R&D Concept of “Realization of ultra-early disease prediction and intervention by 2050.”

February 2020
Ministry of Education, Culture, Sports, Science and Technology

1. Moonshot Goals
Within the Moonshot Goals (decided on January 23rd, 2020, by Plenary session of Council for Science, Technology and Innovation), the Ministry of Education, Culture, Sports, Science and Technology (“MEXT”), with Japan Science and Technology Agency (“JST”) as a research and development promotion agency, will undertake research and development activities for achieving of the following Goal.

<<Moonshot Goal>>
“Realization of ultra-early disease prediction and intervention by 2050”

• Establishment of a system for disease prediction and evaluation of pre-symptomatic states through integrated analysis of the entire functional network between human organs, and suppression and prevention of disease onset, by 2050.

• Establishment of a strategy that enables the conversion of a pre-symptomatic state to a healthy state, by clarification of functional changes in human physiology along life course considering the comprehensive network between organs, by 2050.

• Identification of disease-related network structures and establishment of innovative prediction and intervention methods by 2050.

• Understanding of the comprehensive network between human organs by 2030.
2. Direction of research and development

Based on the discussion and proposal made in the Moonshot International Symposium (held in December 17, 18, 2019), direction of research and development at present is shown as follows.

(1) Area and field to promote challenging R&D

Particularly considering Japan’s decreasing birthrate and aging population, it is important to increase healthy lifespan expectancy. To do this, it is necessary to go a step further than 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 at extremely early disease stage or before becoming symptomatic.

To realize ultra-early disease prediction and intervention, it is necessary to promote R&D on the technologies as shown in Fig.1 (observation, manipulation, measurement, analysis, database creation), and advance understanding of the comprehensive network between human organs through integrating these technologies. In these research fields and areas, challenging R&D should be promoted.

![Fig.1 Main fields and areas of R&D required for realization of ultra-early prediction and intervention.](image-url)
(2) Research subject for realization of MS Goal

The image in Fig.1 is the area and field for challenging R&D to be promoted under the Moonshot Research & Development Program. R&D that contribute to the achievement of this MS goal "realization of ultra-early disease prediction and intervention by 2050" should proceed. In order to have the most effective and efficient countermeasure, the most cutting edge scientific trends shall be researched and used for R&D.

And in concrete terms, the aim is to perform an integrated analysis of the networks between organs and based on this develop a system that simulates these networks. Development of such a system will also contribute to predicting and preventing diseases at an early stage.

In conducting R&D, various sources and types of knowledge and ideas will be adopted, stage gates will be established. And evaluation will be conducted to promote R&D to achieve Goal.

In addition, from the viewpoint of smoothly implementing research results in society, a system that enables researchers in various fields to participate in ethical, legal, and social issues will be considered.

(3) Direction of research and development for realization of the Goals

○ By 2030

Understanding of the comprehensive network between human organs by 2030.

○ By 2050

Establishment of a system for disease prediction and evaluation of pre-symptomatic states through integrated analysis of the entire functional network between human organs, and suppression and prevention of disease onset, by 2050.

Establishment of a strategy that enables the conversion of a pre-symptomatic state to a healthy state, by clarification of functional changes in human physiology along life course considering the comprehensive network between organs, by 2050.

Identification of disease-related network structures and establishment of innovative prediction and intervention methods by 2050.

Understanding of the comprehensive network between human organs by 2030.
In order to realize ‘ultra-early disease prediction and intervention’, first of all, we need a comprehensive understanding of the network between human organs. In addition, we need to establish a database containing comprehensive information about the network between all organs at the cellular level. Finally, it is necessary to develop and commercialize ultra-early disease prediction and intervention technologies based on a simulation system. Therefore, we aim at understanding the comprehensive network between human organs by 2030. Fig. 2 shows how to proceed with R&D to achieve the Moonshot Goal by realizing the ambitious R&D plan.

Fig.2 R&D process toward the realization of ultra-early prediction and intervention
Summary of content which is analyzed in the Initiative Report presented in Moonshot International Symposium is shown, as follows:

(1) Structure of research fields and technologies

The MS goal will be driven by data research, which has rapidly increased its presence in recent years, and develop and use innovative basic technologies (observation, manipulation, measurement, analysis) to increase understanding of health and disease and ultimately detect and prevent disease onset early through analyzing the comprehensive networks between organs. Ambitious R&D is required.

