Moonshot International Symposium
December 18, 2019

Working Group 2

Realizing a human life that “continues to improve both physically and psychologically” through complete understanding of biological functions such as the nervous system and related tissues

Initiative Report

Contents

EXECUTIVE SUMMARY

Over the past century, the average human life expectancy has more than doubled thanks in large part to advances in science, technology and medicine. In particular, the aging of Japan outweighs most other nations. An increasing burden of chronic diseases driven by Japan's aging population presents unprecedented societal challenges with projected healthcare spending of 66 trillion JPY in 2040. Overcoming the burden of chronic diseases is therefore a stupendous national priority. However, our understanding on chronic diseases remain devastatingly incomplete. As a result, the majority of existing therapeutics are for symptom management only or partial disease modifiers. Patients often have to live with chronic diseases and eventually succumb to disease progression or to recurrence.

We believe that conventional approach, where research focuses on a small number of contributing factors in specific organs, is not effective for currently intractable chronic disorders. The human body is a network of mutually dependent organs and there is a growing evidence that our health is the outcome of how these organs interact and function as a network.

Our Moonshot (MS) Goal is therefore "**By 2050, realization of ultra-early disease prediction and intervention based on the Whole Body Network Atlas for longer, fuller and happier lives**.". The initial goal of this program is development of "the Whole Body Network Atlas", a database that describes how organs interact with and influence each other at the cellular level. New biological and computational models, together with novel technologies for biosensing, will be developed and contribute to the development of the Atlas. Important functional network of organs and its role in the context of human biology will be identified through these activities. The Whole Body Network Atlas will subsequently serve as a database foundation for understanding diverse responses of the human body to disease-related insults. In some cases, a cause of disease triggers multiple sequences of events among the organs and finally manifest into signs and symptoms, disease progression and organ failures. Alternatively, the network of organs responds to the same cause of disease in robust and resilient ways to conquer such disease cascades. Difference between the two responses will serve as an important basis for identifying key factors for ultra-early disease prediction and fundamental intervention. To identify key factors that switch the system-level responses in the network of organs, "Whole Body Simulator", a high-performance computing system for the cellular interaction in the whole body, will be designed and implemented. Whole Body Simulator will elucidate the earliest signs of disease as well as the best means of interception to address fundamental causes so that disease progression is halted before the point of no return and for the restoration of fully healthy state.

Our approach is boldly unique and leverages Japan's existing strengths in biomedical science, imaging, and mathematics. In order to accelerate innovations, both national and international collaborations will be sought. Also, for maximizing industrial potential, from the outset we will proactively identify precompetitive areas for collaboration and explore public private partnerships.

This is an opportunity for Japan to become an epicenter of innovation, leading the world through health.

WG2：Realizing a human life that “continues to improve both physically and psychologically” through complete understanding of biological functions such as the nervous system and related tissues

I. VISION AND PHILOSOPHY

1. The Moonshot 「Area」「Vision」 for setting MS 「Goals」 candidate

The visionary council, which consists of experts, proposed the 3 Areas, 13 Visions, and examples of 25 MS Goals that Moonshot Research and Development Program should aim for. The aim is to set ambitious targets and concepts for a social agenda that are difficult to tackle but will have profound impact once resolved. (See Fig.1)

Working Group 2 discusses the following Area and Visions for setting MS Goals candidate.

[Area]

- *Leveraging the Aging Society*
  Turning the aging society into the innovative and sustainable society by harnessing diversity through techno-social transformation
- *Exploring frontiers with science and technology*

[Vision]

- *Society without health anxiety: everyone can enjoy life until 100 years old (achievement of well-aging)*
- *Reproducing and controlling key biological processes (biotech)*
- *In-depth understanding of neural and associated systems（brain/nerve system)*

[Examples of MS Goal candidate to be used as reference]

21) Creation of digital model of entire nerve system and adjacent systems (by 2050)
4) Dramatic improvement of QOL among the elderly (by 2035)
5) Preventive measures to maintain wellness (by 2040)
19) Complete digital mapping and externalization of the entire reproductive processes (by 2050)
20) Human hibernation (by 2050)

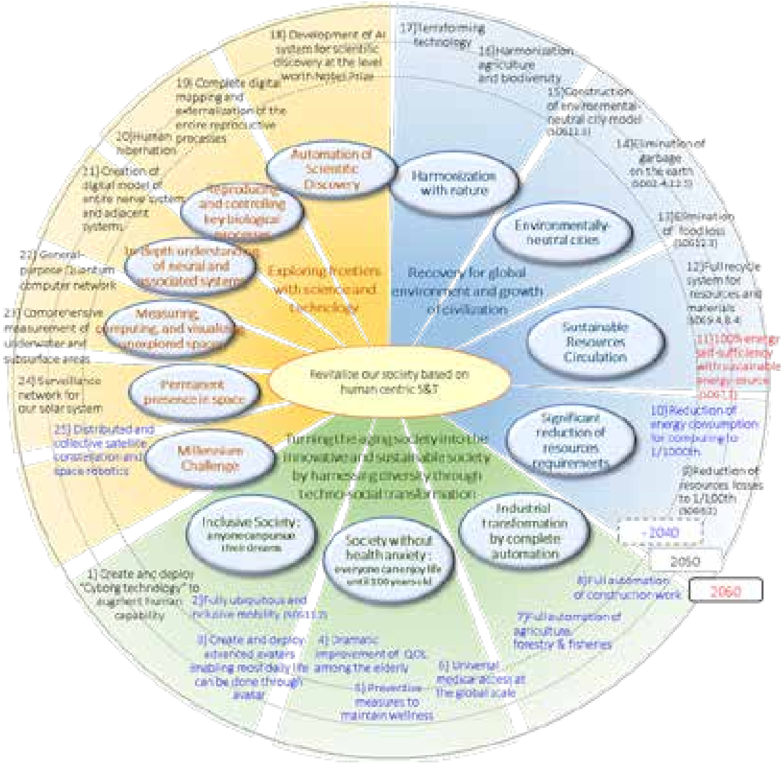

Fig.1-1. Future visions and 25 MS goal examples

2. Concept of MS Goal candidate

2-1. MS Goal candidate

- By 2050, realization of ultra-early disease prediction and intervention based on the Whole Body Network Atlas for longer, fuller and happier lives.

2-2. Target

- By 2050, we establish a system for disease prediction and evaluation of the pre-symptomatic states. This will be achieved by integrated analysis of the entire functional network between human organs and will ultimately realize the suppression and prevention of disease onset.
- By 2050, we establish a strategy that enables the conversion of a pre-symptomatic state to a healthy state. Functional changes in human physiology along life course will be clarified from the viewpoint of a comprehensive network between organs.
- By 2050, we identify disease-related network structure, including molecular targets as its component, and establish innovative prevention, diagnosis, and treatment methods.
- We establish non-invasive techniques applicable to human subjects for observing and manipulating organ networks.

2-3. Concepts

The rate of population aging in Japan is expected to be one of the highest among high income countries. Therefore, the Japanese government sets "the extension of healthy life expectancy" as a priority measure in the "future investment strategy".

