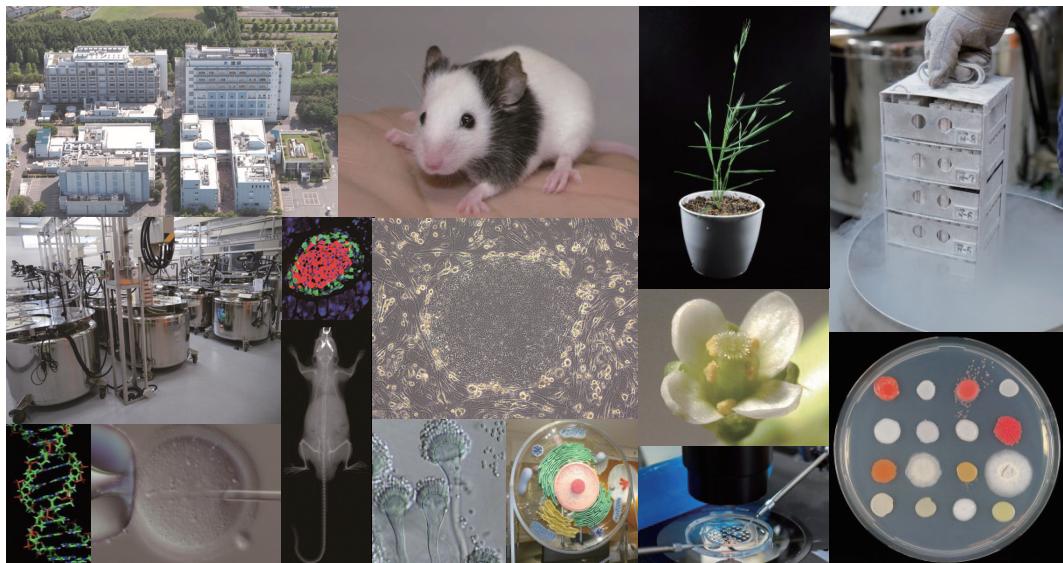




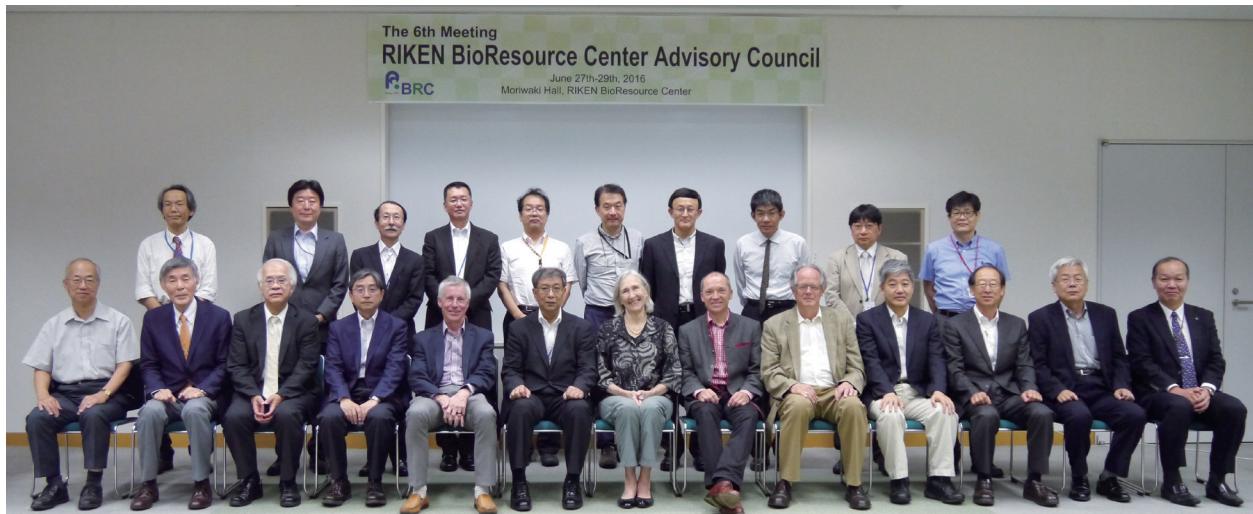
# The Report

## The Sixth Advisory Council Meeting of the RIKEN BioResource Center

June 27 – June 29, 2016



*Foundation for Discoveries  
And  
Access to the Future*



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Dr. Takahata, Dr. Yonekawa, Mr. Funada  
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**Dr. Ohkuma, Dr. Nakamura, Dr. Kobayashi, Dr. Yoshiki, Dr. Masuya,  
Dr. Abe, Dr. Ogura, Dr. Murata, Dr. Wakana, Dr. Gondo  
(The 2<sup>nd</sup> row, left to right)**

**[Black: AC members / Gray: BRC members]**

**June 27 – June 29, 2016  
RIKEN BioResource Center  
and  
Okura Frontier Hotel Tsukuba**

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## **The List of the Advisory Council Members**

### **[Core Members]**

#### **Dr. Stephen D. M. Brown**

Director, Mammalian Genetics Unit, Mouse Genome Centre  
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#### **Dr. Maarten Koornneef**

Emeritus Director, Max Planck Institute for Plant Breeding Research, Cologne,  
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#### **Dr. Barbara Knowles (Chairperson)**

Adjunct and Emeritus Staff Professor  
The Jackson Laboratory, United States of America

#### **Dr. K.C. Kent Lloyd**

Professor, School of Veterinary Medicine  
University of California, United States of America  
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#### **Dr. Martin Hrabě de Angelis**

Director, Institute of Experimental Genetics, Helmholtz Zentrum München  
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#### **Dr. Naoyuki Takahata**

Professor Emeritus/ The Former President,  
The Graduate University for Advanced Studies, Japan

### **[Chairpersons of Resource Committees and Review Committee]**

#### **Dr. Hiromichi Yonekawa [Resource Committee of Experimental Animals]**

Researcher/ The Former Vice Director,  
The Tokyo Metropolitan Institute of Medical Science, Japan

#### **Dr. Kiyotaka Okada [Resource Committee of Experimental Plants]**

Professor, Faculty of Agriculture, Ryukoku University, Japan

**Dr. Tatsutoshi Nakahata [Resource Committee of Cellular Materials]**

Deputy Director, Center for iPS Cell Research and Application

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**Dr. Sumio Sugano [Resource Committee of Genetic Materials]**

Professor, Graduate School of Frontier Sciences, The University of Tokyo, Japan

**Dr. Makoto Watanabe [Resource Committee of Microbial Materials]**

Professor, Graduate School of Life and Environmental Sciences

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**Dr. Toshihiko Shiroishi [Review Committee]**

Vice Director, National Institute of Genetics (NIG),

Professor, Mammalian Genetics Laboratory, Genetic Strains Research Center, NIG,

Research Organization of Information and Systems, Japan

## Terms of Reference for the BRAC from the RIKEN President and the BRC Director

Item	TOR for the BRAC from the RIKEN President	<i>TOR for the BRAC from the BRC Director</i>	<i>TOR for the Resource* and Review Committees** from the BRC Director</i>
1-1	Research achievements (The BRC's standing in the world, contribution to society)	<p><i>a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)</i></p> <p><i>b. Responses to previous comments and advice</i></p>	<i>Same as for the BRAC</i>
1-2	Self-analysis on strengths and weaknesses	<i>Is the self-analysis of strengths and weakness adequate?</i>	<i>Same as for the BRAC</i>
1-3	Plans (the mid- to long-term(5 to 10 years)): the direction for the BRC to take, well-defined policy to achieve rapid progress	<i>Mid- to long-term plans: direction and well- defined policy to allow the BRC to achieve rapid progress</i>	<i>Is the plan reasonable for the medium to long term?</i>
2	Areas within the BRC's field of research, as well as possibilities for cross-disciplinary integration of research for comprehensive re-evaluation with the possibility of fundamental restructuring	<p><i>a. Same as the President's TOR</i></p> <p><i>and</i></p> <p><i>b. Evaluation of four new proposals</i></p>	<p><i>a. Have appropriate fields been earmarked for future prioritization</i></p> <p><i>and</i></p> <p><i>b. Evaluation of four new proposals</i></p>
3-1	Pioneer a research management model for maximizing research and development results	<i>Same as the President's TOR</i>	<i>Same as the President's TOR</i>
3-2	Lead the world in achieving new research	<i>Are the policies for future resource infrastructure</i>	<i>Same as for the BRAC</i>

	and development results through scientific excellence	<i>and technology development appropriate?</i>	
3-3	Become a hub for science and technology innovation	<i>Same as the President's TOR</i>	<i>Innovation hub</i>
	(i) Collaborations with industry, government, and academia	<i>Same as the President's TOR</i>	<i>Same as the President's TOR</i>
	(ii) Collaborations within the BRC	<i>Same as the President's TOR</i>	<i>Same as the President's TOR</i>
	(iii) Continuous operation and attracting new users	<i>Same as the President's TOR</i>	<i>Same as the President's TOR</i>
3-4	Serve as a focal point for global brain circulation: recruitment system	<i>Same as the President's TOR</i>	<i>Same as the President's TOR</i>
3-5	Foster the development of world-class leaders in scientific research	<i>Same as the President's TOR</i>	<i>Training of global human resources</i>
	(i) Within the BRC	<i>Same as the President's TOR</i>	<i>Same as the President's TOR</i>
	(ii) External	<i>Same as the President's TOR</i>	<i>Same as the President's TOR</i>
4	The BRC activities towards maximizing RIKEN's achievements as a whole, including collaboration between centers	<i>Same as the President's TOR</i>	<i>Collaborations among the RIKEN Centers</i>

Five Resource Committees responsible for each of five Infrastructure Divisions: Experimental Animal, Experimental Plant, Cell Engineering, Gene Engineering, and Microbe.

One Review Committee responsible for Key Technology Division and Bioresource Frontier Programs: Bioresource Engineering, Mammalian Genome Dynamics, Mouse Phenotype Analysis, Evaluation of Human Disease Models, Mutagenesis and Genomics, and Knowledge Base of Mouse Phenotype.

## **Terms of Reference for the 10th RAC**

1. The 10th RAC is asked to evaluate RIKEN's response to the recommendations made by the 9th RAC.
2. The 10th RAC is asked to address the directions RIKEN should take on research and development strategy under its fourth mid-term plan.
3. Under the RIKEN Initiative for Scientific Excellence put forth by the new president, we place special emphasis on the five strategies shown below. The 10th RAC is asked to evaluate whether activities for these strategies are progressing adequately. We also ask for recommendations on any new tasks to be implemented.
  - (1) Pioneer a research management model for maximizing research and development results
  - (2) Lead the world in achieving new research and development results through scientific excellence
  - (3) Become a hub for science and technology innovation
  - (4) Serve as a focal point for global brain circulation
  - (5) Foster world-class leaders in scientific research
4. While our research activities are directed at solving problems that confront society, we believe there are still areas that we have yet to address. We ask for recommendations on new areas of research that RIKEN should undertake or targets we should strive for.

# The Report

## Executive Summary of BioResource Center Advisory Council

- Each of the five current BRC Resource Divisions (Animal, Plant, Microbe, Cell and Gene Engineering) Programs perform to the top of international standards as does the Key Technology Development Division.
- Two of the five BRC Frontier Programs will be refocused to support the new BRC-proposed project initiatives: *Human Disease Mouse Models, Human iPSC Resources and Symbiosis*.
- The BRC Divisions have exceeded their mission goals over the last five years.
- The BRC will amply support the RIKEN Initiative “*to lead the world in achieving new research and development results through scientific excellence*” in the targeted areas of: Aging, Genetics & Epigenetics of Human Diseases, Single Cell Analysis, and Symbiosis.

## **Response to Terms of Reference from the President of RIKEN**

### **1. Mid- to long-term plans: direction and well-defined policy to allow the BRC to achieve rapid progress**

The achievements, and the strengths and weaknesses of each Division and the BioResource Frontier Programs were evaluated individually and discussed. Overall, the scale and scope of the proposed future resource and research activities in each of the Divisions are world leading and provide a solid foundation for cutting-edge research in the fields of genetics and genomics. Two Frontier Programs, in which the proposed future work can no longer contribute to the changing mission and direction of the RIKEN BRC, and therefore can no longer provide the strong strategic foundation for the development of future research within RIKEN, are noted for change. Taking into account the need to appropriately support the new projects proposed we recommend RIKEN's investment in these areas should be refocused to the future Team plans. We commend these new areas of resource creation recognizing that each will provide important tools for the use of the international biomedical and agricultural communities and will foster key research to underpin the wide new goals in science and health care.

## **EVALUATION OF THE BIORESOURCE INFRASTRUCTURE DIVISIONS**

### **Experimental Animal Division**

#### **Division Head: Dr. Atsushi Yoshiki**

The Division has achieved great success and our evaluation overall is excellent. The numbers of mouse lines archived and distributed are very commendable and internationally competitive. The Division has developed excellent techniques and achieved high levels of quality control in terms of both genetic and microbiological status. Both collection and quality management will continue to remain important as a key deliverable of the Division and is an important priority for the future. Given the explosion in the generation of mouse lines by CRISPR/Cas9, it will be necessary to develop a rigorous selection process. Key criteria need to be developed and it will be important that the acquisition of mutant mice is restricted to genetically-defined mice of the second or later generations.

The Division is closely linked with the planned *Next-Generation Human Diseases Model* team, and there are clear synergies with regard to technology development,

including the improvement of genome editing technology for the development and dissemination of human disease models, as well as the emergence of conditional and imaging tools. Overall, the establishment of a new resource of mouse lines, which serve as models for intractable diseases and diseases of aging, is an important direction that addresses fundamental biomedical questions in an aging population. Together the Experimental Animal Division and the Next-Generation Human Diseases Model team will provide a critical hub for the BRC and underpin the long term aim of the BRC to be a key underpinning for biomedical research and therapeutic development within Japan and further afield.

