. 2017. Computational design of treatment strategies for proactive therapy on atopic dermatitis using optimal control theory. ***Phil.Trans.R. Soc. A***., 375: 20160285, **Citations: 15**
6. **E. Domínguez-Hüttinger**, N. J. Boon, T. B. Clarke, and R. J. Tanaka. 2017. Mathematical modelling of colonization, invasive infection and treatment of Streptococcus pneumoniae, ***Front. Physiol.*** 8: 115, pp.1–14, **Citations: 28**
7. L. F. Méndez-López, J. Dávila-Velderrain, **E. Domínguez-Hüttinger**, C. Enríquez-Olguín, J. Martínez-García, and E. R. Álvarez-Buylla. 2017. Gene regulatory network underlying the immortalization of epithelial cells. ***BMC Syst. Biol.,*** 11(24), pp.1–15, **Citations: 32**
8. **E. Domínguez-Hüttinger**, P. Christodoulides, K. Miyauchi, A. D. Irvine, M. Okada-Hatakeyama, M. Kubo, and R. J. Tanaka. 2017. Mathematical Modeling of Atopic Dermatitis Reveals 'Double switch' Mechanisms Underlying Four Common Disease Phenotypes, ***J. Allergy Clin. Immunol*** 139:1861-72, **Citations: 45**
9. M. D. A. van Logtestijn, **E. Domínguez-Hüttinger**, G. N. Stamatas and R. J. Tanaka. 2015. Resistance to water diffusion in the stratum corneum is depth-dependent. ***PLoS ONE*** 10(2):e0117292, **Citations: 47**
10. **Domínguez-Hüttinger E.**, M. Ono, M. Barahona and R.J. Tanaka. 2013. Risk factor-dependent dynamics of atopic dermatitis: modelling multi-scale regulation of epithelium homeostasis. ***Interface Focus*** 3:20120090, **Citations: 23**
11. Tecalco-Cruz, A., M. Sosa-Garrocho, G. Vázquez-Victorio, L. Ortiz-García, **E. Domínguez-Hüttinger E**. and M. Macías-Silva. 2012. Transforming growth factor-beta/SMAD target gene skil is negatively regulated by the transcriptional cofactor complex SNON/SMAD4. ***The Journal of Biological Chemistry*** 287(32): 26764-26776, **Citations: 43**
12. Elena Álvarez-Buylla Roces, Juan Carlos Martínez-García, José Dávila Velderrain, **Elisa Domínguez-Hüttinger** and Mariana Esther Martínez-Sánchez. 2018. "Modeling Methods for Medical Systems Biology - Regulatory Dynamics Underlying the Emergence of Disease Processes." Editorial: **Springer. Series: Advances in Experimental Medicine and Biology** (https://doi.org/10.1007/978-3-319-89354-9). (BOOK), **Citations: 4**

(4) Others (Other achievements indicative of the PI's qualification as a top-world researcher, if any.)

None

Appendix 3-1 FY 2022 Records of Center Activities

1. Researchers and center staff, satellites, partner institutions

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

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

Special mention

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

1-2. Satellites and partner institutions

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

<Satellite institutions>

Institution name	Principal Investigator(s), if any	Notes
RIKEN Center	Hideo Yokota	
NTT	Kunio Kashino Shingo Tsukada	
The University of British Columbia	Nozomu Yachie	
National Autonomous University of Mexico	Elisa Domínguez Hüttinger	

< Partner institutions>

Institution name	Principal Investigator(s), if any	Notes
Systems Biology Ireland at University College Dublin		
Institut Curie		
Cincinnati Children's Hospital Medical Center		
Department of Psychiatry and Behavioral Sciences at Stanford University		