To increase healthy lifespan expectancy, the realization of ultra-early disease prediction and prevention is one of the most important strategies for a healthy society. Based on this perspective, it is necessary to go a step further from the conventional approach of treating the disease after the onset and start an innovative research program with the new concept of disease prevention by identification of extremely early disease stages and preclinical stages.

Relatively simple relationship between etiology and pathophysiology is thought to exist in the case of infectious diseases and hereditary disorders. Conversely, core pathophysiology of chronic diseases, such as diabetes and dementia, is dysfunction of interactive network of organs. We aim to realize a Moonshot Goal "ultra-early disease prediction and intervention based on the Whole Body Network Atlas for longer, fuller and happier lives." by establishing innovative methods for early diagnosis of chronic diseases caused by the dysfunction of interactive network of organs, together with the methods of intervention that can reverse the pre-symptomatic state to a fully healthy state.

Specifically, we attempt to create "whole body simulator", which simulate the interactive network of all the internal organs in human body. This simulator will be utilized to establish methods for the optimization of personalized medical care and disease prevention. Construction of "whole body simulator" requires the establishment of the 'Whole-body Network Atlas', a database containing the comprehensive information about the network between all the organs at the cellular resolution. For the database construction, we will first attempt to achieve system-level understanding of the functional network between organs in the whole body, together with the complete understanding of the causal relationship and system's response to interventions. This research will lead to establishment of new therapeutic methods through the understanding of the disease recovery mechanisms, which can be studied by the analysis of pathological states of cooperative network between the organs and active manipulation of the network.

The pioneering attempt proposed in this document has not yet to be implemented in large research initiatives in Europe (Human Brain Project) and the United States (Human Cell Atlas, Brain Initiative). Therefore, global collaboration of this project with other large research programs in other countries is essential. In addition, in the course of this ambitious research program, valuable outcomes are expected to be generated and contribute to medical industries. Thus, we will also promote collaboration with private companies.

In the next phase of discussion and implementation of Moonshot Programs in the field of medicine, the goal should be set to cover the realistic problems in future medicine and the outcome should be valuable in the field of medicine and healthcare. The Moonshot Program in the field of medicine should aim at dramatic improvements in Quality of Life (QoL) and preventive wellness through development of new technologies for health monitoring and disease intervention, which are based on the scientific understanding of human biology.

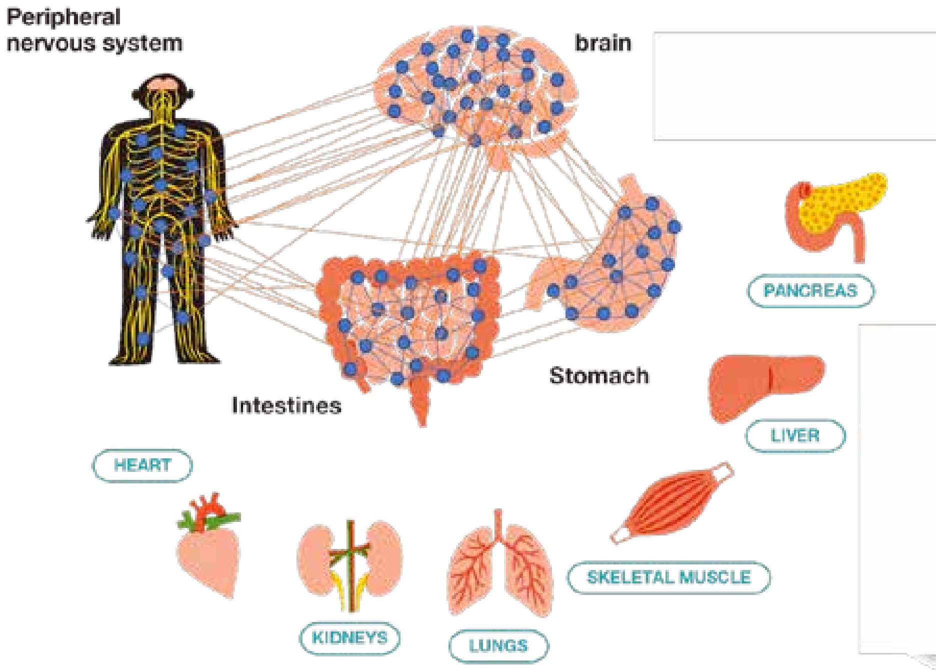

Fig1-2. Concept of understanding on a comprehensive network between organ

3.Why Now?

Since 1900, human life expectancy increased by more than 40 years. In particular, Japan excels in both longevity and healthy living as the population benefits from relatively high standards of hygiene, education, infrastructure and universal medical services. Japan currently ranks 2nd for healthy life expectancy in the world after Singapore. What is also remarkable is that according to recent survey 1 in every 2 elderly individuals (at 65 or older) desires to work. Looking to the future, by 2050 the proportion of elderly will exceed 35% of national population (i.e. more than 35 million people) and there will be over 680,000 centenarians. An increasing burden of chronic diseases driven by Japan's aging population presents unprecedented societal challenges with projected healthcare spending of 66 trillion JPY in 2040. In addition, there is an excess of two trillion yen in import over export of pharmaceutical products in Japan. Overcoming the burden of chronic diseases (Diabetes, hypertension, hyperlipidemia, arteriosclerosis, degenerative diseases such as dementia, psychiatric disorders such as schizophrenia and depression caused by network failure, allergies, collagen diseases, etc.) that mainly develop after adulthood is therefore a stupendous national priority. This is also an opportunity for Japan to become an epicenter of innovation, leading the world through health.

Even though these chronic diseases are devastating and claim many lives, our current scientific understanding on them is alarmingly incomplete. As etiology and pathophysiology remain unclear, we are unable to address them fundamentally. Since most existing therapeutics are for symptom management only or partial disease modifiers, patients often have to live with chronic diseases and eventually succumb to disease progression or to recurrence.

We believe that conventional approach, where research focuses on a single organ, tends to yield relatively limited and possibly biased view of a disease. If we are to capture how organs interact with and influence each other for the human body to function as a whole, we may discover and develop entirely new ways of disease prediction and intervention. In recent years, there is growing evidence that the human body is a network of mutually dependent organs and our health is the outcome of how these organs interact and function as a network.

Examples of putative interactive organ network are as follows:

- Parkinson's Disease: pathologic alpha-synuclein protein is proposed to spread from the gastrointestinal tract via the vagus nerve into the brain.
- Alcohol hepatitis: Alcohol increases the permeability of the gust lining to allow cytolysin-producing *Enterococcus faecalis* which damages hepatocytes
- Cancer: The circadian clock may be implicated in the regulation of cancer initiating cells, metabolism of cancer cells and alteration of disease progression
- Rheumatoid arthritis: Electrical vagus nerve stimulation results in anti-inflammatory signals (e.g. inhibition of TNF production).
- Viral infection: Choline acetyltransferase expressed by T cells plays a fundamental role in chronic viral infection.