## **Experimental Plant Division**

### **Division Head: Dr. Masatomo Kobayashi**

Three important plant resources have been developed by this Division.

1. *Arabidopsis*: Collecting and distributing unique mutants and lines (FOX lines over-expressing *Arabidopsis* or rice cDNA and CRES-T lines), reliable quality-control, and distribution to many overseas / domestic researchers are highly evaluated. These long-time efforts underscore the BRC one of the major *Arabidopsis* resource centers.
2. *Brachypodium*: This organism has been newly established as a standard model of monocots. The Plant Division contributes to this system by collecting mutants and developing experimental techniques (e.g. CRISPR/Cas9). Nearly 30 domestic laboratories have started to use it for their research and they all recently met at the BRC. Further efforts in this direction are required and there is a need to coordinate with the international community.
3. Cultured plant cell lines: This unique resource is requested both by overseas/domestic researchers because cultured cell lines are not distributed in other resource centers.

In the evaluation by the Resource Committee of Experimental Plants, the need for frequent revision of their website, generated in collaboration with the researchers in informatics field, is pointed out and the need for continuing improvement in the convenient use of the Division's databases. They plan to make resource platforms supporting the understanding of the molecular systems of plants in both basic and applied agricultural research and will focus their efforts on using genome-editing technology to build the resource both collaboratively and internally. They will continue to transmit this information through "how to" instructions on their web site and by

training courses held at the BRC. As for future plans a focus on plant-microbe symbiosis will be undertaken together with the Microbe Division with the goal of building a critical hub for resources in plant science.

## **Cell Engineering Division**

### **Division Head: Dr. Yukio Nakamura**

RIKEN BRC has become one of the world's leading supplier of cells and the new facility for the Division is at a world standard. Quality control management (cells are free of bacteria, fungi, Mycoplasma, and correctly identified) is the major precondition for providing cells. The Division has provided cells in increasing numbers over time and their source has been attributed to an increasing number of publications over time. They have established a series of training course for their users in vitrification methods, in fundamental cell culture techniques.

Recently, a large number of disease-specific iPSC from human patients have been deposited and their distribution hinges on their ability to differentiate and their genetic stability must be ascertained. There are other new tasks associated with distribution of these cells. As an example, users are not necessarily prepared to deal with the particular cell culture conditions for successfully maintaining iPSC in their own laboratories, so venues must be established to disseminate this technology. Furthermore because of the complexity of the research ethics involved in using disease-specific iPSC, it may be necessary to promote their use by offering support for the documentation attached to these patient's cells. Training courses for work with human ES cells are underway. New teams and new locations will be necessary to establish a system for efficiently and effectively distributing these newly deposited pluripotent cells so that they can be put to use as soon as possible. ESC and iPSC are also highly useful for deriving functioning differentiated cells and it is quite possible that they will be used in future research, so their preparation should also be considered.

Since many of these pluripotent cells derive from laboratories in Kyoto, future plans suggest a new BRC laboratory in Kyoto should be established to speed the transition to making these cells available to research laboratories. This and the distribution of cells from Tsukuba will require substantive rearranging of the Cell Engineering Division's mission. This planning is currently underway and will require a substantive budget increase.

## **Gene Engineering Division**

### **Division Head: Dr. Yuichi Obata, Presenter: Takehide Murata**

A strong point of this Division is the size of the collection, with over 4 million items, consisting of many uniquely held items that comprise the largest DNA resource in Asia. It has well developed infrastructure for storage, distribution and quality control and it distributes 1,000-2,000 items to 500 institutes, 20% to international institutions. The resource is used by a substantial number of customers. However, a weak point is that it is not widely known at home and abroad. Improvement in branding is necessary especially in light of the success of their major competitor (Addgene) in both collecting useful resources and promoting the use of their collected resources.

*It should be noted that the combination of the well-reviewed Gene Engineering, Cell Engineering and Experimental Animal, Experimental Plant and Microbe Divisions all in one location at the BRC is a great asset and should be used in a major professional branding and marketing effort for the BRC.*

## **Microbe Division (Japan Collection of Microorganisms-JCM)**

### **Division Head: Dr. Moriya Ohkuma**

Excellent results have been achieved in collection, distribution, and the number of research papers published by users, quality management, and preparation of genome information. Considering the center's standing within this field (ranking no 2 in number of registration of newly identified microorganisms), JCM is a world-leading microbial resource center and has greatly contributed to the development of microbial research in Asia, for which it acts as a central hub for microbial resources.

Because microbial symbionts greatly affect the growth and health of host animals and plants, and because recognition of their importance is rapidly increasing, it is reasonable to strategically collect indigenous microbes affecting human and plant growth in the next 5-10 years. Also, strategic collections of microbes that degrade and convert biomass, and microbes influencing iron corrosion, are very important for solving the social and environmental issues of the world.

To produce sufficiently enhanced performance in the future, it is important to represent specific methods and working structures in connection with collecting such microbial resources and to deal appropriately with the Nagoya Protocol. To increase the number of new users and expand resource projects, it is now necessary to stimulate new users

through open invitations to microbiologists in developing countries. Training in management aspects by BRC is an important step in the establishment of a BRC centered network in developing countries.

As JCM has many employees who are close to retirement age, the BRC must make plans for technological continuity so that these transitions go smoothly. Since there are a small number of symbiotic microbial strains and model plants for current symbiosis research, a new resource frontier project on culturing complex and symbiotic microbes and developing model plants has been developed to establish a new resource of microbial symbionts and model plants. Accordingly, it would be reasonable to create a Symbiosis Research Platform.

## **EVALUATION OF THE KEY TECHNOLOGY DEVELOPMENT DIVISION**

### **Bioresource Engineering Division**

#### **Division Head: Dr. Atsuo Ogura**

The Advisory Council highly values and appreciates the many significant successes of this Division, which contribute to developing a foundation for bio-resource projects. Examples include further development of mouse somatic cell nuclear transfer, development of micro-insemination and improvement of methods for reliable cryopreservation. These research/development projects have been important for the efficient maintenance of existing resources and establishment of new resources. This Division has also made great achievements in the field of basic biology including epigenetic regulation of mouse development that can be applied to the resources, such findings are of interest to many teams at the BRC. This Division is an appropriate location for developing new genetic engineering technology required for the Center to progress, and its importance will not change in the future.

## **EVALUATION OF THE BIORESOURCE FRONTIER PROGRAMS**

### **Technology and Development Team for Mammalian Genome Dynamics**

#### **Team Head: Kuniya Abe**

The establishment of the EpiSC (Epiblast Stem Cell) line by Wnt-signaling inhibition has had a major impact as a foundation for stem cell resource development. This is an excellent example of how research leverages the future value of a biorepository. The method can be used as blueprint for other pathways and other purposes. The Advisory

Committee expects that this discovery will make a major contribution to resource development in the future. Dr. Abe plans to explore aspects of the CRISPR/Cas9 gene editing system to allow activation and repression of gene expression, epigenetic modification and genome imaging, a very desirable direction for the BRC teams at present. His team has actively established interaction with industry (e.g. Olympus) and is in active discussion with Drs. Ogura, Nakamura and Yoshiki about needs within their divisions.

Dr. Abe is very active in domestic and foreign graduate student training, a benefit as these students bring knowledge of the resources to their communities. Dr. Abe's work permits an active innovation process, which is of direct benefit to its resource functions.

### **Technology and Development Team for Mouse Phenotype Analysis: Japan Mouse Clinic**

#### **Team Leader: Dr. Shigeharu Wakana**

The advisory committee applauds the Team for having constructed and implemented a comprehensive mouse phenotyping pipeline, which measures up to international standards. Providing access to the research community has contributed to the growth and development of the life sciences in Japan. Participation in the International Mouse Phenotyping Consortium (IMPC) has made Japan's presence known in this field on an international level. To implement a new research direction on aging-related diseases, reflective of the aging society in Japan, a project to be conducted in collaboration with the IMPC, significantly augments the research by providing unique platforms for phenotyping aging normal and mutant mice. The additional focus on the evaluation of "maternal nutritional effects" are also seen to be important and highly appreciated and in line with the RIKEN goal to explore epigenetic control mechanisms. This latter experimental set up should be revisited so that one can distinguish somatic versus intergenerational factors.

### **Team for Advanced Development and Evaluation of Human Disease Models**

#### **Team Leader: Dr. Tetsuo Noda**

Dr. Noda's team has pursued projects in three highly competitive biomedical areas: analyzing ENU-derived mouse mutants with disease phenotypes and identifying the causal genes; utilizing patient-derived xenograft system to evaluate human cancer cells in collaboration with the JFCR, in which he established the stability of the tumor with passage, their ability to metastasize and to provide an effective targeted drug for

personalized medicine; and developing an NMR-based metabolomic analysis system. His talented team has produced a series of papers in high-profile journals and established exceedingly useful platforms to evaluate personalized medicine in cancer. The question asked in past reviews was the relevance of these projects to the BRC. At this review it was also not obvious how these excellent research projects could be tied into the bioresources and into future bioresource projects.

### **Mutagenesis and Genomics Team**

#### **Team Leader: Yoichi Gondo**

This Team has developed significant and widely used resources in mouse genetics. Most importantly they have created a deep and extensive library of ENU-induced mouse mutants. More recently they have worked on estimates of spontaneous mutation rates using next-generation sequencing of the C57BL/6JJcl strain. Moreover, PacBio single molecule sequencing of the C57BL/6 reference genome may provide a useful foundation for mouse genomics and genetics and is commendable. A recent focus has been on the use of ENU for investigating epistasis and identifying polygenes, though this work is at an early stage. However, overall the contribution of these recent endeavors to the BRC mission is not obvious. In addition, the feasibility of elucidating gene-to-gene interactions based on the ENU-induced mouse mutations is also not clear. We discuss below the need to refocus the investment made in the area of mutagenesis and genomics.

### **Technology and Development Unit for Knowledge Base of Mouse Phenotype**

#### **Unit Leader: Dr. Hiroshi Masuya**

This Unit has developed a user-friendly and integrative mouse phenotype database, as well as software for other resources of the BRC and has developed a web system for resource deposition for the entire BRC. The results of his efforts have greatly exceeded expectations in improving the information infrastructure in the BRC as a whole. Furthermore, the Unit has made a notable international contribution by the introduction of the RDF format into the IMPC project. This unit has the capability to take over the activity of the Bioresource Information Division. Dr. Masuya is well regarded in the mouse genetics community and we recommend that he take on formal responsibility for both the Division and the Technology and Development Unit.

## **2. Areas within the BRC's field of research, as well as possibilities for cross-disciplinary integration of research for comprehensive re-evaluation with**

## **the possibility of fundamental restructuring**

### **Mutagenesis and Genomics Team**

The Mutagenesis and Genomics Team has been responsible for the characterization and dissemination of the ENU Mutant Mouse Library. This important resource provides an extensive library of point mutations in diverse genes. This set of mouse mutant alleles will remain an important resource for the mouse genetics community and will continue to be a key BRC resource for many years to come. With the advent of CRISPR/Cas9 gene editing, further development of the ENU library is not merited. Nevertheless, it will be important to maintain the ENU library for the foreseeable future as it provides many novel mouse mutant alleles that will be very valuable in genetic and functional studies.

The ongoing work of the Team has focused on a variety of approaches to the utilization of Next Generation Sequencing (NGS) and ENU mutagenesis in mouse genetic studies. To date, these include: 1) the determination of spontaneous mutation rates and 2) the potential use of ENU to uncover epistasis and to identify polygenes. There have also been some observations made on the nature of alternative splicing in CRISPR/Cas9-induced mutations. However, while Dr. Gondo is an excellent geneticist and the work is interesting, overall it does not provide a firm strategic foundation for future developments in mutagenesis at the BRC and its future resource and technological needs. Moreover, some of the proposed work in the discovery of, for example, body weight polygenes is extremely challenging and risky and the outcomes in terms of gene discovery are uncertain.

It is therefore necessary to refocus this area of investment. The new developments and applications in CRISPR/Cas9-induced mutagenesis represent a key opportunity for the BRC to grow new and exciting resources and research that interfaces with the clinical and human genetics community. We recommend for the future that CRISPR/Cas9 should be a key development and technological platform in the areas of mutagenesis and genomics, and we support the emergence of the plan for a “Next-Generation Human Disease Model Team” (see below). The aim of the new team to use genome editing to create mouse models of intractable diseases, coupled with phenotyping at the Japanese Mouse Clinic, will be a fundamental and powerful new resource for the BRC which outreaches to the wider biomedical sciences community within Japan and beyond.

### **Team for Advanced Development and Evaluation of Human Disease Models**

This Team has produced extremely interesting and important data that indirectly (ENU-induced mouse models of human disease) and directly (human-derived xenografts) relate to biomedical research. Dr. Noda has taken the time to personally supervise this research and has brought much of it to publishable conclusion. As such, the valuable work produced has been a unique collaborative research effort between the cancer institute and the BRC. However, because these projects do not relate to the long-term goals of the BRC, the Advisory Committee suggests the investment in these interesting research projects should be redirected to the plans for the new Teams outlined below.

## **NEW PROPOSALS**

The Committee agrees whole heartedly with the proposal to establish new teams: Next-Generation Human Disease Model Team, the Higher-order Cell Characterization Team, the Drug-discovery Cellular Basis Development Team and the Symbiosis Project Team.

### **Next-Generation Human Disease Model Team**

We discuss above the imperative to establish this new team which will be critical in generating important mouse model resources for the wider clinical and human genetics communities. We propose that the current investment in the Mutagenesis and Genomics Team should be refocused to this Team.