2. Holding international research meetings

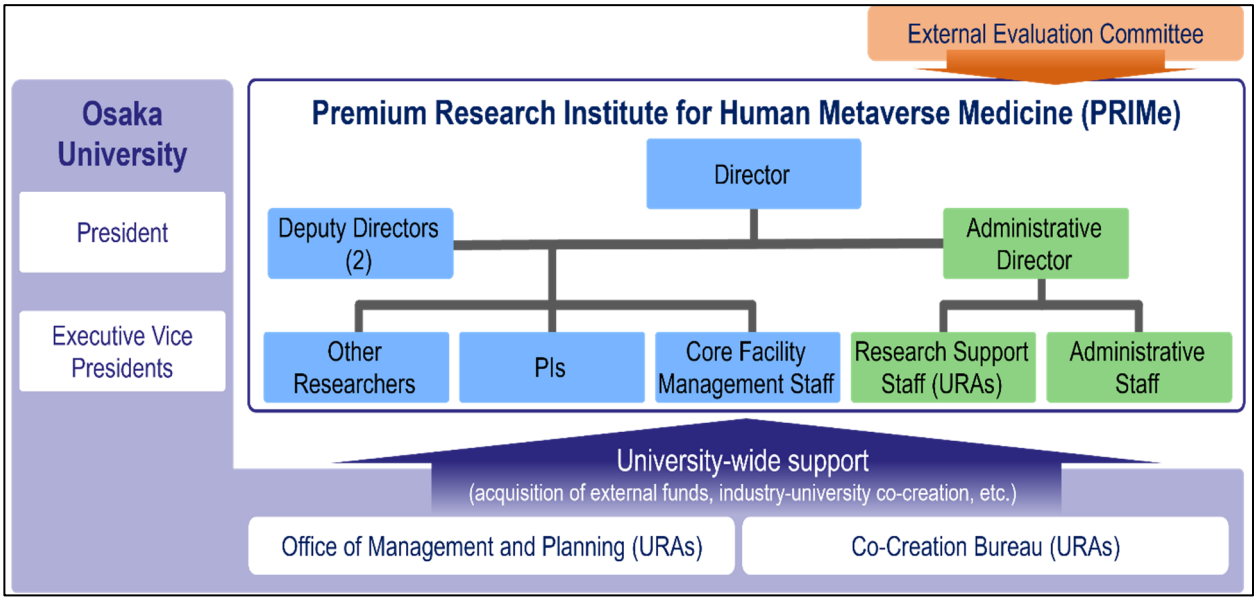
- Indicate the number of international research conferences or symposiums held in FY2022 and give up to three examples of the most representative ones using the table below.

FY 2022: 1 meeting

Major examples (meeting titles and places held)	Number of participants
WPI-PRIMe Kick-off Symposium, RIHGA Royal Hotel Osaka	Total participants:580 Total participants:(on site):130 Total participants:(website/zoom) : 450

3. Diagram of management system

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



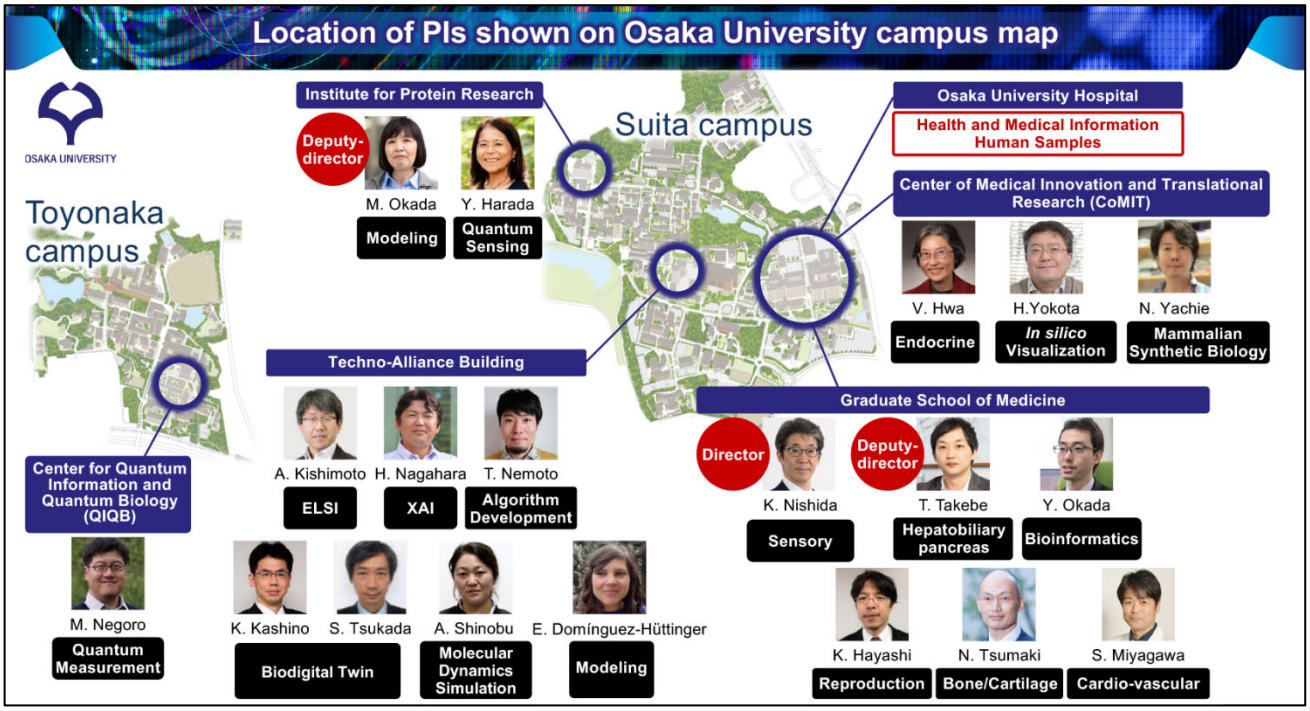
Management and Support System of the Center