The accumulated knowledge from these studies on the interaction network between organs would enable the prediction of chronic and other diseases. Furthermore, this would bring novel treatment and alleviation methods.

In order to predict diseases, an effective strategy is to develop a large-scale simulation system, "Whole Body Simulator", based on the combination of computational modeling and data collection. The Whole Body Simulator can be utilized to elucidate the earliest signs of disease as well as the best means of intervention. At present, we have little information on the comprehensive network between human organs for integrated analysis and understanding of the interaction between organs. Therefore, we should collect this information comprehensively and understand the functional relationship between organs. From the viewpoint of network analysis, there are some ongoing projects in the world, such as Brain / MINDS (Japan), Brain Initiative (US), Human Brain Project (Europe) which cover the brain, and the Human Cell Atlas Project which covers the whole body. However, no project aims to understand the comprehensive network between human organs.

For integrated analyses of the comprehensive network between human organs, we need to utilize both biological and computational technologies to develop essential technical components. Rich human resources in these research fields is an advantage of Japan. Furthermore, there is a tendency that many research projects are subdivided into relatively small field. To achieve the MS Goal, cross-sectional research projects should be realized under the MS program. In addition, the development of new therapeutic technology utilizing simulation-based disease prediction requires close collaboration between industry and academia. Thus, we aim to build a cross-sectional R&D system with industry-academia collaboration under the Moonshot program.

If we successfully find effective solutions for chronic diseases, people can live longer fuller and happier lives. These solutions will also deliver tremendous growth opportunities and contribute to prosperity in Japan and around the world.

4. Changes in industry and society

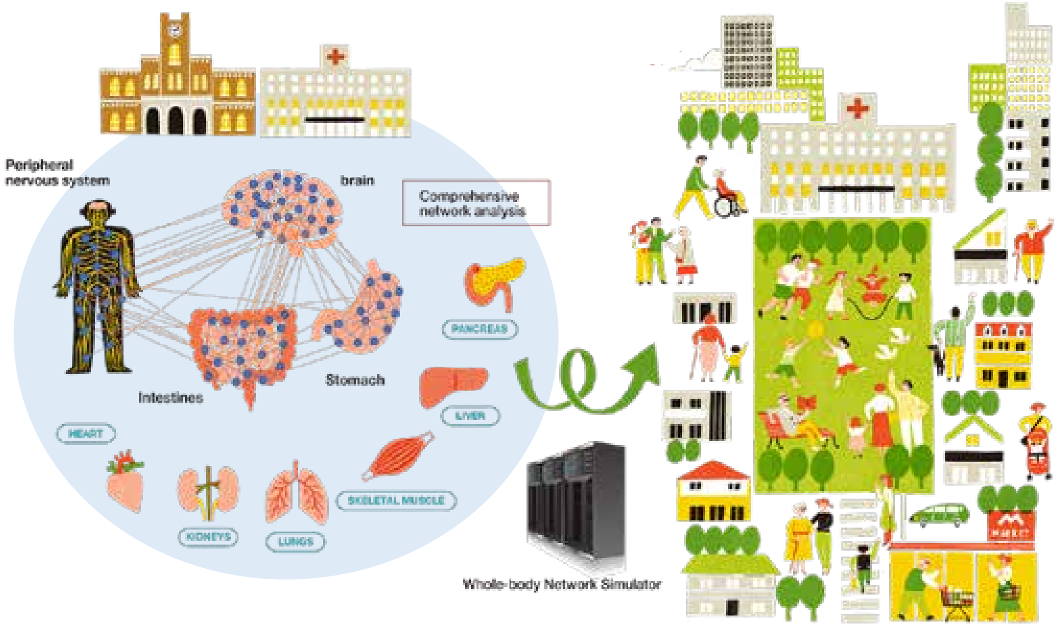

Fig1-3. Vision of a society

4-1. Overcoming chronic diseases

Cancer, heart diseases, cerebrovascular diseases, dementia, mental ill-health (e.g. schizophrenia, depression), orthopedic diseases, ophthalmic diseases and metabolic diseases (e.g. diabetes mellitus type 2) are all devastating and claim many lives. Yet, there are no effective solutions today. While considerable efforts are being made for compression of morbidity and increasing health awareness to improve life styles, much more must be done to address these chronic diseases with early detection and fundamental intervention.

An increasing burden of chronic diseases driven by Japan's aging population presents unprecedented societal challenges with projected healthcare spending of 66 trillion JPY in 2040. Overcoming the burden of chronic diseases is therefore a stupendous national priority. Furthermore, the challenge is not unique to Japan. Globally, chronic diseases are currently the major cause of death among adults in almost all countries and the toll is projected to increase by a further 17% in the next 10 years. For instance, 264 million people are estimated to suffer from depression resulting in the estimated cost to the global economy of US$ 1 trillion per year in lost productivity. As for diabetes mellitus type 2, which increase the risk of many other chronic diseases, recent estimates suggest that the number of people with diabetes across the world will increase from 415million in 2015 to 642million by 2040, and the global cost of diabetes is set to almost double to $2.5 trillion by 2030.

Accordingly, if we successfully find effective solutions for chronic diseases, people can live longer fuller and happier lives. These solutions will also deliver tremendous growth opportunities and contribute to prosperity in Japan and around the world. This is indeed an opportunity for Japan to become an epicenter of innovation, leading the world through health.

4-2. Compensation for senescence and congenital diseases by the robustness of the network

The human body is inherently robust and resilient. Even when a function is reduced or lost, we adapt with compensation mechanisms to minimize damage. For example, in case amyloid and tau accumulation takes place in the brain, it is believed that the brain can create new networks to compensate and such neuroplasticity helps the retention of cognition in many people. This robustness exists not only in the brain but also in other organs and within the network of organs. When one closes the eyes, other sensory organs become more sensitive. This sort of responsive robustness is an important physiological phenomenon, that may be known but not yet fully exploited for addressing functional decline in aging or functional loss in congenital diseases.

4-3. Strengthening competitiveness of the health and medical industry

The innovation in understanding the diseases leads to various medical technologies such as pharmaceuticals and medical devices, and will greatly contribute to strengthening the competitiveness of the health and Japanese medical industry. In addition, since the comprehensive network between organs is more complex compared to conventional research themes focused on individual life phenomena, the clarification of the comprehensive network between organs must create technological innovations. The integration of biological and computational approaches is expected to produce progress in observation, measurement, manipulation, and analysis technologies. For example, the technological development of imaging-related equipment, particularly well developed in Japan, it can be expected to create world-leading observation and measurement equipment, and the related life science industry will be greatly benefited.

Over the past century, the average human life expectancy has more than doubled thanks in large part to advances in science, technology and medicine. Recent medical innovations brought cure rates of almost 100% to Hepatitis C and near normal life expectancy to HIV patients. Cancer treatments significantly increased survival rates, achieving 25% decline in death rates since the 1990s. Yet, we must admit that R&D for health and medical industry remains hopelessly inefficient. Typically, the generation of a new drug requires more than 2.6 billion USD and 10-15 years. Cost of failure is so great that many companies struggle to advance drug development for chronic diseases.