### **Higher-order Cell Characterization Team**

Since “it is difficult to conduct detailed differentiation capacity analysis for all cells,” the Committee suggests that consideration be given to the possibility of a “cloud sourcing” function. In other words, researchers come to the bank for a certain period (under the guidance of the member of the Cell bank) and analyze their differentiation capacity using standard methods, or offer cells, the details of whose differentiation capacity are unknown, and the users share their differentiation capacity results with the bank. Together with the Gene engineering division, the generation of viruses expressing a marker gene under control of tissue-specific and /or differentiation stage-specific gene promoter is also important. Cells can be generated in which specific differentiation can be detected as the expression of marker gene.

### **Drug-discovery Cellular Basis Development Team**

The Committee considers the concept of a Drug-discovery Cellular Basis Development Team to be important, so the Committee requests that this intention be conveyed to Director Shinya Yamanaka of CiRA at Kyoto University, so that the direction of research can be worked out as soon as possible. Having no medical information or information about differentiation capacity included is rather senseless. Even if this review decreases the total number of cells to be characterized, the Committee requests that the BRC proceed according to the proposal.

### **Symbiosis Research Platform Team**

The Advisory Council sees the symbiosis platform as a very promising initiative because it links two BRC divisions together and provides many opportunities to act as a hub in national and international research, including other RIKEN (especially CSRS) and non-RIKEN institutions, on mycorrhizal fungi. The challenge is to get good culture technology, an approach not without risk, but it may work with the proposed innovative approaches planned. To combine this with the Brachypodium system seems promising. It is not clear how much international competition will be encountered, which brings forward the notion of participation in the international Brachypodium community, bringing the possibility of serving as its acknowledged resource.

### **3.1 Pioneer a research management model for maximizing research and development results**

Over time, Dr. Obata wisely developed an appropriate management structure to accommodate the constant change inherent in the cutting edge research that the BioResource Center supports. To this end the major BRC Divisions, which maintain and manage the premier Research Resources, (Experimental Animal, Experimental Plant, Cell Engineering, Gene Engineering and Microbes) are supported by the Key Technology Development Division and a series of Frontier Programs that can shift over time. This structure allows major changes in direction in a rather short period of time. This flexible management model is now being deployed to make a shift in direction.

### **3.2 Lead the world in achieving new research and development results through scientific excellence**

The BRC, as a world leading Bioresource-Center, requires a well-balanced portfolio comprising infrastructure and research development. The BRC, as a sensible reaction to current and future developments in the biomedical and plant research fields, will now

undergo major shifts with respect to its research/resource portfolio. New teams in the area of next generation human disease models, iPS cell culture systems for higher order of cell characterization and drug development, and a research platform for plant symbiosis have been proposed. The BioResource Advisory Council strongly encourages the Director of the BRC to go forward with the restructuring that will be necessary to complete this shift in direction, by formalizing the new teams necessary to complement their world-class resource infrastructure. *The Advisory Council realizes that this shift requires a reduction in the existing research teams. Furthermore, we are aware that the breadth of these new directions will require substantive new funding to accomplish and we encourage the budget planning necessary to hire a new scientist to head a facility in Kyoto and to fund the new directions in the current Divisions in Tsukuba.*

### **3.3 Become a hub for science and technology innovation**

The BRC has generated a portfolio of internationally leading resource and research programs in a broad variety of genetics and genomics systems from the mouse, and is developing current and new resources required to expand and maintain their excellent mouse, human and mouse cell, plant, microbe and gene resources. The Director has recruited and fostered outstanding program leaders with the vision and expertise to continuously develop excellent new resources to the ever changing research community. With their interlinked synergies they provide a critical mass of activity and outreach. Each Division as well as the BioResource Frontier Programs already have active mechanisms for outreach and resource dissemination allied to appropriate web and informatics structures for data dissemination to academia and industry. These leading resource and research programs at the BRC, together with the infrastructure for distribution of resources and dissemination of information, creates a global hub for science and technology innovation. The BRC's central role in biology and science within Japan and further afield is a catalyst for many streams of biological and medical research, with important ramifications across society, medicine and healthcare. *Awareness of these resources in the international scientific community may be increased by embarking on a professional marketing and branding program.*

### **3.4 Serve as a focal point for global brain circulation: recruitment system**

The BRC should continue actively recruiting qualified Japanese or foreign PI's using advertisements in international journals. Recruiting more women should remain a priority.

### **3.5. Foster the development of world-class leaders in scientific research**

The BRC interacts with the scientific community in a need-to-know manner and as such it has an opportunity to transfer techniques and technology to its users by offering a series of courses, “how-to” films and webinars. The reputation of the cell, animal, microbe, plant, and gene engineering divisions should direct the users to the series of courses that exist. However, a concerted effort should also be made to attract young scientists, or those changing fields who require re-education in the technologies available and who do not know about the BRC. *A professionally directed “marketing” effort about these educational opportunities to the scientific community at large will also increase awareness and usage of the resources themselves.*

The BRC is acutely aware of their requirement to train its own professional staff through courses, seminars, and potentially by a one-on-one mentoring system. There are graduate students in the laboratories, some through the Master’s/Doctoral Program in Life Science Innovation program of the University of Tsukuba and some from RIKEN’s International Program Associate program. They also operate a summer workshop in collaboration with the Nanjing University, which is externally funded. Perhaps extension of this summer course to other areas in China and throughout Asia should be considered. The staff is well aware that the pattern established by students when they return to their home countries increases awareness and usage of various resources. Knowledge of proper resource collection, preservation and maintenance ensures educated extension of a collection program.

### **4. BRC activities towards maximizing RIKEN’s achievements as a whole, including collaboration between centers.**

The BioResource Advisory Council has carefully reviewed the activities of the BRC in the light of maximizing RIKEN’s achievements as a whole. We clearly see the extremely positive effect of RIKEN BRC on RIKEN as a whole on several levels:

1. The RIKEN-BRC has built up an international reputation through its distribution of biomaterial (16,000 samples per annum) to 68 countries. At the same time the role of BRC for the scientific community in Japan cannot be overestimated. With some 3,000 users per annum for domestic research institutions and about 10 percent of those for RIKEN internal customers the BRC serves as a national core infrastructure (National BioResources Project) for life science in Japan.
2. The interaction with industry, with well over 2,000 distributed item per annum is strong, and is also important for the overall recognition of RIKEN.

3. The well-established QC system (ISO9001) and the reproducibility of material and data is the prerequisite for solid science. The BRC has proven to be a reliable partner in this respect, increasing the reputation of RIKEN as a trustworthy partner. The BRC has reduced the “resources with defects” to 0.01% (average bioresources: within a community that supplies products for collection with ~10% defects in microbial or genetic contamination).
4. The training and education programs of the BRC are very important for the proper education of the next generation researchers and technicians. Courses and internet videos are widely accepted and used and spread the knowledge of these wonderful resources.
5. The new resource and research themes of the BRC are being directed into the major new RIKEN and government research projects areas (i.e. Aging, Genetics and Epigenetics, Human Disease Research, and Symbiosis).

## Agenda for the Sixth Advisory Council Meeting of RIKEN BioResource Center

Date: June 27- June 29, 2016

Venue: RIKEN BioResource Center and Okura Frontier Hotel Tsukuba

### **Day1: June 27 (Mon)**

Time	Subject	Presenter	Venue
14:00-15:00	Opening Remarks	Dr. Shigeo Koyasu, Executive Director, RIKEN Dr. Yuichi Obata, Director, RIKEN BioResource Center	
15:00-15:30	Experimental Animal Division	Dr. Atsushi Yoshiki, Head Dr. Hiromichi Yonekawa, Chair	
15:30-16:00	Bioresource Engineering Division	Dr. Atsuo Ogura, Head Dr. Toshihiko Shiroishi, Chair	RIKEN BioResource Center
16:00-16:30	Cell Engineering Division	Dr. Yukio Nakamura, Head Dr. Tatsutoshi Nakahata, Chair	
16:30-17:00	Gene Engineering Division	Dr. Takehide Murata, Dr. Sumio Sugano, Chair	
17:00-17:15	Break		
17:15-17:45	Technology and Development Team for Mammalian Genome Dynamics	Dr. Kuniya Abe, Team Leader Dr. Toshihiko Shiroishi, Chair	

<b>Time</b>	<b>Subject</b>	<b>Presenter</b>	<b>Venue</b>
17:45-18:15	Mutagenesis and Genomics Team	Dr. Yoichi Gondo, Team Leader Dr. Toshihiko Shiroishi, Chair	
18:15-18:45	Technology and Development Unit for Knowledge Base of Mouse Phenotype	Dr. Hiroshi Masuya, Unit Leader Dr. Toshihiko Shiroishi, Chair	
18:45-19:15	Team for Advanced Development and Evaluation of Human Disease Models	Dr. Tetsuo Noda, Team Leader Dr. Toshihiko Shiroishi, Chair	
19:15-19:45	Move to Okura		
19:45-21:00	Formal Reception	All BRAC and BRC Members	Okura Frontier Hotel

**Day2: June 28 (Tue)**

<b>Time</b>	<b>Subject</b>	<b>Presenter</b>	<b>Venue</b>
8:30-9:00	Move to RIKEN from Hotel		
9:00-09:30	Technology and Development Team for Mouse Phenotype Analysis	Dr. Shigeharu Wakana, Team Leader Dr. Toshihiko Shiroishi, Chair	
9:30-10:00	Microbe Division	Dr. Moriya Ohkuma, Head Dr. Makoto Watanabe, Chair	
10:00-10:30	Experimental Plant Division	Dr. Masatomo Kobayashi, Head Dr. Kiyotaka Okada, Chair	
10:30-10:45	Break		RIKEN BioResource Center
10:45-12:00	Presentation and discussion on Terms of Reference from the President of RIKEN	Drs.Obata, Ohkuma, Kobayashi, Yoshiki, Nakamura	
12:00-13:00	Lunch		
13:00-14:00	New Projects(x4)	Drs.Obata, Ohkuma, Kobayashi, Yoshiki, Nakamura	
14:00-15:00	Drafting the Report	Closed meeting	
15:00-15:15	Break		
15:15-17:00	Drafting the Report	Closed meeting	
17:00-17:15	Break		
17:15-19:00	Drafting the Report	Closed meeting	
19:00-19:30	Move to Okura		
19:30-21:00	Official Reception	All BRAC and BRC Members	Okura Frontier Hotel

**Day3: June 29 (Wed)**

<b>Time</b>	<b>Subject</b>	<b>Presenter</b>	<b>Venue</b>
8:30-9:00	Move to RIKEN from Hotel		
9:00-12:00	Finishing the Report	Dr. Barbara Knowles	RIKEN BioResource Center
	Closing Remarks	Dr. Yuichi Obata	
12:00-12:30	Report from the Chair of BRAC, Dr. Knowles to RIKEN Executive Director, Dr. Koyasu via TV conference		

Note: Each pair of PI and Chairs has 10 minutes for a presentation and then Q&A session for 10 minutes.

## The List of the RIKEN Participants

<b>Dr. Shigeo Koyasu</b>	Executive Director, RIKEN
<b>Dr. Yuichi Obata</b>	Director Division Head, Gene Engineering Division
<b>Dr. Kuniya Abe</b>	Deputy Director Team Leader, Technology and Development Team for Mammalian Genome Dynamics
<b>Dr. Atsushi Yoshiki</b>	Coordinator Division Head, Experimental Animal Division
<b>Dr. Masatomo Kobayashi</b>	Coordinator Division Head, Experimental Plant Division
<b>Dr. Yukio Nakamura</b>	Coordinator Division Head, Cell Engineering Division
<b>Dr. Moriya Ohkuma</b>	Division Head, Microbe Division (Japan Collection of Microorganisms)
<b>Dr. Atsuo Ogura</b>	Division Head, Bioresource Engineering Division
<b>Dr. Shigeharu Wakana</b>	Team Leader, Technology and Development Team for Mouse Phenotype Analysis (Japan Mouse Clinic)
<b>Dr. Tetsuo Noda</b>	Team Leader, Team for Advanced Development and Evaluation of Human Disease Models
<b>Dr. Yoichi Gondo</b>	Team Leader, Mutagenesis and Genomics Team
<b>Dr. Hiroshi Masuya</b>	Unit Leader, Technology and Development Unit for Knowledge Base of Mouse Phenotype
<b>Mr. Takashi Funada</b>	Director, RIKEN Tsukuba Branch
<b>Mr. Wataru Ishikawa</b>	Director, BioResource Center Planning Office

## **Responses of the BRC Resource Committees and Review Committee to the Terms of Reference from the BRC Director**

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**Item 1-3. Is the plan reasonable for the medium to long term?**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- Specific explanations have been offered regarding future policies centered on resource infrastructure projects and the direction for the BRC has been stated explicitly. This can be understood to mean that resource infrastructure projects are taken as the core, with key technology projects situated adjacent to them, and then outside those the newly established bioresource-related research programs, which include newly established development divisions.
- Now that CRISPR/Cas9 has been developed, the advantageous position of the mouse in a repository appears to have declined greatly. It is important to formulate measures for seeing that the advantageous position held so far can be assured into the future.
- Thought should be given not only to exchanges of information and technology, but also to include large-scale reassessments of personnel. It would be a good idea if steps to engage in major review are also visible from outside the BRC.
- Specific research themes and measures related to epigenomics and disease are not necessarily articulated clearly, and further examination is probably needed.
- With development of the new technology referred to as CRISPR/Cas9, the enormous quantity of ES cells created in the Knockout Mouse Project from 2006 will end up simply being preserved and not being used as resources. In other words, it is possible that the enormous amount of research funding expended could end up having been wasted. Taking this into consideration, it appears that the time has come to reexamine its commitment as a resource center, so it will be necessary to work out measures for coping with the situation.