Director :	Kohji Nishida
Deputy Director :	Takanori Takebe, Mariko Okada
Administrative Director :	Takefumi Doi
PIs :	Katsuhiko Hayashi, Vivian Hwa, Shigeru Miyagawa, Noriyuki Tsumaki, Nozomu Yachie, Yoshie Harada, Makoto Negoro, Shingo Tsukada, Takahiro Nemoto, Yukinori Okada, Kunio Kashino, Hajime Nagahara, Ai Shinobu, Hideo Yokota, Astuo Kishimoto, Elisa Domínguez Hüttinger
Research Support Staff (URAs) :	Maki Tani, Takako Igi, Ryu Imamura, Bidadi Haniyeh, Ayako Kiriyama, Cui Chenlu
Administrative Staff :	Shingo Murakami, Hiroko Umeda, Naohisa Kido, Itsuro Takami, Satomi Utsunomiya, Aya Hirono, Mineko Tanimoto, Saori Hayakawa, Kana Okuno, Hisano Nakajima

(Name list as of May 1, 2023)

4. Campus Map

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



This map shows the locations of our PIs' laboratories on Osaka University campus.

5. Securing external research funding*

External research funding secured in FY2022

Total: 480,225,329 yen

[Accuired large-scale research grants (35,000,000yen+ in secured amount)]

Organization	Fund Name	PI	Funding amount (Secured amount)
AMED	Practical Research Project for Rare / Intractable Diseases	Kohji Nishida	59,500,000yen
AMED-CREST	Innovation and Clinical Research Center Project	Kohji Nishida	39,500,000yen
AMED	the Acceleration Program for Intractable Diseases Research utilizing disease-specific iPS cells	Noriyuki Tsumaki	173,463,847 yen

- Describe external funding warranting special mention. Include the name and total amount of each grant.

* External research funding includes "KAKENHI," funding for "commissioned research projects," "joint research projects," and for others (donations, etc.) as listed under "Research projects" in Appendix 3-2, Project Expenditures.

Appendix 3-1a FY 2022 Records of Center Activities

Researchers and other center staff

Number of researchers and other center staff

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

a) Principal Investigators

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

(number of persons)

	At the beginning of project	At the end of FY 2022	Final goal (Date: March, 2027)
Researchers from within the host institution	11	11	11
Researchers invited from overseas	4	3	5
Researchers invited from other Japanese institutions	5	5	5
Total principal investigators	20	19	21

b) Total members

	At the beginning of project		At the end of FY 2022		Final goal (Date: March, 2027)	
	Number of persons	%	Number of persons	%	Number of persons	%
Researchers	20		21		67	
Overseas researchers	3	15	2	10	20	30
Female researchers	5	25	5	24	14	21
Principal investigators	20		19		21	
Overseas PIs	3	15	2	11	4	19
Female PIs	5	25	5	26	6	29
Other researchers	0		2		35	
Overseas researchers	0	#DIV/0!	0	0	12	34
Female researchers	0	#DIV/0!	0	0	6	17
Postdocs	0		0		11	
Overseas postdocs	0	#DIV/0!	0	#DIV/0!	4	36
Female postdocs	0	#DIV/0!	0	#DIV/0!	2	18
Research support staffs	7		8		13	
Administrative staffs	3		6		10	
Total number of people who form the "core" of the research center	30		35		90	