In Fig. 3, the strength areas of Japan are indicated by double circles. In general, Japan holds a leading position in various core technologies and life phenomena research, that lead to health and medical technology improvements. Regarding databases and clinical data, there is a world shortage of these assets, and they are in particular demand in Japan. However, regarding cohort usage, a relatively large cohort composed of super elderly persons only exists in Japan, and Japan
has the world’s largest scale and highest quality genome cohort. By expanding these advantages and performing strategic integration, we expect to create results with great impact.

(2) R&D trends in related fields
Here we describe existing large scale projects that are relevant to MS goal.

① Large US projects“Brain Initiative”
・ 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 1. Overview of the US Brain Initiative

<table>
<thead>
<tr>
<th>Research area</th>
<th>Participating research institutions</th>
<th>Implementation period and Budget etc.</th>
</tr>
</thead>
</table>
| 1. Technology development by utilizing the results of nerve and brain research | ・ Federal government agency NIH, NSF, DARPA, IARPA, FDA, DOE             | ・ From 2014 to 2025
| 2. Brain function visualization by promoting dynamic imaging                    | ・ 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. | ・ Approx. $430 million in FY2019
| 3. Brain function research                                           |                                                                        | ・ 21st Century Cures Act will contribute to approx. $1.5 billion in FY2017-FY2026 |
| 4. An integrated understanding of brain function and behavior            |                                                                        | ・ Budget in FY2019 includes $120 million under this bill                 |
| 5. Promotion of use to patients                                           |                                                                        |                                                                         |
Large European Union research project『Human Brain Project』

- 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.

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

Large Japan research project『Brain/MINDS』(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.

### Table3. Overview of Japan 『Brain/MINDS』

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

**International project 『Human Cell Atlas』**

・ 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 4. Overview of International Project 「Human Cell Atlas」

<table>
<thead>
<tr>
<th>Research area</th>
<th>Participating research institution</th>
<th>Implementation period and Budget etc.</th>
</tr>
</thead>
</table>
| ・ Sample adjustment / analysis technology of Brain / Immune (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) Strengths of Japan, trends in global research community

Table 5 shows 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)”
  Regarding measurement data analysis, basic research such as medical image processing is active in Japan, but there are restrictions on the data that can be handled and the absolute number of participating researchers is
insufficient. 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 5. International comparison of related research and technical fields

<table>
<thead>
<tr>
<th>Country, Region</th>
<th>Phase</th>
<th>Brain and neuroscience</th>
<th>Optics Imaging</th>
<th>Bioimaging</th>
<th>Data analysis (AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Current status</td>
<td>Trend</td>
<td>Current status</td>
<td>Trend</td>
</tr>
<tr>
<td>Japan</td>
<td>Basic research</td>
<td>◎ → ◎ → ◎ \ → ○</td>
<td>↘</td>
<td>◎ → \ → ○</td>
<td>↘</td>
</tr>
<tr>
<td></td>
<td>Applied research</td>
<td>○ → ○ → ○ → △ → →</td>
<td>&lt;&lt;</td>
<td>○ → ○ → ○ → △ → →</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Basic research</td>
<td>◎ → ◎ → ◎ \ → ◎</td>
<td>↘</td>
<td>◎ → ◎ → ◎</td>
<td>↘</td>
</tr>
<tr>
<td></td>
<td>Applied research</td>
<td>◎ → ◎ → ◎ \ → ◎</td>
<td>↘</td>
<td>◎ → ◎ → ◎</td>
<td>↘</td>
</tr>
<tr>
<td>EU</td>
<td>Basic research</td>
<td>○ → ◎ → ◎ \ → ◎</td>
<td>↘</td>
<td>○ → ◎ → ◎</td>
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</tr>
<tr>
<td></td>
<td>Applied research</td>
<td>○ → ◎ → ◎ \ → ◎</td>
<td>↘</td>
<td>○ → ◎ → ◎</td>
<td>↘</td>
</tr>
<tr>
<td>China</td>
<td>Basic research</td>
<td>△ ↑ ○ ↑ ○ ↑ ○</td>
<td>△ ↑ ○ ↑ ○</td>
<td>△ ↑ ○ ↑ ○</td>
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<tr>
<td></td>
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<td>△ ↑ ○ ↑ ○ ↑ ○</td>
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</tbody>
</table>