Committee for Experimental Plant Resource

- The BRC considers researcher support to be its primary function. It is not sufficient, however, to take a stance of just waiting for use by researchers. It is necessary to take an active stance, to collaborate with researchers in Japan and other countries, and to take steps for the advancement of international research by developing

resources. The team system that is being planned is a good proposal, but steps should be taken to raise the standard of research on each team, for example by actively including researchers from outside RIKEN on the team, by providing research grants through research support projects made widely available through open calls.

- The expression, "work on resources is not research" may invite misunderstanding. It is true that the resource work consisting of the preparation of resource foundations is not stand-alone research in itself, but it should be counted as one area in the research field. The BRC is giving careful consideration to prioritization.
- The picture for future budgets is worrisome, but the way that pains have been taken to keep each resource project moving forward in a well-balanced manner is commendable. So far as research and development is concerned, it is important that this be advanced not just by the BRC alone, but also in cooperation with other RIKEN centers. It would be advisable to listen to the views of the various Resource Committees and proceed with this work, while examining the content of bioresources in the next generation.
- Regarding industry-academia-government collaboration and implementation in society and it is to be hoped that readily explicable measures will be put in place.

#### Committee for Cell Resource

- There seems rather strong pressure to reform from the new President's management policy and assuming that simply maintaining and expanding a world-class foundation is insufficient, the Committee would like to support a new plan. Serious trouble is anticipated when it comes to executing the plan, so the Committee expects the BRC to pursue this goal with unflagging determination.
- When formulating a mid- to long-term plan, it would be a good idea to step back, take a look at the BioResource Center's philosophy, and try restructuring the plans accordingly. For example, there is the question of what bio-resources are to be dealt with. There is no room for discussing about whether cells are bio-resources, but when dealing with questions such as "How should we think about technology?" or "How should we think about information?", the content of the plan must be flexible.
- It is expected most of the attention will be devoted to disease-specific iPS cells and treated cells, but it will be necessary to obtain a budget and personnel for these cell infrastructures. Also, the BRC should strengthen its collaboration with other Japanese research institutions to administer projects efficiently.

- Along with the rapid dissemination of iPS cells, the demand for animal cells, including mouse cells, is expected to decrease.

#### Committee for Genetic Resource

- Considering the rapid rate at which science advances, specific plans must have the corresponding flexibility to change according to circumstances.
- The BRC fulfills the role of both a science and technology hub, so its function as a hub is central, and it is necessary to take measures in a focused manner without diluting that function. Furthermore, in order to surpass Addgene in terms of function and in terms of projects, success in the hub function must come first. It will be necessary to formulate issues, and clarify the prospects for the sharing of roles with other institutions while implementing personnel and budgetary measures.
- In order for the BRC to continue achieving creative results, it is important that research activities should be made integrative and collaborative. The BRC should pursue still closer cooperation with infrastructure projects and development programs while also taking steps for adequate coordination in a variety of different initiatives. In terms of providing cross-cutting support for projects, it is essential that the functions of sequence determination systems and information analysis be strengthened. Achievement in these matters appears likely to further facilitate exchange between projects.

#### Committee for Microbe Resource

- There are some issues in the area of microbiology that need to be investigated specifically, so a detailed examination of other fields is also recommended.
- A variety of efforts to obtain new users are needed.
- The actual performance in Asia has met expectations. It is expected that developing countries such as those in South America and Africa will be cultivated.

#### Review Committee

- If budget reductions in the past and budget restoration in the present fiscal year signifies a demand for building a reborn BRC. Unless some reconfiguration of research teams takes place, the BRC cannot be considered reborn. However, the record of RIKEN BRC to date in connection with bioresources is very much to be commended, and there is ample reason in that for the BRC to continue even as it is. Consequently, it is only natural for the BRC to continue in existence, and discontinuation of the BRC is unthinkable as an alternative. If RIKEN BRC is to be

reformed in the effort to reach still greater heights, however, then the current proposal presents a direction with ample possibilities. Furthermore, given a RIKEN that declares itself to be on the cutting edge of science, then the periodic reconfiguration of teams is an essential issue for the medium to long term.

**Item 2a. Have appropriate fields been earmarked for future prioritization?**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- The quality management of preserved strains is a crucial point for bioresource projects, so this is a point on which steps should be taken for continuing priority in the future.

Committee for Experimental Plant Resource

- Under the Center Director's leadership, the management, planning, and other administration of the various resource infrastructure divisions is being given appropriate consideration. In order to increase the value of the resources, it will be necessary to implement various phenotype analyses of resource information, in a broad sense. These will serve as distinctive features of the BRC. A system for quantitative phenotype analysis of plants is in the process of being launched in Tsukuba (the Shinozaki Group).

Committee for Gene Resource

- The Committee agrees 100% that it is time for a drastic reassessment that is not just the equivalent of putting up a signboard with a new name on it, and expresses our respect for the decisiveness of that examination.
- This appears appropriate under current conditions. However, care should be taken regarding flexibility.
- Given the needs of society today, selection of the two main themes of "realizing a long-life society" and "clarifying the symbiosis between host and microorganism" is assessed as plausible, but in the manner of implementation, it must be committed to raising the level of the hub function.
- The fact that research oriented to drug discovery is situated as a field to be prioritized in the future may possibly further advance the research conducted at the BRC to date, and the fact that it is to be implemented with appropriate partners is also commendable. With regard to symbiosis research, as well, this seems capable of advancing the results achieved by the Center to the maximum extent by means of

research activities conducted through infrastructure projects, development programs, and stable collaboration of industry, academia, and the government.

- Implementation will require considerable financial and personnel resources to be made available. Furthermore, it will be essential to conduct joint research with third parties. It will also be necessary to pursue joint work with future users from the very beginning of research.

#### Committee for Microbe Resource

- The three-tiered project structure is appropriate, and placing the bioresource infrastructure project as the core is anticipated to contribute to the stable advancement of the sciences in Japan.

#### Review Committee

- The three-tiered project structure is appropriate, and placing the bioresource infrastructure project as the core can be anticipated to contribute to the stable advancement of the sciences in Japan.
- Given the present circumstances in Japanese universities, RIKEN BRC is being called on to perform the role not just of preserving resources, but also of supporting the systematic analysis of mouse behavior, of organizing large-scale epigenome projects using mice, and so on. The BRC should establish its position as a center that supports experimentation of kinds that are not possible for universities and individual researchers. In that sense, this Center should expand its scale and work to become a system that can meet the needs of larger numbers of users.
- Fields that have achieved compliance with international standards should be left in place.
- The present teams and units appear, with some exceptions, to have toned down their initial excitement and matured. This change seems natural, considering the advances made in science and the changes in what is demanded by the times. If teams and units are to be reconfigured, then it would be desirable to select themes that can be anticipated to extend from five to 10 years into the future.

## **Item 2b. Evaluation of four new proposals**

### **(1) General evaluation and comments on the proposal of the four new projects**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- The four proposed teams are backed by the precision and highly reliable quality management with respect to the BRC activities up to now in experimental animals, experimental plants, cells, microorganisms, and genes, as well as by their phenotype analysis, and they are commendable as a medium to long-term plan based on fundamental revision with this foundation.
- The proposal calls for the creation of four new teams in bioresource-related research development programs and for steps to be taken to prioritize them and it is appropriate in terms of field and theme. However, as to the question of what individual themes will become the focus, it will be necessary to engage in thorough information exchange with the various research communities involved and on that basis to give close and careful consideration to approaches capable of highlighting Center characteristics.

Committee for Cell Resource

- The plan takes the current four teams and one unit in the BioResource Frontier Programs and reorganizes them into five to six teams, but it will be necessary to explain sufficiently that the objects of each team's development activities are closely linked to the needs of resource operations.
- Partly for historical reasons, this Center's BioResource Frontier Programs have, until now, been composed mainly of teams that use mice as their subjects. The current radical reform includes launching four teams: 1) Symbiosis Research Team, 2) Next-generation Human Disease Model Development Team, 3) Higher-order Cell Characterization Team, and 4) Drug-discovery Cellular Basis Development Team. In particular, Teams 2) to 4) must be strongly promoted.
- Generally, the emphasis is appropriate. Even though the direction of emphasis in the cell resource projects is correct, when reorganizing the program teams, it will be

important to look at the other resource projects and make careful decisions about whether the distribution of human, financial and time resources is appropriate throughout the Center.

- The content of the proposal is basically appropriate, but the time frame is unclear. (Obata: we need to start in 2018, at the beginning of the next five year plan) Instead of dealing with this over a five-year period, it is essential to respond to this as rapidly as possible.
- The collaboration between iPS cells and model animals is extremely important, so this should be strongly promoted. However, the current explanation feels a bit weak.

#### Committee for Genetic Resource

- With regard to Next-generation Human Disease Models and Higher-order Cell Characterization, it will be important to build stable systems for cooperation with medical institutions as well as to further investigate the diseases and related matters that are to be designated as the objects of research.
- With regard to Drug Discovery and Symbiosis, the plan is based on appropriate collaboration and actual results. With regard to human disease models, it will be necessary to take advantages of completion of the mouse genome sequence (reference sequence) in collaboration with industry, academia, and government, as well as to start this plan.

#### Committee for Microbe Resource

- Of the four new teams planned, those other than the Symbiosis Research Team have actual performance results and are judged to be easy for the Japanese people to accept, due to their links to medical treatment. The Next-generation Human Disease Model Development Team, which is developing a model mouse for designated incurable diseases and age-related diseases, and the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team, which both use the iPS cell platform, are appropriate.

#### Review Committee

- The idea of drastically restructuring the present bioresource-related research development program and establishing a Symbiosis Research Team, a Next-generation Human Disease Model Development Team, a Higher-order Cell Characterization Team, and a Drug-discovery Cellular Basis Development Team

that are responsive to demands from society, is readily understandable, and this is reasonable as a medium- to long-term plan.

- It would be desirable to reconfigure this project from the perspective of why the project will be in the interest of the Japanese people, who are stakeholders. With regard to fields that are being prioritized, it is considered essential that projects be carried forward by researchers who are at the forefront of the field concerned. However, there is no explanation of policy with regard to personnel recruitment, so evaluation is difficult. Of four themes, two have to do with iPS cells and one has to do with resources involving individual mice, and this appears to be lacking in balance. It does not appear necessary for the BRC to pursue research on resources that are specialized in iPS cells.
- Tie-ups with corporations can be expected in drug-discovery cellular target basis development, but there is some doubt about symbiosis and designated incurable diseases.

## (2) The Next-generation Human Disease Model Team

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- The preparation of mouse resources to serve as models, in particular for designated incurable diseases that impose a major burden on the patient and caregiver, and for lifestyle-related diseases that become an increasing risk with senescence and aging, is the correct course to take and one that is in accordance with society's demands. It is important to proceed with this while also collaborating with outside organizations. With regard to the senescence model, there are still some reasons to examine the choice of genetic background of disease mouse models.
- The Next-generation Human Disease Model Team will be important in developing next-generation resource infrastructure. Contributing to international public relation activities and obtaining the international recognition and positive evaluation of these resources can also be considered important roles. Therefore, a team leader should be chosen who can collaborate closely with the Experimental Animal Division and Engineering Divisions. The leader should be recognized in other countries and should receive the support of researchers in Japan. The leader must be able to select and produce next-generation human disease models. It is to be hoped that the next generation human disease model development team will be created by a leader who possesses these capabilities.
- The creation of a Next-generation Human Disease Model Team is movement in an appropriate direction, and it is an initiative that responds to the growing need in research communities. However, the outlook for the extent to whether model animals of designated incurable diseases will satisfy BRC user demands should be examined in specific detail on the basis of fact. In other words, it is necessary for the BRC to explicitly explain its basic policy related to mouse collection and development. Furthermore, it is not necessarily guaranteed that genetic mutations that induce disease phenotypes in humans will produce similar phenotypes in mice. It is necessary to develop disease models for which there are greater needs. Most rare diseases models may risk having only limited number of users.
- Production of disease models overlaps in many parts with basic research. The

question of whether this kind of project should be carried out by a resource center must be given careful consideration. As experienced experts in that field see it, there is a possibility that the models will not be usable. Projects with stronger technology development aspects are better.

- In order to prepare model mice for designated incurable diseases, lifestyle-related diseases, and so on, it will be necessary in future to take steps for collaboration with researchers in clinical fields.
- From what perspective was the theme of "development and expression analysis of next-generation mouse for visualizing autophagy and mitophagy" adopted? Also, was discussion conducted within the BRC as to whether or not this theme was to be of great importance to the BRC in the future? These points require explanation.

#### Review Committee

- With regard to next-generation human disease model development, the plan is to use genome editing and other up-to-date methodologies to create a model mouse for diseases designated incurable by the Ministry of Health, Labor and Welfare, for diseases of aging, and so on. The model mouse with added characterization information obtained by the characterization platform will then be provided under the plan. This is based on the record of collaboration within the BRC up to now, and the plan covers issues with a high degree of novelty.
- On the point of how to pursue research in diseases of aging, however, it will be necessary to do more than simply experiment with long lived animals. More distinctive research needs to be planned, given RIKEN's standing in leading-edge research.
- Next-generation Human Disease Model can be considered reasonable as a project, but it will need to develop pathological models for which there is greater need. Most rare diseases have a limited number of users.
- Regarding the Human Disease Model Development Team plan, there is some doubt about its reasonability. Mutant mice are important in disease model mice, but that importance is thought to vary with the field. In cancer research, for example, models that recreate human disease at the tissue level and genetic mutation level are important, such as in the case of patient-derived xenograft (PDX), as shown by Team Leader Noda. Degenerative diseases were cited as an example of where disease model animals should be developed, but the creation of mice with mutations of well-known for association with ALS or Alzheimer's disease should not be made the central focus of resource-related research. More important than that

might be the development of models that recreate the degenerative disease mechanism of mutation at the protein level by injecting samples from the brains of human patients directly into mouse brains. In any event, the participation of researchers who are on the leading edge, as Team Leader Noda is in cancer research, is essential in the various individual disease areas.