	At the beginning of project		At the end of FY 2022		Final goal (Date: March, 2027)	
	Number of persons	%	Number of persons	%	Number of persons	%
Doctoral students	0		2		21	
Employed	0	-	0	0.0	5	23.8

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

Appendix 3-2 Project Expenditures

1) Overall project funding

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

(Million yens)

Cost items	Details (For Personnel - Equipment please fill in the breakdown of fiscal expenditure, and the income breakdown for Research projects.)	Total costs	Amount covered by WPI funding
Personnel	Principal Investigators :13	36	3
	Center Director and Administrative Director	11	5
	Other researchers :4	7	0
	University Research Administrators :4	3	1
	Administrative staffs :8	13	11
	Subtotal	70	20
Project activities	Research startup cost (newly appointed PIs) :3	17	14
	Research startup cost (other PIs) :10	35	28
	Rental fees for facilities / Cost of utilities	36	7
	International symposium related cost :1	18	16
	Public relations or advertising cost	2	1
	Personnel Dispatch cost	1	1
	Subtotal	109	67
Travel	Domestic travel costs	1	1
	Overseas travel costs	4	3
	Subtotal	5	4
Equipment	Basic equipment	491	491
	Equipment renovation costs	12	0
	Subtotal	503	491
Research projects (Detail items must be fixed)	Project supported by other government subsidies, etc. *1	87	0
	KAKENHI	14	0
	Commissioned research projects, etc.	376	0
	Joint research projects	46	0
	Others (donations, etc.)	43	0
	Subtotal	566	0
Total		1253	582

Costs (Million yens)

WPI grant in FY 2022	582
Costs of establishing and maintaining facilities	5
Repairing facilities	
(CoMIT Bldg, 194㎡)	2
(Techno-Alliance Bldg, 327㎡)	3
Costs of equipment procured	491
Cell Sorter System	96
High Resolution Mass Spectrometer	120
All-in-One Fluorescence Microscope	29
High Content Imaging System	72
Confocal Laser Scanning Microscope	40
High-sensitivity Confocal Laser Scanning Microscope System	100
Automated DNA extractor	10
Ultra Low Freezers	4
Automated Electrophoresis Station	7
Imaging Systems	8
Fixtures	5

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

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

2) Costs of satellites

(Million yens)

Cost items	Details	Total costs	Amount covered by WPI funding
Personnel	Principal investigators：5		
	Other researchers：0		
	Research support staff：0		
	Administrative staff：0		
	Subtotal	0	0
Project activities	Subtotal	0	0
Travel	Subtotal	0	0
Equipment	Subtotal	0	0
Research projects	Subtotal	0	0
Total		0	0

Appendix 4 FY 2022 Status of Collaboration with Overseas Satellites

1. Coauthored Papers

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

Overseas Satellite 1 RIKEN Center (Total: 0 papers)

Overseas Satellite 2 NTT (Total: 0 papers)

Overseas Satellite 3 The University of British Columbia (Total: 0 papers)

Overseas Satellite 4 National Autonomous University of Mexico (Total: 0 papers)

2. Status of Researcher Exchanges

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

Overseas Satellite 1: RIKEN Center

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022	0	0	0	0	0
	0	0	0	0	0

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022	3	0	0	0	3
	0	0	0	0	0

Overseas Satellite 2: NTT

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022	0	0	0	0	0
	0	0	0	0	0

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022	4	0	0	0	4
	0	0	0	0	0

Overseas Satellite 3: The University of British Columbia

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022	0	0	0	0	0
	0	0	0	0	0

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022	1	0	0	0	1
	0	0	0	0	0

Overseas Satellite 4: National Autonomous University of Mexico

<To satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022	0	0	0	0	0
	0	0	0	0	0

<From satellite>

	Under 1 week	From 1 week to 1 month	From 1 month to 3 months	3 months or longer	Total
FY2022	1	0	0	0	1
	0	0	0	0	0