Our fundamental issue is that for most chronic diseases, etiology and pathophysiology remain unclear. As a consequence, the majority of existing therapeutics are for symptom management only or partial disease modifiers. Patients often have to live with diseases and may eventually succumb to disease progression or to recurrence.

We believe that conventional approach, where research focuses on a single organ, tends to yield limited and possibly biased view of a disease. If we are to capture how organs interact with and influence each other for the human body to function as a whole, we may discover and develop entirely new ways of disease prediction and intervention. In recent years, there is growing evidence that the human body is a network of mutually dependent organs and our health is the outcome of how these organs function as a network. For instance, Alzheimer's Disease has remained a mystery despite many years of painstaking and diligent research efforts. In recent times, researchers believe that Alzheimer's Disease has multiple, interrelated causes (inflammation, misfolded proteins, mitochondrial dysfunction, vascular disease, synaptic loss, and eventually loss of our neurons) that result in a cascade of dysfunction. This means that an effective intervention is likely to be a combination of treatments targeting more than one of these causes. Given such complexity and sequential nature, we believe that the most practical approach is to address chronic diseases ultra-early, way before signs and symptoms start to appear so that disease progression is halted before the point of no return and for the restoration of fully healthy state.

If we can identify effective methods for ultra-early prediction and intervention based on the functional network database of all the human organs (The Whole Organ Network Atlas) as well as biological and computational simulations (The Whole Body Simulators), we can open up our research and development to greater possibilities. Ultra-early interventions that fundamentally address diseases are likely to require new modalities and technologies. Should we intervene before a cascade of dysfunction kicks in, it may be possible to manipulate or artificially induce the body's inherent robustness and resilience.

II. STATISTICAL ANALYSIS

1. Structuring of MS Goal

Our MS Goal is "By 2050, realization of ultra-early disease prediction and intervention based on the Whole Body Network Atlas for longer, fuller and happier lives". This Working Group's approach is boldly unique and leverages Japan's existing strengths described in Figure 2-1. In addition, given the increasing potential of data driven research, we will focus on 4 specific areas for innovative technologies and future applications: observation (imaging), operation (biological manipulation), measurement (genome, omics etc.) and analysis (AI etc.). To realize our ambition with speed and operational excellence, biomedical researchers will work hand in hand with not only each other but also mathmaticians and computer scientists.

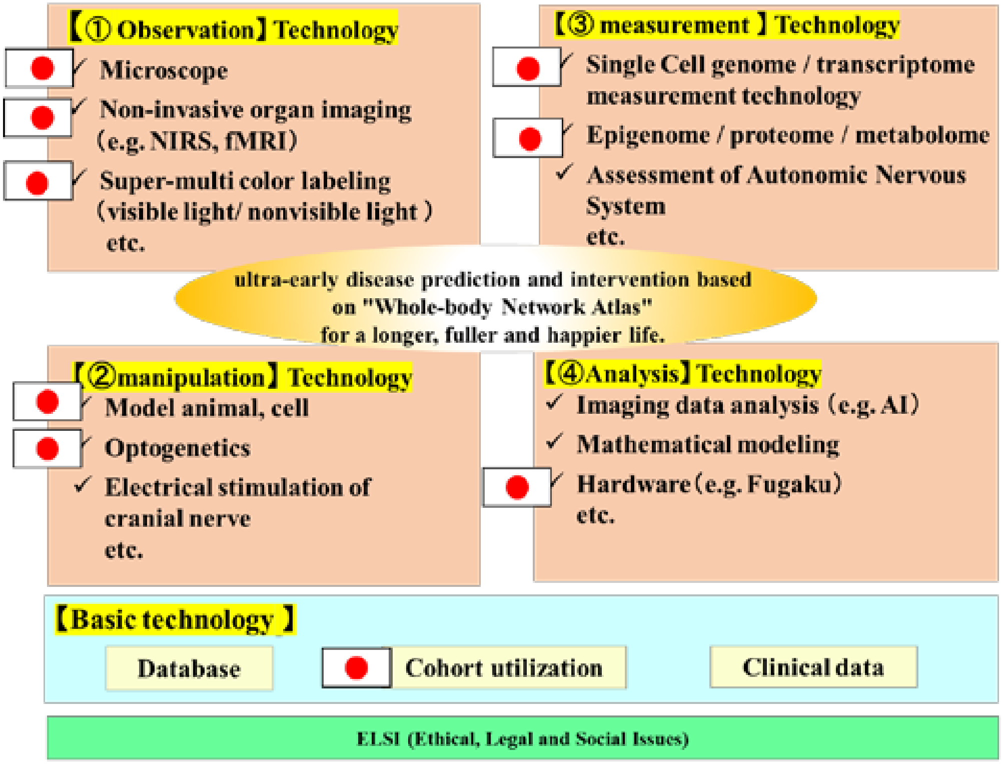

Fig.2-1. Overall structure overhead view (the strength areas of the country are indicated by the Japanese flag.)

In Fig. 2-1, the strength areas of the country are indicated by the Japanese flag. In general, the country holds a leading position in various elemental technologies and life phenomena research, that lead to health and medical technology improvements. Regarding data infrastructure, there is a world shortage of these assets. Specifically, in Japan, there is a high demanding trend. However, for example, a relatively large group composed of old-aged individuals only exist in Japan. The country possesses the largest scale and highest quality genome group in the world.

By expanding these advantages and performing strategic integration, it is expected to create results with great impact in the Japanese people and to ethnicities, in industry, and in science.

2. Science and Technology Map

In order to find effective solutions for major chronic diseases described above, this Working Group's areas of interest are brain/nerve, psychiatry, cancer, stem cells, immunity, digestion and circulation. According to the NISTEP Science Map 2016 (Figure 2-2), there is currently a noticeable knowledge gap between the area of brain/nerve and psychiatry and the area of cancer, stem cells, immunity, digestion and circulation. This means that our MS initiative is likely to encounter both challenges and opportunities for new discoveries. Our novel findings on how the organs interact with and influence each other at cellular and molecular levels will lead to the creation of new research ecosystem where creative people and ideas can gather and grow.