- When proceeding with the preparation of model mice for designated incurable diseases, lifestyle-related diseases, and so on, in the future, it will be necessary to seek even more extensive collaboration with researchers and institutions in clinical fields.

#### Committee for Genetic Resource

- In the Next-generation Human Disease Model Development, it will be essential to collaborate on designated incurable diseases and diseases of aging with medical research fields (laboratories, universities, and other such academic institutions), and a strategy for that purpose is necessary. Candidates that have been proposed include not just genes, but also (which is better) the creation of model mice in response to requests from academia.
- The Next-generation Human Disease Model Development is expected to become a beneficial project given the context of mouse resources at the BRC, but it will be necessary to leave the diseases to be addressed unspecified at present, and instead retain the flexibility to aim at topics that arise at any given time.
- As genome editing technology advances, the time will probably come when disease mice for single-gene defects can readily be produced. Readiness to support such activity and the development of suitable technology will be required. It would seem that supplying mice with expressions reduced to the point of a difference, even in the case of single gene defects, or the technical innovation in a method of producing such mice, is important. Since the number of mice required cannot be managed by a single researcher, the value of the BRC is likely to be enhanced.

**(3) and (4) The Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Cell Resource

- Supplying differentiated cells will be very attractive to users, but it is believed that user friendliness and adaptability to cryopreservation differ greatly depending on the degree of differentiation. Since greater advances in technology development are still needed in this respect, it will be important to conduct joint research and proactively pursue collaboration with specialized institutions.
- It is necessary to provide sufficient explanations of how each team's objects of development are closely linked to research needs. On that point, it was easily possible to understand the relation to operations of the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team.
- The Committee agrees that the four newly developed teams should play an active role in the BRC. The launch and development of the Next-generation Human Disease Model Team, the Higher-order Cell Characterization Team, and the Drug-discovery Cellular Basis Development Team are especially important.
- Since other research institutions and consortia are also considering the development of teams for drug-discovery cellular resources, enhancing collaborative ties and cooperation with them should be considered in order to contribute to the establishment of many drug discovery platforms.

Committee for Experimental Animal Resource

- Regarding the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team, the BRC position appears to have been made clear. That is, in other words, to proceed on the basis of rigorous, close examination of the basic nature of iPS cells (with confirmation of differentiation capacity, total genome sequence, and genome editing as the three key supports). On this point, the BRC appears to assure its own unique identity, which is unlike other institutions. The question of what kind of iPS cells to be selected appears likely to be most important, and it appears that the evaluation will differ by whether (1) the BRC will

conduct a close examination of the basic nature of iPS cells selected by CiRA, or (2) the BRC will have its own unique selection criteria. If (2) is the case, then how to divide up the territory with the CiRA will become important. It will be necessary to clarify this issue.

#### Review Committee

- Regarding the two teams concerned with iPS cells both have plans to further heighten the predominance of these original resources that are founded in unique research originating in Japan. Both teams should be prioritized in the future, and the plans are appropriate and commendable.
- With regard to the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team (differentiated cell provision system), it is necessary to clarify the mission definition and the allocation of roles for each.
- With the exception of the Higher-order Cell Characterization, the names of the themes alone will be able to communicate their importance to the public. In that regard, Higher-order Cell Characterization will require full explanation.
- Including iPS is in line with the flow of the times, but it will probably be necessary to set up arrangements to enable demonstrations of the BRC's uniqueness so that the BRC does not end up in the role of a subcontractor to the CiRA. In terms of providing bioresources, this is entirely commendable, but personally, from the perspective of supporting bioresources with pioneering research, the innovative nature of the direction taken would become clearer if it included areas that do not present prospects for immediate results, such as three-dimensional organ formation utilizing animals, rather than just mass culturing.
- iPS is a field in which it is easy to see prospects for industry-academia collaboration. It should be possible to freely configure the allocation of roles and so on with the CiRA. It is easy to understand the necessity for providing bioresources and the contribution, but there was little explanation of the fundamental innovations involved.

#### Committee for Genetic Resource

- With regard to the application of iPS cells to drug discovery, higher-order cell characterization is extremely appealing, but there is some doubt as to how many disease traits can be reproduced at the cellular level for use in drug screening.
- Higher-order Cell Characterization and Drug-Discovery Cellular Basis Development are important, and the intent in them is understood to signify that the

BRC bears crucial responsibility for a key element in national government projects. This will bring about the implementation of a large-scale joint system with core research institutions in Japan, including the CiRA.

- In Drug-Discovery Cellular Basis Development, cell differentiation technology and differentiated cell quality management technology will be necessary. Establishing these technologies will require the allocation of considerable resources as well as experience. It will be necessary to clarify the BRC's roles in this large-scale joint project as well as its budget.
- In fields where new initiatives will be undertaken in the future, coordination with the RIKEN Center for Developmental Biology will be a key. Implementation in the new priority fields of Higher-Order Cell Characterization and Drug-Discovery Cellular Basis Development will require further full examination of the substance of cooperative systems, taking the new functionality of this center. In this case, it will be necessary not only to clarify the positioning of the BRC in terms of bioresource projects, but also to significantly expand the personnel and funding required for initiatives in the new fields.

## (5) The Symbiosis Research Platform Team

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Plant Resource

- It is anticipated that the symbiosis research platform will undergo major growth in the future.
- Apparently a symbiosis research platform is to be set up, but there are already numerous institutions and researchers around the world that are moving ahead with large-scale analyses related to symbiosis. It will be important to consider how to highlight the uniqueness of efforts of the BRC. RIKEN is fully equipped with analysis platforms of every type in its laboratories, and it is to be hoped that collaborative efforts will be pursued. It can also be anticipated that different materials from different sources and using different soil will produce different results, so it will also be necessary to give careful thought to sample materials.
- In terms of symbiotic systems, *Arabidopsis thaliana* does not have a symbiotic relationship with mycorrhizal fungus, so there is a question as to whether it is appropriate for symbiosis research. Symbiosis research is most advanced in *Lotus japonicus* and other leguminous plants, and perhaps these could be newly introduced for this purpose.
- Research teams for the purpose of promoting collaborative research are being considered, and it would be a good idea if this could be realized in a way that helps to acquire a budget for it. A symbiosis research team with plant-microorganism collaboration would fit with trends in research.

Committee for Microbe Resource

- The plan to reassess the research and development teams that have achieved their objectives and to launch new research and development teams concerned with microbes and plants is reasonable.
- Sophisticated research using model life forms can be performed for microbe and plant symbiosis, but the results are self-contained, and it is unknown when and what kind of users are assumed during this resource development. If this is considered to be research aimed at supplying resources, that idea should be

reconsidered.

- Concerning the Symbiosis Research Platform, the Committee can understand the judgment of the Center Director that, in the mid- and long-term view, new research and development teams related to microbes and plants should be launched. Among the fields that should be emphasized, the Microbe Division and Plant Symbiosis Platform has positive prospects, but it would be desirable to declare more specifically what results can be expected. In particular, it is necessary to explain the role of the Microbe Division and the significance of using fastidious microbes.
- The Committee can understand wanting to take advantage of the respective strengths (internal factors) of the Experimental Plant Division and the Microbe Division, but quite a few resources are needed. Some doubt remains whether “More Efficient Use of Fertilizer and Establishing Agricultural Methods without Excessive Use of Chemicals,” which has been mentioned as an “exit point” for this research, is an issue that RIKEN BRC ought to deal with. Further discussions about which issues RIKEN BRC should deal with should be held.
- The plan coordinating every step with JCM operations should be made, including the consignment to JCM and the publication of the microbes separated in the midst of the Symbiosis Team’s research, etc. The Committee’s suggestion is to formulate the ways in which the recently presented expanded genome information is made use of for promoting the use of JCM resources, and to show it together with the short- and mid-term output.

#### Review Committee

- In the project to prepare a platform for symbiosis research, analysis of the interaction between plant and microorganism genomes can contribute to elucidation of the genomic mechanisms of environmental response, disease and pest response, and so on. These are important research issues with promise for the future. Bioresource infrastructure projects within the Center should extend further these themes in ways that increase the already close collaboration between the Experimental Plant Division and the Microbe Division, as well as with the RIKEN Center for Sustainable Resource Science and other such centers and units.
- Symbiosis research is a theme with a large degree of novelty and a wide range of fields, and as with the other themes, it can be expected to be capable of responding to strong worldwide demand. This research is also viewed as having the potential to suggest new concepts for ecology and numerous other research fields.
- With regard to the Symbiosis Research Platform, proposals are being made for

plans based on the actual record of collaboration between the BRC and the RIKEN Center for Sustainable Resource Science (CSRS).

#### Committee for Genetic Resource

- The symbiosis research platform is unique and is anticipated to yield unexpectedly significant results.
- With regard to the preparation of a symbiosis research platform, the future understanding of plant symbiosis in agriculture and forestry and its active application will be of importance to Japan, which faces the fundamental issues of limited land and difficulty in providing its own food supply. The significance of plans to realize groundbreaking agricultural technologies is understandable. However, careful investigation is required to determine whether or not research results obtained using model plants and model soil can truly be applied in practice to industrial crops. It is also necessary to keep this model research from falling into complacency. A good approach may be to pursue joint research with expert farmers so as to convert the experience of the expert farmer into theory.
- Select a number of industrial crops that are high in order of priority for usefulness in improving the future food situation in Japan (and the world).

#### Committee for Experimental Animal Resource

- The Symbiosis Research Platform is extremely attractive in the way that it has taken a step forward in analyzing the relationship between the individual plant and the resident bacteria in that plant in terms of the individual plant and the environment, so that analysis should be more specific, more comprehensive, and founded in genome science. It is also indicated that the multiple development divisions at the BRC will engage in cooperative work. Similar things could be said of the experimental model animals. The individual animal and its intestinal flora, skin surface microbiotas exert significant influence on the individual animal's phenotype. In light of the above circumstances, it appears that this team's results and future developments with regard to experimental animals will be also something to look forward to.

**Item 3-1. Pioneer a research management model for maximizing research and development results**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- In general, efforts are regarded favorably as continuing to yield actual results despite budget reduction.
- If the resource infrastructure project that serves as the foundation and the development projects that are to enhance the added value are implemented in a thoroughly collaborative manner, then steps can be taken to optimize Center management and make it more efficient.
- Infrastructure projects will provide an important foundation supporting research in the life sciences in Japan. In order to obtain an understanding of the importance of resource centers, which should be sustained by the national government, and to obtain permanent funding of their operating budget, the RIKEN president and representatives should present their case to the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and other ministries (including the Ministry of Finance). Public relation activities should be taken more seriously than before. The development of outstanding human resources to pursue the development and practical application of new technologies as well as to engage in steady, unfailing administration is extremely important as a measure to increase efficiency and optimization of Center management.
- Based on experience to date, it should soon become possible to approximate the number of the BRC users in Japan. It is necessary to consider efforts toward increased efficiency on the basis of that total number of users.
- In order to discuss increasing efficiency and optimization of management, information on the budgets allocated to each division will probably be needed. It will facilitate discussion at the next meeting of the committee to have information materials on the status of budget allocations to the divisions within RIKEN BRC.

Committee for Experimental Plant Resource

- Selection and concentration are the missions of the BRC, and measures must be

taken to provide appropriate budgets accordingly. It is to be hoped that the system for mutual checking of the organization's activities shall be reinforced.

- In terms of project management, however, there are budget and personnel constraints that are difficult, and it will be necessary to indicate policies for how to heighten project efficiency and related matters.
- To advance further, it will be necessary to improve the analytical technology infrastructure in order to enhance the value of resources. Systematic measures should be taken to provide sequencers for genome analysis and transcriptome analysis, mass spectrometers for metabolite analysis, imaging equipment for phenotype analysis, and so on, as well as to train technical personnel to use them.
- Amidst demands for research quality and results, the existence of personnel shortages cannot be denied. There are expectations of personnel support in FY2016, and it is to be hoped that this will be continued.

#### Committee for Cell Resource

- The Committee agrees with the BRC's taking the direction of both securely maintaining the bioresource infrastructure projects and trying to move forward with new BioResource Frontier Programs. While remaining in compliance with the Center's mission, the Committee would like the BRC to continue acquiring funds from the national government and RIKEN in greater amounts than before as well as aiming to acquire funding from outside sources.
- Unlike the majority of research programs at RIKEN, the BioResource Center must have stable, basic operations as an integral feature. Therefore, the meaning of optimization and greater efficiency ought to be different, and it is necessary to look into the issue more deeply. Moreover, since resources are limited, more flexible possibilities should be looked into, as suggested on the evaluation sheet for the Cell Engineering Division, including greater openness and crowd sourcing.
- The increase in the FY2016 budget for the BRC, an important part of our research foundation, is an extremely good thing. The Committee would like the BRC to conduct operations so as to obtain a budget for supply projects clearly separated from the resource supply projects at the heart of the BRC and the teams that conduct research and development. The BRC should consider and promote any aspects that can be made more efficient through collaboration by looking closely at and dealing with resources across organizational boundaries.