Appendix 5　FY 2022 Visit Records of Researchers from Abroad

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

Total: 3

	Name	Age	Affiliation		Academic degree, specialty	Record of research activities (Awards record, etc.)	Time, duration	Summary of activities during stay at center (e.g., participation as principal investigator; short-term stay for joint research; participation in symposium)
			Position title, department, organization	Country				
1	Vivian Hwa	64	Cincinnati Center for Growth Disorders/Cincinnati Children's Hospital Medical Center・Basic Science Director	USA	Academic degree: Microbiology, PhD Specialty: Growth deficiency disease, Genetics	None	2023.3.13-2023.3.16 (4days)	perticipation as principal investigator in WPI-PRIMe KICK-OFF SYMPOSIUM and short-term stay as PI
2	Elisa Domínguez Hüttinger	38	National Autonomous University of Mexico | UNAM・Institute for Biomedical Investigation	Mexico	Academic degree: PhD Bioengineering Specialty:Systems Biology	Level II Member of the National System of Researchers, 2022-2027 Scientist-in-Residence award, 2023 College for Life Sciences Fellowship, Wissenschaftskolleg zu Verlin, 2021 Posdoctoral fellowship from the Japan Association for the Promotion of Science, 2019 Sofía Kovalevskaia award from the Mexican Society for Mathematics, 2018	2023.3.13-2023.3.16 (4days)	perticipation as principal investigator in WPI-PRIMe KICK-OFF SYMPOSIUM and short-term stay as PI
3	Nozomu Yachie	42	Associate Professor, School of Biomedical Engineering (SBME), The University of British Columbia	Canada	Academic degree:PhD Synthetic biology, Information science	Allen Distinguished Investigator, Allen Institute, 2022-present Canada Research Chair (Tier 2) in Synthetic Biology, Canadian Institute of Health Research (CIHR), 2020-present Minister's Young Scientists Award, Ministry of Education, Culture, Sports, Science and Technology, Japan, 2020 PRESTO Researchership, Japan Science and Technology Agency (JST) , 2014-2018 Banting Fellowship, National Sciences and Engineering Research Council of Canada (NSERC), 2012-2014	2023.3.10-2023.3.15 (6days)	business meeting, perticipation as principal investigator in WPI-PRIMe KICK-OFF SYMPOSIUM and short-term stay as PI

Appendix 6 FY2022 State of Outreach Activities

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

Activities	FY2022 (number of activities, times held)
PR brochure, pamphlet	5 (Pamphlet (Japanese), Poster, Kick-off Symposium flyer, Kick-off Symposium program brochure, Nature Index Japan Advertisement (Offprint))
Lectures, seminars for general public	1 (Kick-off Symposium, Mar 14, 2023)
Teaching, experiments, training for elementary, secondary and high school students	0
Science café	0
Open houses	0
Participating, exhibiting in events	1 (WPI Science Symposium, Nov 23, 2022)
Press releases	3 (Announcement of the Kick-off of PRIMe (Oct 12, 2022), Introduction of research result of Prof. Tsumaki published in Nature Comms (Feb 15, 2023), Announcement of the Kick-off Symposium (Feb 21, 2023))
Publications of the popular science books	0
Others （Promotional film）	2 (Promotional Film (English), Promotional Film (Japanese))
Others （Lab tour for medical school students）	1 (Lab Tour co-hosted with WPI-IFReC, Mar 9, 2023)
Others （Advertisement）	6 (Sankei Shimbun (for Osaka City, Mar 4, 2023), Yomiuri Shimbun (for Osaka City, Mar 4, 2023), Sankei Shimbun (for Hokusetsu area, Mar 5, 2023), Sankei Shimbun (for Kitakawachi area, Mar 8, 2023), Nature Index Japan 2023 (Mar 8, 2023), Nikkei Shimbun (for Osaka area, Mar 11, 2023)

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

Outreach Activities and Their Results

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

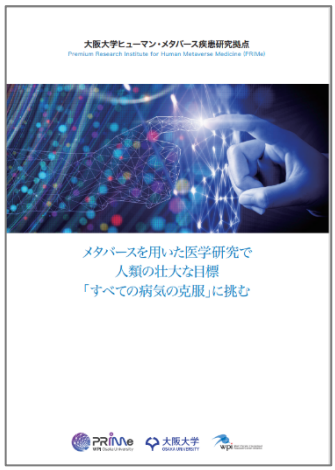
Examples:
- As a result of using a new OO press-release method, a OO% increase in media coverage was obtained over the previous year.
- By holding seminars for the public that include people from industry, requests for joint research were received from companies.
- We changed our public relations media.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