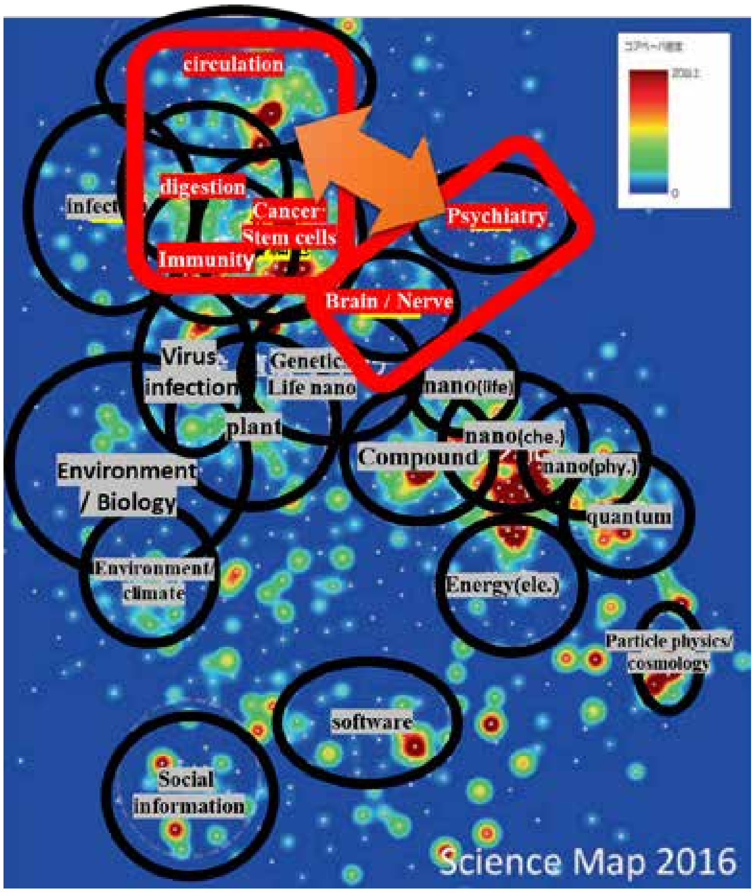

Fig. 2-2. the Science Map

The NISTEP Science Map 2016 published in September 2018. The research and development focus of this Working Group consists mainly of four basic technologies: observation technology (imaging), operation technology (i.e., biological manipulation), measurement technology (i.e., Genome, Omics, etc.), and analysis technology (i.e. AI, etc.). The strategy to achieve the Working Group goals is on how to develop and utilize these technologies. In addition, data infrastructure is also important. Following the trends of Europe and the United States (such as Human Cell Atlas), the construction of domestic databases, and the use of characteristic domestic cohorts are not left to individual researchers, and the country has a strong desire to build strategically.

3. Strengths of Japan, Trends in global research community

3-1. Research trends International Benchmark

Based on "CRDS Panoramic View Reports, life science / clinical medicine (2019)", Table 2-1 was created to show how Japan currently compares with other major nations in research and technical areas that are relevant to this Working Group. In basic research Japan has established its strengths in:

- "Brain and neuroscience"

  Japan is a world leader in this field. For many years Japan has carefully maintained both human resource and research resource among universities and research institutes. As a result, physiological technologies for analyzing the nervous system were developed to a high standard. Forming cross-functional research groups for integrated research was also beneficial to pursue specific areas and new academic interests. In recent years, Japan's "marmoset (primate) brain clarification project" was internationally recognized especially for investigating functional brain molecules through sedated animal analysis.

- "Optics / Imaging" and "Bioimaging"

  Japan's leading position is exemplified by successful development of small organic molecule-based probes for imaging – a fruit of historical strength in synthetic organic chemistry.

  In addition, Japan is a pioneer in the area of imaging technologies such as PET, MRI, and NMR. For example, fMRI, an important tool that directly measures the blood flow in the brain to observe brain activity, was invested in Japan.

Data analysis and artificial intelligence (AI) are increasingly important. Historically, Japan's researchers were quite active in this field making considerable contributions. However, in recent times, the amounts of financial investment in other countries have been greatly surpassing that of Japan. Consequently, at present, Japan is not in a position to claim Data analysis and AI as its strength. Strategically promoting this field is essential for the future.

Table 2-1 International comparison of related research and technical fields

Country, Region	Phase	Brain and neuroscience		Optics Imaging		Bioimaging		Data analysis (AI)	
		Current status	Trend	Current status	Trend	Current status	Trend	Current status	Trend
Japan	Basic research	◎	→	◎	→	◎	↘	○	↗
	Applied research	○	→	○	→	○	→	△	→
US	Basic research	◎	→	◎	↗	◎	→	◎	↗
	Applied research	◎	→	○	↗	◎	→	◎	↗
EU	Basic research	○	→	◎	→	◎	→	○	↗
	Applied research	○	→	◎	→	◎	→	○	↗
China	Basic research	△	↗	○	↗	○	↗	◎	↗
	Applied research	△	↗	△	↗	○	↗	◎	↗

3-2. Trends in global research community

Here we describe existing large scale projects that are relevant to this Working Group.

(1) Brain research

① Large US projects『Brain Initiative』(Table 2-2)

- In April 2013 the former US president Mr. Barack Obama announced the "Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative", and the project started in 2014.
- The project mission is the "development and application of technology for understanding human brain function". The project is aimed at the development and application of new technologies to elucidate how the brain functions through the interaction of individual brain cells and neural circuits. It also aims to elucidate the complex relationship between the brain and behavior that enables the recording, processing, use, storage, and withdrawal of a large amount of information.

Table 2-2. Overview of the US Brain Initiative

Research area	Participating research institutions	Implementation period and Budget etc.
1. Technology development by utilizing the results of nerve and brain research 2. Brain function visualization by promoting dynamic imaging 3. Brain function research 4. An integrated understanding of brain function and behavior 5.Promotion of use to patients	・Federal government agency NIH, NSF, DARPA, IARPA, FDA, DOE ・Private foundation, research institute, and private company National Photonics Initiative, Brain & Behavior Foundation, Simmons Foundation, The Kavli Foundation, Allen Institute for brain, Janelia Research Campus, Salk Institute for Biological Studies, Google, GlaxoSmithKline, GE, etc.	・From 2014 to 2025 ・Approx. $430 million in FY2019 ・21st Century Cures Act will contribute to approx. $ 1.5 billion in FY2017-FY2026 ・Budget in FY2019 includes $120 million under this bill

② Large European Union research project『Human Brain Project』(Table2-3)

・The Human Brain Project started in 2013 as EU-FET（Future and Emerging Technologies）.

・Its purpose are:

— integration of brain science, information and communication technology, and medical treatment

—construction of ICT integrated infrastructure research platform, and data integration.

・Experimental basic research has been performed to provide data for this purpose.

Table2-3. Overview of EU Human Brain Project

Research area	Participating research institution	Implementation period and Budget etc.
1.Mouse Brain Organization 2.Human Brain Organization 3.Systems and Cognitive Neuroscience 4.Theoretical Neuroscience 5.Neuroinformatics Platform 6.Brain Simulation Platform 7. High-Performance Analytics and Computing Platform 8.Medical Informatics Platform 9.Neuromorphic Computing Platform 10.Neurorobotics Platform 11.Central Services 12. Ethics and Society	・EU-FET（Future and Emerging Technologies）Flagship program 112 organizations in 24 countries ・In Japan, Okinawa Institute of Science and Technology and RIKEN participate in this project.	・From 2013 to 2023 ・$11 billion / 10 years

③ Large Japan research project『Brain/MINDS』(Table2-4)
（Brain Mapping by Integrated Neurotechnologies for Disease Studies）

・The purpose is to map brain structures and functions at various levels and to improve the efficiency and sophistication of primate (marmoset) genetic manipulation technology and optical system technology. In addition, through these technologies, the project will elucidate the whole aspect of neural circuits that perform higher-order functions in the brain of primates at the neuron level, and to contribute to overcome mental and neurological diseases and enhance information processing technology.