#### Committee for Genetic Resource

- Efficiency improvements are being pursued amid various constraints. Optimization and efficiency improvements in academic institutions, which are based on diverse values unlike those of private enterprise, will no doubt also require axes of evaluation that differ from ordinary measures.
- It is to be hoped that active steps will be taken to obtain outside funds. In the case of infrastructure projects, however, considering the nature of their operations, the necessary funding should probably be sought within RIKEN. In addition, it will be necessary to build a system for the support of projects in the Center as a whole.
- At present, the environment in which the BRC is situated is undergoing major changes, and this is ideal timing for the Center director, the president of RIKEN, and the MEXT to act together as one to discard the past and effect a transformation. It should be made possible to collect distribution fees (distribution profit), as a rule, up to an amount that guarantees the maintenance and advancement of the resource project. The self-restrained approach of a non-profit is especially strong in the MEXT, and no specific advance was observed in this regard.
- The mission of the Center places the resource infrastructure project first, and it should be advanced as a center for preservation and resource of supply for the collective research property of the research community in Japan and in the world. Development projects should be left up to other research institutions as their main focus, while the main theme of the BRC is keeping the resource infrastructure project.

#### Committee for Microbe Resource

- Despite the high marks from the BioResource Advisory Council (BRAC) and the Committee's suggestions for further enhancements of the BRC, harsh circumstances occurred, with budget reductions of about 10% compared to the previous year for a period of several years. However, optimization and greater efficiency in management were achieved, and a budget for the replacement of outdated and worn-out equipment was obtained in the FY2015 supplementary budget. Furthermore, the FY2016 budget increased to a level close to that in FY2013. The Committee highly approves these efforts to increase the budget at last.
- By giving projects a three-level structure and introducing retirement systems and fixed-term employment systems, sufficient efforts are made to guarantee the continuity and mobility of technology, which is highly rated.
- Since bioresource infrastructure projects are low-profile projects, the need to show that the BRC is essential tends to remain out of the spotlight. It is necessary to

emphasize the usefulness of resource projects by appealing to people through the implementation of development projects.

- Concerning obtaining outside funding, if the BRC promotes technology development, collaboration with companies is essential toward societal implementation. The Committee hopes that guidelines and policies will be formulated.

#### Review Committee

- It is a good idea to state explicitly that the BRC is not seeking just any outside funding. It must have continuous funding that is in line with the BRC principles. Otherwise, it could become difficult to distinguish the BRC from common research institutions. It is appropriate that the policy for efforts to actively seek outside funding requires that compatibility with the mission of RIKEN BRC first be taken into account.
- Increasing efficiency and optimization of management is essential in order that not only the core of the BRC three-tiered structure, but also the system for assuring BRC's economic foundation over the long term can be pioneering in nature.
- Where funding and related matters are concerned, the BRC should incorporate systems for actively receiving support from corporations, not just from the national government. Government research funding as a whole is diminishing. In this context, government funding as a whole will be thrown out of balance if RIKEN acts as an organization that pursues only its own research results. It is necessary for RIKEN to act capably to build cooperative relationships with universities.
- Management based on a system of recruiting for limited terms may tend to hamper research intended to develop seeds for future technology. It is necessary, however, to strive for research on seeds that can be expected to grow in the future.

**Item 3-2. Are the policies for future resource infrastructure and technology development appropriate?**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- It is crucial that funds continue to be supplied for the BRC mission from the national government and RIKEN.
- In related technology development, the necessity for improvement of genome editing, for live imaging, information analysis, and other such technologies, is clear, and implementation of the respective projects is anticipated. In the context of limited resources, these projects should be advanced efficiently through collaboration within the BRC, within RIKEN, and with other institutions.
- In making future decisions on policy, it will be important to make a full study of user needs, take urgency and degree of importance into consideration, clarify the issues to be addressed, and steadily achieve them one by one.
- Genome editing technology is expected to become increasingly widespread in the future, and it is commendable that measures for handling this technology have been put into place at all points. As stated in the evaluation of experimental animals, clear criteria should be established for the preparation of resources for genome edited mice.

Committee for Experimental Plant Resource

- The rate of growth in life science research continues to increase, so it will probably be necessary to observe movements in research internationally and respond flexibly.
- The policy of deploying technology and resources that individual laboratories cannot support themselves is commendable.
- While basic research on plants is not readily linked to benefit to the society, the new technology of genome editing has become possible to use. If useful improvements on model plants emerge, then similar trials on a variety of crop plants can be anticipated, and these will lead toward practical applications. It has been mentioned that practical applications for genome editing in *Brachypodium distachyon* will be pursued, and this looks promising.

- Cooperating with the National BioResource Project in order to maintain the all-Japan system should assure the continuity of resource projects at RIKEN. It will be necessary to continually review what is needed and envisioned for next-generation bioresources and international trends. It will be important to collaborate with the Japan National Institute of Genetics.

#### Committee for Cell Engineering Resource

- Since “it is difficult to conduct detailed differentiation analysis for all cells,” the Committee suggests that consideration be given to the possibility of a “crowd sourcing” function. In other words, researchers come to the bank for a certain period (under the guidance of the bank) and analyze the differentiation capacity using standard methods, and have the user share differentiation capacity analysis results with the bank.

#### Committee for Gene Engineering Resource

- Taking research trends into consideration, at the same time the BRC is thinking ambitiously resource infrastructure, it is also engaging in steady development of basic technologies.
- With regard to disease research and comparative medicine in the field of cancer, the positioning of cancer cell lines should be undertaken with deliberation. In the case of established cell lines, there is a greater possibility that continued in vitro handling makes them more susceptible to genome variations and phenotype changes, and there is some doubt as to whether researchers will find them of interest. Fresh cells from patients should be used, but the value is halved in this case if they are not paired with cells from patients' normal tissue regions. This also involves the problem of informed consent, and care must be taken.
- In metagenome research, there is some doubt as to whether appropriate soil can be chosen. The content of the microbiome appears likely to differ with the locality, the use of agricultural chemicals, and the status of fertilization. The bacterial floras are also thought to differ with the target plant. Close coordination and joint research with specialists is essential with regard to the bacterial flora in the human intestines, on the skin, and in the mouth.

#### Committee for Microbe Resource

- Human indigenous microbes, fastidious microbes and genome information are themes linked to each other, and synergistic effects are expected.

- Human indigenous microbes are mentioned as an area for resource infrastructure, and fastidious microbes, genomic information, and gene manipulation technology as resources are mentioned as topics for research and technology development in the future, and those policies are appropriate. The policies for preparing technology and research, which are difficult to respond to by individual laboratories, are commendable.
- The Committee would like the BRC to take further steps in technology development for the use of fastidious microbes and to continue collecting and preparing resources that can be put to use in the areas of health and the environment.

Review Committee

- It would be better to conduct sufficient user surveys when making future policy decisions.
- It is necessary to sort out the BRC mission again to identify what it is.
- If RIKEN BRC is being required to show how much added value it can place on resources for preservation, then it will be necessary to improve and expand, the systematic analysis of mouse behavior and the analysis of that behavior using informatics.
- Public relations should not just relate how Center activities contribute directly to the happiness of humankind, but should also refer to how they contribute to academic issues, such as by resolving ecological issues in the case of symbiosis research.

### **Item 3-3. Innovation hub**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

**(i) Collaborations with industry, government, and academia.**

*Has the BRC sufficient achievements, and are plans made based on the achievements?*

Committee for Experimental Animal Resource

- It is necessary to indicate what objectives have been set with regard to industry-academia-government collaboration, and what kind of results have actually been achieved in individual cases of collaboration.
- Given the BRC personnel and the techniques and resources possessed by individual members, the number of collaborations provided appears entirely too small.

Committee for Experimental Plant Resource

- It is important to create collaboration between RIKEN and the National Agriculture and Food Research Organization (NARO), operated by the Ministry of Agriculture, Forestry and Fisheries (MAF), prefectural test stations, and private enterprise. Possibilities include, for example, the Strategic Innovation Promotion Program (SIP) “Technologies for Creating Next-Generation Agriculture, Forestry and Fisheries” and other such arrangements. At the same time, collaboration with universities is also important. RIKEN is well placed to become a hub for these research collaborations. In order to raise the level of Japan's research capabilities, substantive collaboration should be started.
- The topic of collaboration with industry raises issues for public resource projects. The price for providing resources to corporations could be increased.

Committee for Cell Engineering Resource

- Japan should play a central role in collecting and supplying ES/iPS cells. Since industry, academia, and governments have high expectations in this area, the BRC must move steadily forward in preparing a firm foundation.
- The Committee understands the general direction of collaborations between industry, academia, and governments, but specific proposals must be presented.

Committee for Gene Engineering Resource

- They are sufficient under the criteria used to date. However, examples of Jackson Laboratory and Addgene suggest the possibility of forms of industry-government-academia collaboration that have not been considered up to now.
- A commitment should be made for the BRC to be the hub function.
- More specific plans are necessary.

Committee for Microbe Resource

- Evaluated solely microbiology field, actual results and plans based on actual results are provided. It would be best if a strategy could be clearly stated how a collaboration between industry and academia in the field of microbial resources related to the environment and health can be achieved, and how to expand it.
- The Committee would like the BRC to make further efforts to collaborate with the industrial sector.

Review Committee

- Unless the BRC controls the collaboration, planning and execution will probably be difficult to carry out.

**(ii) Collaborations within the BRC**

Committee for Experimental Plant Resource

- Industry-academia-government collaboration will probably face difficulties from the start in the field of basic research on plants. The MAF has also undergone major changes recently, and it appears that their laboratories that had been conducting basic research have been taking steps to transition toward practical applications. There is a certain geographical advantage in this since MAF laboratories locate in Tsukuba. An opportunity may rise for effective collaboration that leads to the advancement and practical application of research.

Committee for Gene Engineering Resource

- Since resource development, preservation, and distribution systems are steadily increasing in importance, cooperation within the Center should be further promoted. It is also important to set up a foundation to support exchanges between projects.

Committee for Microbe Resource

- The BRC collaborates sufficiently with the Japan Society for Microbial Resources

and Systematics and the World Federation for Culture Collections.

#### Review Committee

- There is sufficient awareness of collaboration within the BRC. There are examples such as symbiosis research is collaboration between the Experimental Plant Division and Microbe Division. Next-generation Human Disease animal Models is collaboration among the Experimental Animal Division, the Technology and Development Team for Mouse Phenotype Analysis, and the Technology and Development Unit for Knowledge Base of Mouse Phenotype.

#### **(iii) Continuous operation and attracting new users**

##### Committee for Experimental Animal Resource

- With regard to the search for new depositors, the planning is well motivated and there are on actual performance results. The preparation of Next-Generation Disease Model mice, of transgenic strains produced by genome editing, and of new reporter mouse strains, as well as related activities, are all appropriate and can be expected to contribute to the search for new users.
- Public relation activities are being conducted at different scientific societies, and it is hoped that these public relation activities will be continued in the future in order to find additional users, with the aim of becoming one of the most advanced resource centers in the world.
- For the search of additional users, selective efforts are underway using surveys of published research papers, press releases, and so on. However, these activities will require securing personnel who are knowledgeable about information collection. If this kind of information collection is to be conducted in addition to everyday operations, it will probably be difficult to collect sufficient information, and it will be necessary to recruit dedicated personnel who are highly skilled in information.
- There is a weakness with regard to grasping users' needs. The new resource projects should come only after adequate surveys are made on the user's needs.

##### Committee for Experimental Plant Resource

- Resource projects should search research needs while sustaining reliability and continuity. Stable management with permanent employment will be necessary.
- It is necessary to not just provide resources, but also to collaborate in research and other activities.
- In the plant divisions in particular, although the number of users in Japan and the

research results (number of research papers) can be maintained, growth is expected to be difficult. If the number of users can be maintained to some extent, that will mean that a full contribution to society is being made. It would seem unnecessary to continue growing. It is necessary to continue finding new users, and perhaps the problem can be avoided by effective explanations. It seems important to concentrate the limited available resources (people and budget) into the growth areas of research for the continuation of the BRC.

#### Committee for Cell Engineering Resource

- It is believed that dissemination of cell culture technology is required in order to find new users. Dependable technology is especially needed for culturing ES/iPS cells. In order to continue supplying these cells, it is necessary to take a proactive approach to technological advice and training technicians who are able to culture ES/iPS cells.

#### Committee for Gene Engineering Resource

- In discovering (expanding the number of) additional users, it will probably also be necessary to make contact with the writers of experimental protocol and manuals. It will also be important to take active steps to show examples of resource utilization by means of websites, lectures, workshops, publications, and so on. Organizing technical workshops and other such events is effective not only for promoting research, but also for expanding the number of users, so this should be pursued even more actively. Meanwhile, it is also necessary to continue enhancing the value of bioresources. In order to add a variety of information (such as meta-information, sequencing information, etc.) to resources, therefore, it will be necessary to reinforce information analysis capacity within the Center and establish close collaboration with outside institutions.
- Bioresource projects have been generally perceived up to now as RIKEN projects. Intensively reinforcement of positioning is the common benefit of the research community.
- The BRC should concentrate all the research materials for research conducted within Japan, at least, in this project.  
A commitment should be made to play the hub function. The BRC should basically concentrate on turning the results of research at other institutions into resources.

#### Committee for Microbe Resource

- With an eye toward the future, the Committee would like the BRC to make preparations for expansion to overseas locations such as Africa and Southern Asia.