(Source) Panoramic View of the Systems and Information (2019)

(Note 1) Phase
Basic research phase: Range of basic research by universities, national laboratories, etc.
Applied research/development phase: Range of technology development (including development of prototypes)

(Note 2) Current level
◎: Particularly remarkable activities and results
○: Remarkable activities and results
△: No remarkable activities or results
×: No activities or results

(Note 3) Trend
↑: Upward trend →: Maintaining current level ↓: Downward trend
PD: Dr. SOBUE, Gen (Chairperson, Aichi Medical University)

1. Policy for Selection and Proposal content
(1) Policy for Selection
Please submit a proposal of a scenario for the set MS Goal, "Realization of ultra-early disease prediction and intervention by 2050". Including both the concept of “forecasting” that predicts the future from current society and technology, and the concept of “backcasting” that suggests what to do now considering 2050 society as a reference point, the proposal should contain an outlook for 3 years, 5 years and 10 years after PM selection, and an outlook for 2050. Please elaborate on feasibility in terms of achieving the MS Goal by 2050, implementing and adapting to society, being challenging and innovative, and integrating ELSI considerations for societal acceptance.

(2) Proposal content
As indicated in the R&D Concept, considering that disease state is formed by a breakdown of the interactive network of organs, the aim here is to enable foresight of network breakdown and the conversion of pre-symptomatic state to healthy state again for chronic diseases such as diabetes and dementia.

In order to comprehensively understand the interdependent networks of each organ, it is important to use mathematical methods such as AI. Please include in the R&D framework ‘2) approaches using mathematical data analysis techniques such as AI and mathematical modeling’ in addition to ‘1) molecular cell / biochemical / physiological approaches’. We seek proposals that focus on networks between organs, rather than focusing only on individual organs.

1) Regarding molecular cell / biochemical / physiological approaches, we are basically considering R&D to clarify the relationship between diseases and interorgan networks. Because there are various strategies to clarify the relationship, we welcome ambitious and innovative ideas not bound by existing examples. The following R&D examples are given for reference. In addition, since data acquisition and analysis related to networks between organs by using conventional data acquisition and analysis techniques alone can be difficult,
proposals that include the development of innovative technologies based on entirely new principles are also welcome. Example R&D includes:

- Elucidating the state of normal network of organs and elucidate the mechanism leading to failure and disease.
- Elucidating the relationship between physiological phenomena and organ changes and diseases.
- Elucidating the relationship between diseases using small model animals that are easier to analyze than humans, understanding the process of outbreak, development and aging as a network change between organs.

2) Regarding mathematical data analysis techniques such as AI and approaches using mathematical modeling, similar to 1) molecular cell / biochemical / physiological approaches, the contents should take into account the interdependent network structure of each organ. We are imagining R&D for extracting, integrating and analyzing big data related to networks between organs, and R&D for constructing mathematical models based on big data. Since these are data-driven R&D, they largely depend on the presence or absence of the data to be analyzed. Therefore, we would like to request research proposals that promote effective and efficient R&D based on the results of existing research or data published in large projects.

2. Policy for promoting R&D
(1) Portfolio management

Taking into account the relationship between multiple R&D projects, portfolio management requires collaboration and competition between PMs. Therefore, for the period after being selected as a PM, the milestones to be achieved 3, 5 and 10 years from the time of being selected will be made clear, and a review of the progress and budget plan shall be conducted in consultation with the PD.

(2) Whole Body Network Atlas (tentative name)

The goal is to have a comprehensive understanding of the interorgan network. In the future, we will capture the comprehensive network state between human organs, build a database (Whole Body Network Atlas (tentative name)) describing the state of the network between human organs, and utilize mathematical models, etc. We aim to develop a simulation system for predicting unstable health
conditions. The specific methodology will be considered after project selection.

(3) Industry – academia collaboration

We expect the progress of R&D to have beneficial ripple effects on the medical industries.