Table2-4. Overview of Japan『Brain/MINDS』

Research area	Participating research institution	Implementation period and Budget etc.
・Acquisition and aggregation of image data such as schizophrenia / depression / dementia / Parkinson's disease / autism ・Comparison with human disease image data / Correspondence between differences and similarities between humans and monkeys ・Identification of neural circuits important for human mental activity ・Development of translatable indicators for brain behavior linked to humans ・Elucidation of the brain and neural circuit using marmoset	【Representative organization】 ・RIKEN ・Kyoto Univ. ・Keio Univ. 【Clinical Research Group】 ・The Univ. of Tokyo ・Kyoto Univ. ・Tokyo Medical and Dental University etc.	・From FY 2014 to FY 2024 ・Government budget: 3,225 million JPY（FY2019）

（2）Human cells (Table 2-5)

①International project『Human Cell Atlas』(Table2-5)

- The purpose is to categorize and catalog the type, state, and lineage of all human cells.
- The project aims to construct a map of human cells including cell types, 3D locations, geographical and racial differences, using a single-cell transcriptome in all major human tissues.
- Advances in measurement technology allowed this project to start. (single-cell analysis made the detailed profiling of each cell possible)

Table 2-5. Overview of International Project Human Cell Atlas

Research area	Participating research institution	Implementation period and Budget etc.
・Sample adjustment / analysis technology of Brain / Immune / Gastrointestinal (Gastrointestinal) / Skin / Tissue ・Software tools, etc.	The United States globally directs this project. ・UK EMBL-EBI, US Broad Institute, US UCSC, Genomics Institute, etc. ・In Japan, RIKEN participate.	・From 2017 ・Supported by the various public and private projects, directed by the Zuckerberg Foundation.

3-3 Current status and issues of life science big projects such as Human Cell Atlas

As described in this section, the global research community is now focusing on in-depth profiling of specific organ or system (e.g. Brain Initiative, Human Brain Project, Brain/MINDS) and extensive cataloguing of human cells. These large scale projects will undoubtedly contribute to the advancement of basic science and enrichment of publicly available knowledge.

Our MS Goal and initiative are complementary to these public endeavors. We thus hope for international and national collaborations so that researchers can benefit from mutual synergy.

What makes the Whole Organ Network Atlas distinct is our focus on the functional relationship among human organs. We believe that this unique approach will lead to new findings on how the organs interact with and influence each other for the human body to function as a whole. Moreover, we expect the Whole Organ Network Atlas to serve as the knowledge foundation of Whole Body Simulator. Biological and computational simulations will unfold the earliest signs of disease as well as the best means of intervention. By 2050, each person will benefit from individualized healthcare where ultra-early disease prediction leads to intervention that effectively reverses disease progression before the point of no return and for the restoration of fully healthy state.

III. SCENARIO FOR REALIZATION

1. Possible scenarios for realizing the MS Goal Candidate

1-1. Basic process flow

In order to realize the MS Goal candidate, “ultra-early disease prediction and intervention based on the Whole Body Network Atlas for longer, fuller and happier lives.”, we aim to establish the innovative approach for the diseases to act on the “state that can still be reversed” prior to the irreversible dysfunction of interactive network between organs, i.e. from the “pre-symptomatic state” to a healthy state. The following two processes are considered necessary to achieve the goals.

- Understanding on the comprehensive network between human organs
- Creation of Whole-body Network Atlas and development and implementation of the prediction system for diseases by Whole-body Network Simulator and new prevention and treatment methods for diseases.

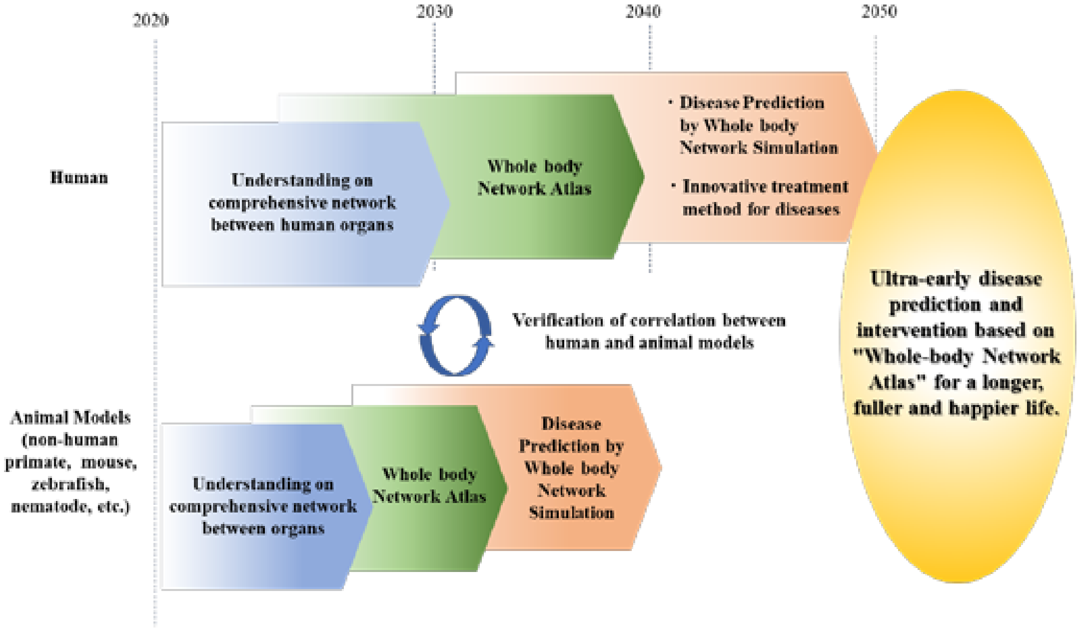

Fig 3-1. Millstones of Innovative Approach for ultra-early disease prediction and intervention based on the Whole Body Network Atlas for longer, fuller and happier lives

(1) Understanding on the comprehensive network between human organs

① Purpose

As mentioned before, researchers assume that various chronic diseases may be caused by interaction of various organs and spreading of disease-related dysfunction through peripheral networks of nerves, blood vessels, and immune cells in earlier stages. The purpose of “understanding on the comprehensive network between human organs” is to clarify the interaction between organs through such hidden networks of the internal organs..

② Methodology

In addition, to the approach of focusing on specific organs in the human body and analyzing their interactive network, construction of experimental system with small model animals may accelerate the research program toward understanding on comprehensive network between organs in the whole body. As an example of the latter, regarding the zebrafish brain, techniques for decoding the activity of all nerve cells as high-speed three-dimensional data have already been developed, and the nature of the neural network that controls the behavior of fish is being clarified.