Review Committee

- With regard to search for new depositors, public relation activities are being conducted at various scientific societies. The planning is well motivated on the basis of actual performance. It is hoped that these activities will be continued in the future, and that more users will be discovered.
- In the case of mutant mouse resources accompanied by information on behavior analysis and on links with human disease, the number of new users is anticipated to increase rapidly. It is necessary to recognize that this state has not yet been reached at present, regardless of the many efforts made. It is necessary to systematically strengthen this aspect.
- There is an impression that the creation of a database itself may have become the objective. What effects provided should be an important issue. At present, the adoption of a big data approach to human medical care has begun. Under these circumstances, it will be necessary to engage in database building in a sufficiently strategic manner so that the value of the animal (mouse) model database will not diminish.

**Item 3-4. Serve as a focal point for global brain circulation: Recruitment system**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- The shortage of female researchers in leadership positions is a problem faced by most Japanese natural science research institutions. It may become necessary to set a quota for women, but it will also be necessary to take care that reverse sex discrimination will not occur.
- It is impossible for RIKEN BRC by itself to create a living environment for foreign researchers for the purpose of taking on a role in the global circulation of scientific talent. It will be necessary to take measures that bring in Tsukuba City and other local government bodies as participants.
- Making international public calls for applicants while also putting out wide-ranging recruiting system including introductions from acquaintances to find suitable personnel is a dependable approach to recruiting.
- As to the BRC research staff, they should be subject to different performance evaluations than research staff at other RIKEN laboratories. For example, if we assume that the BRC research staffs have a considerable percentage of their time taken up by day-to-day operations, then it would be a mistake to apply the same evaluation criteria to research staffs who are able to direct 100% of their time to research. It is necessary to take strong measures to have this point understood by the upper RIKEN management.
- Since an adequate career path has not been created for personnel who conduct support operations, various problems have arisen. However, if the shift to indefinite-term employment within RIKEN can be accompanied by the creation of a career path for transfer of employment outside RIKEN, this will make human resources both more stable and more mobile.
- As to temporary staff from other agencies, a system must be put in place to enable some kind of career advancement based on their duties, or most of them will probably quit after about one or two years. One way of having superior personnel stay at their work longer, and also of recruiting promising new personnel, might be to establish a system within RIKEN for ranking personnel by their qualifications.

- If four new teams are launched, the capabilities of the personnel who belong to the existing teams should be carefully assessed and they should be reassigned to appropriate positions accordingly. The recruiting of required new personnel should then take place after that.

#### Committee for Experimental Plant Resource

- From the perspective of research management, it is difficult to know how to evaluate the contributions made by research personnel to maintaining resource quality and other such mission activities. Unless research support activity is evaluated fairly, it will probably be difficult to secure personnel for the resource divisions.
- Careful attention should be paid to developing and hiring human resources capable of exerting advanced skills in a continuous and stable manner.
- Development of human resources and exchanges of personnel are necessary. Collaboration with University of Tsukuba and the Japan National Institute of Genetics should be sought, so that high-quality personnel should be recruited. Human resources well-suited to resource research and operations are also being developed in the RIKEN CSRS.
- Careful consideration of the living environment is important. Traditional cultures and freedom of religion should be respected, but prudence should be exercised in supporting any particular religion.

#### Committee for Cell Resource

- Recruitment for the BioResource Center is something other than seeking the researcher most inclined to do cutting-edge research, so it is necessary to consider different hiring practices.
- Working toward optimization of hiring practices (fixed-term, indefinite, etc.) should be continued, in such ways as planning and setting them according to the duties that the employee is expected to perform.
- Hiring people from the corporate world also should be considered.
- The following possibilities should be considered: “Would it be possible to exchange human resources with bioresource centers worldwide?” “Would it be possible to set up a system in which personnel and funding are offered from a company, and the bioresources and the results are shared between the BRC and the company?”
- It will be essential to obtain human resources who can promote two opposite tasks: pursuing cutting-edge subjects and maintaining fundamental technology.

### Committee for Genetic Resource

- When new terms start, there will be a drastic shortage of human resources. If useful results for each topic are to be anticipated five to ten years into the future, the numbers of personnel assigned in each field to date will have to be drastically increased.
- Exchanges with university personnel (particularly with doctoral candidates and postdoctoral research fellows) are valuable opportunities to hear their views regarding the usefulness of bioresources collected and prepared by the BRC. For this purpose, it is necessary to organize a variety of technical workshops, seminars, and so on, as well as to set up systems for accepting larger numbers of students.

### Committee for Microbe Resource

- The living environment is often to be overlooked although preparing a research environment that is up to international standards.
- Many human resources are achieving success at foreign universities and research institutions, but it is regrettable that these do not include institutes in South Korea, Thailand, the Philippines, and other countries with deep ties to Japan. The Committee would like the BRC to deepen ties with these countries.

### Review Committee

- It seems that collaboration should be sought with universities and negotiations should be carried out with the national government so as to create a system that can provide continuing employment to staff members who possess technology knowledge and experience. A place such as RIKEN BRC, where support is the main activity, should be especially outspoken about this.
- The career paths for personnel who engage in support activities have not been adequately established, so various different problems occur. The personnel situation will stabilize and also achieve greater fluidity if indefinite-term employment within RIKEN is adopted and a career path that allows for job transfer outside RIKEN is created.
- With regard to increasing the ratio of women who are researchers, there are difficulties by comparison with the case of women on the technical staff. It may become necessary to set a quota for women, but it will be necessary to take care that reverse sex discrimination will not occur.
- As regards foreign researchers as PIs, requiring fluency in the Japanese language

will probably impede almost all hiring. How much foreign researcher employment in positions other than PI can be increased is an issue.

- It is an essential and urgent issue that living environment infrastructure be improved.
- There appears to be a necessity to create a new mechanism that did not exist before, including the mechanisms in that should involve recruitment for the BRC alone, or whether it should recruit for RIKEN as a whole and then assign personnel appropriately.
- There has been talk that in Japan as a whole, so much funding has been directed to iPS cell research that budgets for other fields have been impacted. For the BRC to provide lateral support for iPS cell research would be in line with the direction of national policy, but it will also be necessary to engage in recruiting with a view to assuring the diversity of research in the future, so that it does not tip over one-sidedly to iPS, and so that some researchers are included who have some distance from iPS cell research.

### **Item 3-5. Training of global human resources**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

#### **(i) Within the BRC**

Committee for Experimental Animal Resource

- As to the research staff, it seems more likely than not that those members of the research staff who have been at the BRC since it was founded, and who have achieved the major objectives (and the enjoyment) of getting the Center started and establishing the systems for managing it, may tend to experience some diminishment of their motivation for everyday operations. It is important to set new objectives that can bring about higher levels of motivation.

Committee for Experimental Plant Resource

- Presently there are few researchers and students from other countries at the BRC, and it seems there is still a ways to go in the training of global human resources.
- The strategic centers that were initiated at RIKEN around 2,000 have reached the time for transition to another generation. It will be important to secure the personnel who will become leaders, and to change to a new generation of research leaders. It is necessary to move forward promptly with examination of the possibilities of some drastic action in 2018.
- It cannot be denied that personnel shortages exist in terms of the substance of activities and planning.

Committee for Cell Resource

- Conducting bioresource research at other laboratories is difficult for the duty of supporting a foundation for cutting-edge research, so training of human resources should be promoted.
- The Committee suggests that the BRC trains human resources and actively recruit for them through mutual exchanges with similar research centers around the world.

Committee for Genetic Resource

- The question of whether there is an appropriate successor as Center Director is

worrisome.

- In order to secure a diversity of personnel, including women, it will be necessary to provide a living environment that allows people to concentrate on projects within the BRC and that optimizes research support.

#### Committee for Microbe Resource

- Training curators from major Asian countries such as China, South Korea, and Thailand at JCM is a valuable activity. It makes a major contribution to building up networks. Even though the staff members do not have enough time, they are judged to have dealt with this well. In particular, training in management of culture collections and in taxonomy for quality management plays important roles in the establishment of culture collections in developing countries. It is expected that once they return to their home countries, saying that they were trained at the RIKEN JCM will give them quite a bit of status.

#### Review Committee

- Considering that there are an appreciable number of researchers who transfer to positions in outside institutions, there are prospects for the continuing production of at least a certain number of researchers in the future. It is to be hoped that further efforts will continue to be made in this regard.

### **(ii) External**

#### Committee for Experimental Animal Resource

- Are there plans for human resource development through collaboration with research institutions in Europe and America?
- It is unclear how the BRC would define internationally oriented human resources. Just holding international workshops and international summer schools and bringing together the people for the courses does not mean "developing internationally oriented human resources" outside the BRC. Feedbacks showing the results achieved by participants in such international workshops and international summer schools are required.

#### Committee for Experimental Plant Resource

- The role as a resource center is coordinated with all-Japan efforts. The substance of activities is closely related with the NBRP, the Integrated Database Project, and other such programs. Since the Japan National Institute of Genetics also performs a

similar function, it will be important for RIKEN and the Japan National Institute of Genetics to join together to advance the development of human resources. The BRC has advanced coordination with the NBRP, and this is the correct direction. It is to be hoped that plans will go forward while also maintaining a balance with regard to animal, plant, cell, gene, and information resources.

- Presently there are few researchers and students from other countries at the BRC, and it seems there is still a ways to increase the training of global human resources.

#### Committee for Cell Resource

- The BRC have sufficient results in accepting researchers from overseas for training, so the BRC should actively advertise its contributions.

#### Committee for Genetic Resource

- Personnel exchange with organizations outside the BRC is useful for furthering research and should therefore be promoted actively.
- With regard to future new fields, the difficulty of issues and intensity of competition are expected. Human resource development and recruiting policy will be extremely important. Improvement of the living environment is also an urgent issue.

#### Committee for Microbe Resource

- The plans lack specificity. The BRC should take young people with bright prospects who already have positions in their own countries. The BRC should also create a basic training program in quality management based on taxonomy and collection management. Since Thai Biotech gathers trainees from surrounding countries every year for a training course, the Committee recommends that some from the BRC participate as lecturers. The BRC is increasing its presence in Asia, but most of the presence in Asia is due to consignments and the number of users who receive the benefits is extremely small. The effect of this training is huge, and can be viewed in the long term and it will be even more valuable in the future.

#### Review Committee

- It is anticipated that the BRC will continue its activities with an awareness of their outwardly directed contributions as before.

#### **Item 4. Collaborations among the RIKEN centers**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Plant Resource

- Since the BRC has stated that "in the next period, the amalgamation of research development issues with other centers will also be taken into consideration," no doubt it will be necessary for the BRC to take the initiative to search out issues. It may also be a good idea to propose a system to open up and develop new research fields that have resources as their basis.
- Collaboration with strategic centers will be important. Development of new resources, resource utilization technologies, analytical technologies, and technical guidance will take on increasing importance in times ahead. So far the development of plant material is a small scale. It will also be important in the future to continue collaboration with RIKEN CSRS. Collaboration between Yokohama and Tsukuba is also important.

Committee for Cell Resource

- Collaboration within the Center is important, and the efficient derivation of research results through collaboration should be actively promoted. In particular, it would be a good idea to have a firm collaboration with Kobe RIKEN.

Committee for Microbe Resource

- Collaborations both outside the BRC and among the RIKEN Centers are sufficient, and the Committee believes that these collaborations will continue to expand.
- These collaborations seem to be based on actual performance. But it is better to establish collaboration by hiring people from outside institutions who have greater freedom.

## Summary of Evaluations and Comments by Respective Resource and Review Committees

### Committee for Experimental Animal Resource Evaluation and Suggestions

#### **Experimental Animal Division**

**Division Head: Atsushi Yoshiki**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)*
  - From the following perspectives, the Division should be evaluated as meeting or exceeding expectations:
    - (1) In spite of limited budgets, the Division has achieved goals for collection and distribution of mouse strains. Quality control and technology development are also worthy of acclaim. In terms of the scale of projects and the quality of those resources, the Division has become an international core facility for mouse resources second to the Jackson Laboratory.
    - (2) The Division has participated in the International Mouse Phenotyping Consortium (IMPC) and set the mouse production on track by genome editing and already supplied the Japan Mouse Clinic genetically mutated mice. The achievement exceeded expectations.
  - The Committee has advised as below for the Division to achieve sufficient outcomes in future:
    - (1) The effort to gain new depositors is important for this project.
    - (2) With regard to the international status and evaluation, it is desirable to evaluate the Division with objective evidence, not just by self-evaluation.
    - (3) The policy regarding the acceptance and distribution of genome edited mice should be documented and disseminated to demonstrate the leadership of the Division.
    - (4) With spreading CRISPR/Cas9 technology, a quicker distribution of resources will become important to increase the future utilization of mice. The criteria for choosing whether a strain should be maintained alive or cryopreserved should be

clarified, and the Committee should recommend increasing live strains in response to users' needs.

- (5) Questionnaire surveys and other means for grasping users' needs should be implemented more actively. Ingenious measures to boost the response rate might be considered, such as providing a credit for distribution to questionnaire respondents. This kind of activity would also provide an opportunity for promoting the BRC.
- (6) For tissue-specific Cre drivers, human disease models, and strains that cannot be readily produced using genome editing, more specific guidelines regarding collection methods should be indicated.
- (7) Knowledge regarding the quality of resources obtained by means of strict quality management operations is important, and it should be published in *Experimental Animals* or other specialist journals.
- (8) Regarding the duplicate efforts of rederivation being done on transfer of mice from the BRC to other institutions, the Division should let animal facility managers know such wasted works unnecessary.

◎ *1-1b. Responses to previous comments and advice*

- From the following perspectives, it can be evaluated as adequately responded:

  - (1) The policies for accepting genome edited mice are appropriate. The policy of actively collecting mouse strains that are difficult to produce even with current genome editing technology is also reasonable.
  - (2) The number of distributions to industry has been improved through communications with pharmaceutical companies and others, which is highly commendable.
  - (3) It is particularly worthy to note that the development of novel mouse models for visualization and neurological disease models in collaboration with RIKEN BSI, University of Tsukuba, and Niigata University.