PRIMe's PR Contents

To widely increase the publicity of the Center, we recently created and started **PRIMe's website** in both English and Japanese from March 2023 (https://prime.osaka-u.ac.jp/). We will publish current topics and news about PRIMe activities as occasions arise. We will improve this website in FY2023 and make it the main platform for enhancing the Center's presence. By continuing to enrich its contents, we believe the website will attract more and more people from all over the world.

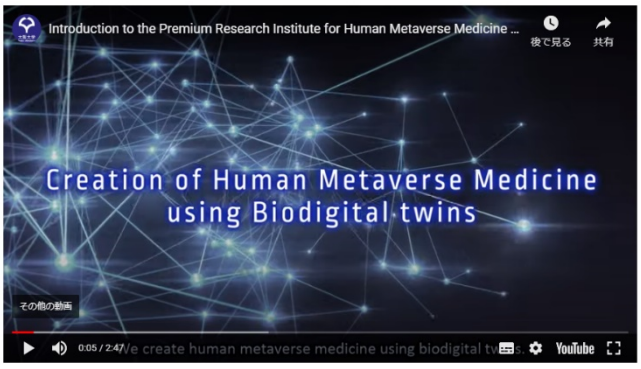
We also published an **Japanese PRIMe pamphlet,** explaining human metaverse medicine, a new science field that we create. This pamphlet was distributed to on-site participants at the PRIMe Kick-off Symposium, and the PDF version is available on the PRIMe website. To promote PRIMe overseas as well as in Japan, we published the English version in the beginning of FY2023.

PRIMe Website (JP/EN)



PRIMe Pamphlet (JP)

Moreover, we think video contents are important for promoting PRIMe globally. In the PRIMe website, viewers can watch **the promotional film**, which introduces PRIMe in two languages. The film was available at Osaka University official YouTube channel last October. The English version has been viewed over 700 times, while the Japanese version has been viewed over 2,700 times by the beginning of this May.



Promotional Film (left: Japanese right: English)

Contribution to Nature Index Japan 2023

PRIMe contributed to the Nature Index Japan special issue published on March 8, 2023. On this issue, Nature focused on the research strength of Japan, rising research stars in Japan, and the latest undergoing research projects in Japan. In the article "Taking Great Technological Strides for Medical Science," Center Director Nishida stated the purpose and vision of PRIMe. This content is available online (https://www.nature.com/articles/d42473-022-00494-3). We also distributed the reprint at the Kick-off Symposium of PRIMe.

PRIMe Kick-off Symposium in March 2023

PRIMe held the kick-off symposium on March 14, 2023 at Osaka in person and online (https://www.osaka-u.ac.jp/ja/news/topics/2023/03/22001). This event was attended and viewed by approximately 580 people (approximately 130 on-site and 450 on the web). The president of Osaka University Shojiro Nishio gave opening remarks. Before the sessions started, Center Director Nishida presented the overview of PRIMe, and wrapped up with a message - "継続が創造を生む（*Keizoku ga souzou wo umu*) / Continuation begets creation" to the audience, which Dr. Tadamitsu Kishimoto gave to celebrate the Center's kick-off. After Nishida's speech, PRIMe PIs and overseas

collaborators in total of 22, who are challenging new research fields, gave presentations on their future research plans in six sessions. Each session was followed by active discussions; the questions raised from the audience implied the society's high expectation toward the feasibility of our Center's goal. Finally, Executive Vice President Takao Onoe successfully concluded the event with his closing remarks.