Findings and technologies from model animals will speed up the whole MS program. Another important component in acquisition of data from functional network between organs is development of innovative technologies for data acquisition from human body. Methodologies that enable long-term acquisition of cellular information from multiple organs at high temporal resolution are required, in combination with novel data acquisition techniques at single-cell resolution.

③ Expected effects and social value

As described above, researches on the zebrafish brain are revealing the nature of the neural network that controls fish behavior. In contrast to the assumption that neurons are the only cellular component involved in decision making, recent findings indicate that the glial cells also contribute to this process. By accumulating findings from multiple model animals with the "understanding on comprehensive network between human organs" approach, we expected to elucidate new biological mechanisms and find new functional molecules, which may contribute to "develop drug discovery, prevention/diagnosis methods".

(2) Creation of Whole-body Network Atlas, Development of whole-body simulator

① Purpose

As mentioned before, the purpose is to suppress and prevent the onset of the disease by a predictive approach for the conversion of a pre-symptomatic state to a healthy state. Simultaneously, we aim to identify disease-related network structures, including target molecules, and establish new prevention, diagnosis, and treatment methods.

② Methodology

To understand the cooperative networks between organs, the 'Whole-body Network Atlas' database describing the relationship of the network at the single-cell level between all human organs should be constructed. It is important to promote efficient development by using human and animal models. To construct the database, it will be recommended to run parallel research programs that utilize model animals effectively. One example is the initial pilot study with model animals and subsequent application of the same technology and methodology to more complex animals. Another possibility is development of multiple simulators spanning specific stages of the life course, such as "early development model", "mature stage model", and "aging model". In each case, several steps are required as test data accumulation, small-scale model simulations based on small-scale data, animal experiments to demonstrate prediction of the biological response from the simulation, model improvement based on the response after intervention. Test data will be released as an open resource, 'Whole body Network Atlas', which will accelerate the development of simulators.

③ Expected effects and social value

Valuable outcomes can be expected even in the process of the pilot database construction before completion of the 'Whole-body Network Atlas'. One possible intermediate outcome is establishment of clear criteria for the detection of "a state that can still be reversed" and " a pre-symptomatic state" before disease onset through the analysis of deviation from the average in the human population data and aberrant behavior of disease biomarkers. These criteria for the detection of pre-symptomatic state will enable early prediction of the chronic diseases (diabetes, hypertension, hyperlipidemia, arteriosclerosis, degenerative diseases such as dementia, psychiatric disorders such as schizophrenia and depression caused by network failure, allergies, collagen diseases, etc.). Furthermore, by developing the Whole-body Simulator, it is possible to perform comprehensive evaluation of day-to-day variation in health conditions. This will help establish medical care optimized for the health conditions of each person.

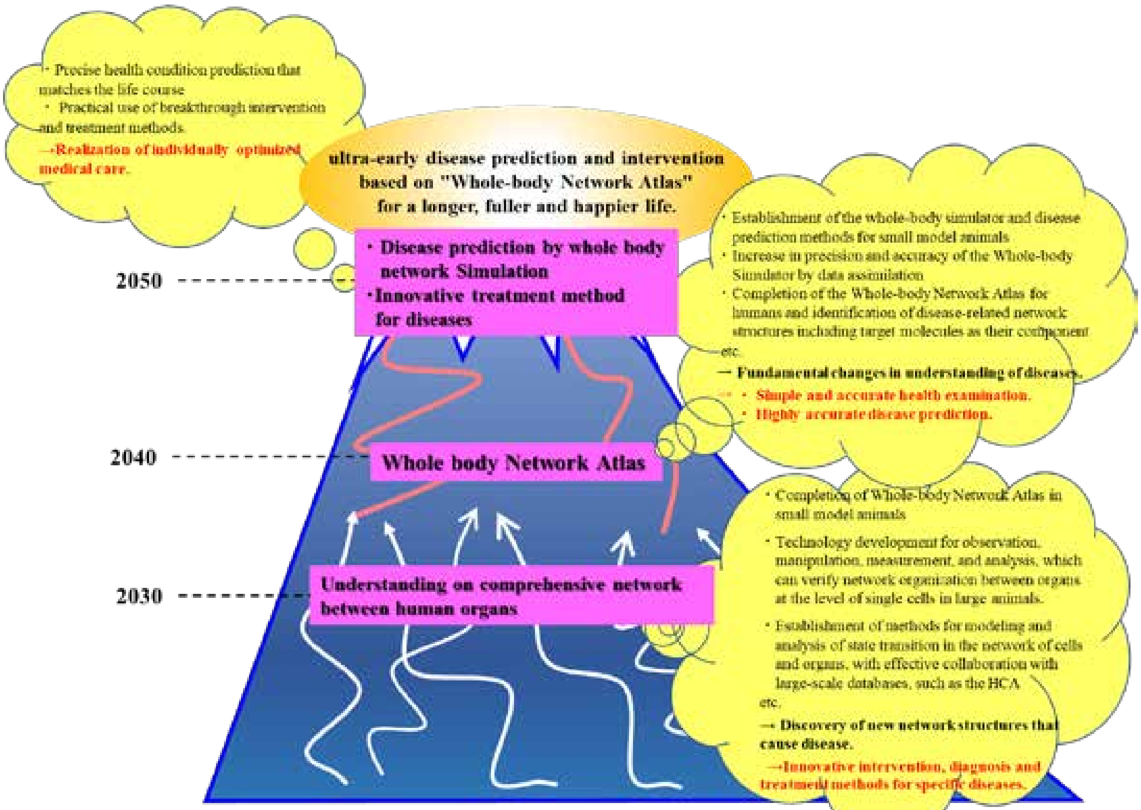

Fig3-2. Output and outcome in each stage (Black sentences indicate output and red sentences indicate outcome, respectively.)

1-2. Example scenarios

Example scenarios are described below. Based on R&D trends, specific images of milestones and technical/social issues are described. The example scenarios only describe the conceptual possibilities and the practical approaches should be proposed from PM candidates. Additional information about the research framework will be released from the Japan Science and Technology Agency in the document for open call of the proposals.

(1) Example scenario 1.

In this scenario researchers takes advantage of small animal models and start from comprehensive network analysis of these model animals to develop network simulators. Application of existing technology to small model animals will be sufficient to complete the short-term pilot study. The obtained knowledge and developed technology will provide the experimental bases that enables the second step of research with larger animals and humans. By combining the resources from the study of small animal models and the HCA cell mapping data expected to be completed within several years, the human Whole-body Simulator will be efficiently developed and open the way for translation of new prevention and treatment methods for diseases.

【Milestone】

In 2050：

- Completion of the whole-body simulator for humans;
- Establishment of prediction methods for diseases based on the understanding of the network structure of interaction between organs;
- Implementation of new preventive and therapeutic methods based on disease prediction;

In 2040：

- Completion of the Whole-body Network Atlas for humans and identification of disease-related network structures including target molecules as their component;
- Establishment of the whole-body simulator and disease prediction methods for small model animals;
- Increase in precision and accuracy of the Whole-body Simulator by data assimilation;

In 2030：

- Identification of disease-related network structures including target molecules as their component in small model animals. Completion of Whole-body Network Atlas in small model animals;
- Establishment of methods for modeling and analysis of state transition in the network of cells and organs, with effective collaboration with large-scale databases, such as the HCA;
- Technology development for observation, manipulation, measurement, and analysis, which can verify network organization between organs at the level of single cells in large

animals;

- Technology development of observation, manipulation, measurement, and analysis to verify network organization between cells and organs with cellular resolution.

(2) Example scenario 2.

In this scenario, the research target is set to human physiology and pathology from the initial stage of the program, without pilot studies in small model animals. Researchers may start from comprehensive network analysis between two specific organs together with development of necessary analytical tools. Subsequently, the Whole-body Network Atlas in humans will be gradually assembled by incorporating other organs in the network or merging multiple databases for the subsets of organs. Construction of models that can predict network transitions will be carried out in parallel.

【Milestone】

In 2050：

- Completion of the Whole-body Simulator in humans;
- Establishment of prediction methods for diseases based on the understanding of the network structure of interaction between organs;
- Implementation of innovative preventive and therapeutic methods based on disease prediction;

In 2040：

- Completion of the Whole-body Network Atlas for humans and identification of disease-related network structures including target molecules as their component
- Increase in precision and accuracy of the Whole-body Simulator by data assimilation;

In 2030：

- Completion of the network analysis between predetermined sets of human organs;
- Technology development for observation, manipulation, measurement, and analysis, which can verify network organization between organs at the level of single cells in large animals
- Establishment of methods for modeling and analysis of state transition in the network of cells and organs, with effective collaboration with large-scale databases, such as the HCA;

(3) Example scenario 3.

This scenario put the initial effort in the simulation of dynamic state transition in the organ network. The process of development, maturation, and aging in model animals can be viewed as the process of formation and remodeling of the functional network between organs. Reliable prediction of state transition in the complex network of multiple organs may be highly challenging. Therefore, it may be reasonable to restrict the research targets to the small subsets of organs. In parallel, the Whole-body Network Atlas in humans will be created, and the established simulation methods of dynamics state transition in the organ network will be applied to humans;

【Milestone】

In 2050：

- Completion of the whole-body simulator in humans;
- Establishment of prediction methods for diseases based on the understanding of the network structure of interaction between organs
- Implementation of innovative preventive and therapeutic methods based on disease prediction;

In 2040：

- Completion of the Whole-body Network Atlas for humans and identification of disease-related network structures including target molecules as their component
- Establishment of the methods for dynamic whole-body simulation and disease prediction method in model animals;
- Increase in precision and accuracy of the Whole-body Simulator by data assimilation;

In 2030：

- Completion of analysis of network between organs for each life stage (e.g. "model of early development", "model of maturation", "model of aging") in model animals. Completion of Whole-body Network Atlas in the animal models;
- Technology development for observation, manipulation, measurement, and analysis, which can verify network organization between organs at the level of single cells in large animals;
- Establishment of methods for modeling and analysis of state transition in the network of cells and organs, with effective collaboration with large-scale databases, such as the HCA;

2. Considerations regarding research promotion toward the realization of Goal candidate

(1) Research and development framework

① Team organization

The research program led by each PM should contain two subgroups that take different approaches. Namely, the first subgroup should focus on "molecular, cellular, and biochemical approaches" and the second group should take the approach based on "AI technologies and mathematical modeling".

It should be noted that the second subgroup is responsible for data-driven research and accumulation of sufficient network data should precede the start-up of this subgroup. Therefore, the timing of establishing the second subgroup requires considerations for alternative strategies, such as the collaboration with other data-oriented research programs and large research initiatives in Europe and US.

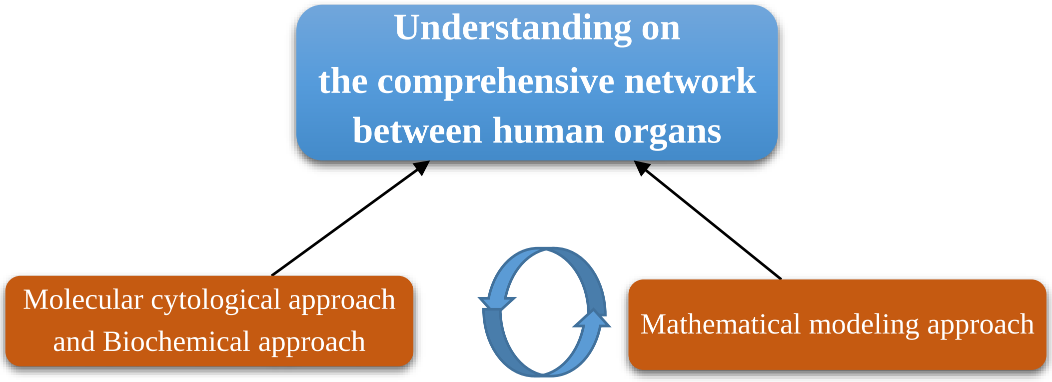

Fig3-3. Strategy of the process for R&D projects

② Collaboration with companies

In the process of developing various approaches to achieve this goal, we expect to create various results that will contribute to the health care segment. Therefore, it is important to collaborate with private companies from the initial stage of the program. In addition, we should operate the program to construct a sustainable system for achieving the MS goal because the Moonshot program will be supported for up to 10 years.

(2) International collaboration

Large projects in Europe and the United States have yet not been able to successfully implement the concept of "ultra-early disease prediction and intervention". Therefore, we hope to establish international collaboration. If the open data acquired by large-scale projects that have already started in Europe and the United States (e.g., Human Cell Atlas) are available, we recommend using them. In addition, PD will consult with PM in the viewpoint of international collaboration.

(3) ELSI

For achievement of the goal, we need to use various personal information related to medical care, etc. This information should be treated carefully. Conduct various activities through dialogue and collaboration among various stakeholders to conduct further research, innovation, and policy formation. By doing so, we will combine efforts to solve social issues. With the recognition that ELSI is a co-driver for innovation, the public seek participation of social scientists and law scholars and will aim to establish science and technology as a culture.

IV. CONCLUSION

In WG2, we started discussion based on ㉑" Creation of digital model of entire nerve system and adjacent systems (by 2050)", ④" Dramatic improvement of QOL among the elderly (by 2035)"⑤" Preventive measures to maintain wellness (by 2040)" ⑲ " Complete digital mapping and externalization of the entire reproductive processes (by 2050)"⑳" Human hibernation (by 2050)" out of 25 related examples of moonshot goals at the visionary council.

For the MS Goal candidate to be accepted by different people as a goal to be achieved by approximately. 2050, we reviewed international trends and the status of domestic projects, and discussed various issues such as the expected milestones and the image of R&D, and the spin-offs expected in the process of R&D.

Based on the above discussion, we propose "by 2050, to realize ultra-early disease prediction and intervention based on the Whole Body Network Atlas for longer, fuller and happier lives." as an MS Goal candidate in WG2

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