Appendix 7 FY 2022 List of Project's Media Coverage

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

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

	Date	Types of Media (e.g., newspaper, magazine, television)	Description
1	Oct. 18 2022	Newspaper 1	[Nikkan Kogyo Shimbun Oct. 18] - Press conference report and introduction about PRIMe
2	Oct. 20 2022	Newspaper 1	[Nikkan Kogyo Shimbun Oct. 20] - Article about the launch of PRIMe and other two WPI institutes
3	Nov. 14 2022	News website 2	[MyNavi TECH+ Nov. 14, QLifePro Nov. 14] - Introduction of research result published in *Cancer Research* by Prof. Y Okada
4	Dec. 2 2022	News website 1	[QLifePro Dec. 2] - Introduction of research result published in *Cell Genomics* by Prof. Y Okada
5	Dec. 10 2022	Newspaper 5	[Nikkei Shimbun Dec. 10, Yomiuri Shimbun Dec. 10, Sankei Shimbun Dec. 10, Mainichi Shimbun Dec. 10, Asahi Shimbun Dec. 13] - Introduction of research result published in *Science Advances* by Prof. Hayashi
6	Dec. 10 2022	TV 1	[NHK Ohayo Nippon Dec. 10] - Introduction of research result published in *Science Advances* by Prof. Hayashi
7	Dec. 10 2022	News website 4	[Jiji Press, Dec. 10, TV Asahi News(Article) Dec. 10, Nikkei Biotech Dec. 12, The Japan News Dec. 28] - Introduction of research result published in *Science Advances* by Prof. Hayashi
8	Dec. 15 2022	Newspaper 1	[Yomiuri Shimbun Dec. 15] - Introduction of research result published in *Science Advances* by Prof. Hayashi (Article for children)
9	Dec. 21 2022	News website 1	[NHK website Dec. 21] - column about ELSI in " News Communicators Bureau" written by Prof. Kishimoto
10	Feb. 20 2023	News website 3	[Jiji Press Feb. 20, Nikkei Biotec Feb. 21, QLifePro Feb. 24] - Introduction of research result published in *Nature Communications* by Prof. Tsumaki
11	Feb. 21 2023	Newspaper 3	[Nikkei Shimbun Feb. 21, Sankei Shimbun Feb. 21, Nikkan Kogyo Shimbun Feb. 21] - Introduction of research result published in *Nature Communications* by Prof. Tsumaki
12	Feb. 21 2023	TV 1	[Yomiuri TV News Feb 21] - Introduction of research result published in *Nature Communitations* by Prof. Tsumaki
13	Mar. 3 2023	Newspaper 1	[Nikkei Sangyo Shimbun Mar. 3] - Introduction of research result published in *Nature Communications* by Prof. Tsumaki

14	Mar. 9 2023	News website 1 (Scientific)	[Nature Review Reumatology Mar. 9] - Article (posted in Scientific websites) of research result published in *Nature Communications* by Prof. Tsumaki
15	Mar. 19 2023	News website 7	[The Guardian Mar. 8, BBC News Mar. 8, BBC News Japan Mar.9, AP News Mar. 18, Asahi Shimbun Digital Mar. 19, CNN Mar. 24, Jiji.com Mar. 25] - Introduction of research result published in *Nature* by Prof. Hayashi
16	Mar. 15 2023	Newspaper 1	[Nikkan Kogyo Shimbun Mar. 15] - Kick-off Symposium report and introduction about PRIMe
17	Mar. 15 2023	News website 2 (Scientific)	[Nature "News and Views" Mar. 15, Science "Sifter" Mar. 16] - Article (posted in Scientific websites) of research result published in *Nature* by Prof. Hayashi
18	Mar. 16 2023	Newspaper 6	[Yomiuri Shimbun Mar. 15&17, Nikkei Shimbun Mar. 16, Sankei Shimbun Mar. 16, Asahi Shimbun Mar. 22, Nikkei Sangyo Shimbun Mar. 24] - Article of research result published in *Nature* by Prof. Hayashi
19	Mar. 17 2023	Newspaper 1	[Yomiuri Shimbun Mar. 17] - Introduction of research result published in *Nature Communications* by Prof. Tsumaki
20	Mar. 22 2023	Newspaper 1	[Nikkei Sangyo Shimbun Mar. 22] - Introduction of PRIMe Director Nishida's comment in the column "Customized medical treatment by using digital twin"
21	Mar. 30 2023	Newspaper 1	[Nikkei Sangyo Shimbun Mar. 30] - Introduction of research about developing MRI by Prof. Negoro
22	Mar. 31 2023	Newspaper 1	[Yomiuri Shimbun Mar. 31] - Article of research result published in *Nature* by Prof. Hayashi