- The Committee points out and advises for further improvement as follows:

  - (1) In order to expand users, it will be necessary to collaborate also with Cell Engineering, Microbe, and other divisions.
  - (2) There is a need to prioritize strains that should be prepared based on the results from surveys of user needs.
  - (3) It will be necessary to develop methods for speedy expansion of living stock in a short time.

- *1-2. Is the self-analysis of strengths and weakness adequate?*
  - From the following perspectives, it can be evaluated as adequately analyzed. The Committee points out and advises for further improvement as follows:
    - (1) It should be evaluated as a major progress in terms of supporting the resource foundation for life sciences in Japan that the number of live strains can be restored up to 500 with partial recovery of the budget.
    - (2) For further gaining trust and increasing use, the Division should strengthen public relations activity. It is important to send messages on the necessity and the importance of the BRC to the mouse research community to secure sustainable funding, as well.
    - (3) Increasing the live strains, starting up a new team for disease model development, and improving information technology are all important issues. It is necessary to clarify cost estimates of personnel, equipment, and operation, and to create roadmaps accordingly.
    - (4) Disease models that incorporate human disease genome information are being developed at numerous other medical research institutions. It would be desirable to explain how to differentiate the BRC from other institutions and how the BRC is unique.
  
- *1-3. Is the plan reasonable for the medium to long term?*
  - From the following perspectives, it can be evaluated as generally reasonable:
    - (1) Establishment of resources to serve as models for rare diseases and diseases for which risk is increasing with ageing is correct as a direction that addresses society's needs.
    - (2) The following directions for collection are adequate. Firstly, mice that cannot be produced using CRISPR/Cas9 should be collected. Secondly, for mice produced using CRISPR/Cas9, the first generation genome-edited founder mice are not accepted for deposition due to mosaicism. Only the genetically-defined mice of the second or later generations which have been published in research papers should be collected.
  
  - The Committee points out and makes suggestions for further improvement as follows:
    - (1) Regarding resource development, it would be strongly recommended to pursue implementation in collaboration with other divisions and development teams.
    - (2) Regarding the development of disease models with human mutations, it is

necessary to clarify which genome information will be used, collect related information, and confirm the validity of methods.

- (3) The most important mission of the BRC is to distribute mouse strains of high quality by advanced quality management. Development of even more highly precise and rapid quality management methods and improvement of phenotyping platforms are necessary.
- (4) It would be desirable to provide explanations of specific research themes and measures regarding relationships with epigenomes and diseases.

◎ *2a. Have appropriate fields been earmarked for future prioritization?*

- From the following perspectives, it can be evaluated as appropriate:
  - (1) Quality management will remain important as a mission of the Division and the steps should continue to be taken to prioritize it in future.
  - (2) For the BRC as a whole, founding a Next-generation Human Disease Model Development Team responds to growing demand from the research community. This response is reasonable as an initiative.
- The Committee points out and makes suggestions for further improvement as follows:
  - (1) Quality management is a most important field. The Division is expected to properly conduct quality control of transgenic mice which will increase even more rapidly in future. The Division should also play an educational role in the quality management.
  - (2) It should be appropriate for the Division to closely collaborate with the new model development team and to act as one group in developing resources. At the same time, if coordination with existing development teams is less than sufficient, steps should also be taken to review and improve that situation.
  - (3) Developing mouse models with human disease mutations is correct as the direction for future, but it will be necessary to select proper human disease mutations of which we can expect users.
  - (4) It would be advisable for this resource project to emphasize continuity over novelty.

◎ *3-2. Are the policies for future resource infrastructure and technology development appropriate?*

- From the following perspectives, it can be evaluated as generally appropriate:
  - (1) The BRC should also aim to make a contribution toward overcoming the issues of

an aged society. The policy of preparing and improving disease models for rare diseases and age-related diseases is worthy of approval.

- (2) New technology development for quality management of resources should be included.
- (3) With regard to technology development, the necessity for improvement of genome editing technology, live imaging, information analysis technology, and other technology is clear. It is recommended that technology development should be original, not merely following the path tread by others.

### *3-3. Innovation hub*

- (i) *Collaborations with industry, government, and academia*
- (ii) *Collaborations within the BRC*
  - This is largely adequate, which is commendable, but those portions that are deemed insufficient are pointed out and advice is given in the following.
- (1) With regard to industry-academia-government collaboration, it would be desirable to explain the objectives with the corresponding achievements.
- (2) It is understood and accepted that collaboration has been done frequently within the BRC, but specific explanations of these collaborations were lacking.
- (iii) *Continuous operation and attracting new users*
  - From the following perspectives, it can be evaluated as sufficient:
- (1) The BRC takes steps to actively pave the way for both collection and distribution of resources, and it is important that this approach be maintained. The plans for collection of next-generation disease model mice, of transgenic strains produced by genome editing, and of new reporter mouse strains, as well as related activities, are all appropriate.
- 3-5. *Training of global human resources*
  - It can be evaluated as sufficiently presented, but for portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
- (1) The BRC has been jointly organizing a Mouse Resource Workshop with Nanjing University, and the plan to continue this in future is commendable. The plan to continue participation in the University of Tsukuba Life Innovation Degree Program and take on a share of the Introduction to Bioresources for graduate students is also excellent.
- (2) However, organizing international workshops and international summer school

does not by itself constitute “developing internationally-oriented human resources.” Feedback from course participants on the subsequent results of their participation will probably also be necessary.

- (3) It would also be preferable to develop plans for future human resource development projects that collaborate with research institutions in Europe and America.
- (4) It is necessary to clarify the definition of internationally-oriented human resources.

● *4. Collaborations among the RIKEN Centers*

- It should be evaluated as sufficiently presented, but for portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
- (1) The development of reporter mice for visualizing autophagy and mitophagy with the Miyawaki Team, Laboratory for Cell Function Dynamics, RIKEN BSI is evaluated as an inter-center collaboration of significance. However, there should be an explanation of whether there are any other plans for collaborations similar to this, and how this kind of collaboration is important for the future of the BRC.

**Committee for Experimental Plant Resource  
Evaluation and Suggestions**

**Experimental Plant Division**

**Division Head: Masatomo Kobayashi**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ 1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society.)
- From the following perspectives, it can be evaluated as meeting expectations:
- (1) Vigorous efforts are being made to prepare *Arabidopsis thaliana* and *Brachypodium distachyon* resources, and the Center receives high ratings internationally on a par with resource centers in America and the United Kingdom. It means that RIKEN is rated highly in plant science at international conferences.
  - (2) A great contribution is being made to the plant research community by the preparation of a foundation for advanced research in plants and by the distribution of specimens. The fact that *Brachypodium distachyon* has been taken up as a model plant for the family of wheat, which is the major source of calories for the human race, and that preparation of an infrastructure for that research is proceeding smoothly, is commendable.
  - (3) Results are being produced as anticipated in the collection and quality control of resources. Consequently, contributions are being made to research paper publication and patent acquisition.
  - (4) It is highly commendable that specimens are being supplied at the highest level of quality in the world.
  - (5) Initially there were concerns about *Brachypodium distachyon*, but it is apparent that the accumulation of research and development of this plant as a resource has advanced.
  - (6) The preparation of resources for functional analysis of *Arabidopsis thaliana* genes, as well as operations for their distribution, have expanded smoothly, and this has been rated highly. In future, heightened value will be sought in resources for the purpose of advancing research in *Arabidopsis thaliana* resources.
  - (7) Making contributions to society involves steady, step-by-step activity, and the unflagging efforts being made are commendable. It would be a good idea if

collaboration with RIKEN public relations could be pursued in relation to these activities.

- The Committee points out and makes suggestions to produce sufficiently enhanced performance in the future:
  - (1) Personnel support appears to be inadequate in proportion to the magnitude of the research contribution being made. This appears to be due to budgetary circumstances, but it is certainly to be hoped that personnel support (staff increases) will be made.
  - (2) The deposition of specimens by individual researchers and the search for additional users are issues that affect the continued existence of these programs, so it is to be hoped that efforts will be continued, while observing trends in Japan and other countries. The time has come when the first generation of *Arabidopsis thaliana* researchers will be retiring, so actively approaching them to ask for depositions could contribute to the dissemination of research results that originate in Japan.
  - (3) It is to be hoped that resources will be prepared with various different strains and associated genome information attached wherever possible.
  - (4) Providing the fundamental plant science research community with *Brachypodium distachyon* as a model will probably be important in providing a foundation for future research on wheat and other such crops.
  - (5) It would be a good idea to present examples of possible applications of *Brachypodium distachyon* to crops.
  - (6) Considering the foundations that contribute to the agricultural crop field, and thinking about future directions, it seems advisable to consider collaborating with other institutions (especially the National Agriculture and Food Research Organization (NARO) and other such institutions and universities) now more than ever.

◎ 1-1b. Responses to previous comments and advice

- From the following perspectives, it can be evaluated as adequately addressed:
  - (1) Matters are being addressed appropriately. As the provider of resources in demand from researchers, it would be advisable to continue collecting comments from researchers.
  - (2) Commendable efforts are being made to expand the number of users, for instance by organizing *Brachypodium distachyon* workshops, exchanging information on genome editing technology, and so on.

- (3) Sincere efforts have been made in response to matters pointed out last time, and improvements are being made.
- *1-2. Is the self-analysis of strengths and weakness adequate?*
- From the following perspectives, it can be evaluated as adequately analyzed.
  - The Committee offers the following suggestions to turn shortcomings into strengths:
- (1) The Committee agrees on the statement that cites improvement of database convenience as a problem. Development of methods and technology for the analysis of imaging data information is slow by comparison with such developments for genome-related information. Collaboration with researchers in information science is necessary.
  - (2) The questions of what kind of imaging data and meta-information are considered necessary, and what methods are best for collecting those kinds of data, should be discussed thoroughly with researchers specialized in the area and steps taken so as not to fall behind international trends.
  - (3) The collection of ecologically variant strains determined by genome sequencing, the provision of added information such as phenotype analysis of gene-disrupting variants and metabolome analysis, the collection of multiple insertion mutants of gene families that have been published as research papers, and other such activities will be important.
  - (4) As shown in the self-analysis, it is to be hoped that an approach will be taken in the direction of making it possible to identify information that is already stored in the database from a variety of different angles and make use of it.
- *1-3. Is the plan reasonable for the medium to long term?*
- From the following perspectives, it can be evaluated as reasonable:
- (1) Overall, the plan for the next five years appears good. In future, information analysis and information provision will probably become important fields in response to the needs of a society undergoing an information revolution.
  - (2) The Committee very much wants to give a boost to this project, which supports the promotion of basic research. For the project's long-term stability, however, it may be necessary to demonstrate effective collaboration with researchers, research institutes, and enterprises that aspire to implementation in society, or to implement other such schemes.
  - (3) At this point, it appears appropriate to have control both of approaches that have an

eye on outcomes and those that are more oriented to basic research.

- (4) Taking globalization and the era of the Trans-Pacific Partnership into account, collaboration between science and agriculture is important, and developments that are not possible at the individual crop plant level can be anticipated.
- (5) The policy that calls for cultivating *Brachypodium distachyon* as a laboratory model for the grass family is acceptable. On the other hand, it is to be hoped that consideration will also be given to collaboration with researchers in agronomics and ecology and so on, and to preparation for specialized field promotion facilities.
- (6) It is to be hoped that steps will be taken to prepare strains based on genome information for the purpose of research on biological activity in model plants.

◎ 2a. *Have appropriate fields been earmarked for future prioritization?*

- From the following perspectives, it can be evaluated as appropriate:
  - (1) Attention is presently being focused on research that seeks to systematically analyze interactions between symbiotic bacteria and plants. Collaboration between laboratories within RIKEN is a strength for yielding results, and it is to be hoped that results will be forthcoming.
  - (2) The inauguration of a symbiosis research team in collaboration with the Microbe Division is timely and to be welcomed. It is to be hoped that closer collaboration will take place with related scientific societies and the research community.
  - (3) It is to be hoped that steps will be taken for the thorough development of key technologies using model plants and for advancement of biosystems research characterized by diversity and complexity.
  - (4) Having understood that this is a very basic field, it is judged to be appropriate.
- The Committee makes suggestions for further improvement as follows:
  - (1) Doesn't stress response differ by species according to genetic background? In future consideration of practical applications, it would appear necessary to present measures for linking the model to the crop.
  - (2) It is fine to pursue symbiosis in general, but it is probably better first to consider items that should be assigned particular priority.
  - (3) It is still necessary to analyze biological systems by transcription factor, and it should be possible to evolve further new approaches.
  - (4) It is not as though there are no preceding studies in the symbiosis field (microorganisms, plants, and insects) already. It is important to collaborate with researchers who have gone before.

- 3-2. *Are the policies for future resource infrastructure and technology development appropriate?*
  - From the following perspectives, it can be evaluated as appropriate:
  - (1) This constitutes resource infrastructure and technology development that has versatility for the user.
  - (2) As a matter of technical policy, priority resources are indicated and administered appropriately.
  - (3) It is to be hoped that the range of users will be broadened and that exploration will proceed while responding to feedback from users.
  - (4) It is apparent that efforts are being made to introduce genome editing and other such new technologies.
  - (5) It is to be hoped that efforts to collect diverse strains of *Brachypodium distachyon* will continue.
  
- The Committee makes suggestions for further improvement as follows:
- (1) The importance of genome-related information and imaging data is expected to increase by comparison with raw plant resources.
- (2) Technology development on the bacteria side for mycorrhizal fungus and other such symbiosis research may be necessary. It seems likely that host-induced gene silencing will also be necessary.
- (3) Various research activities centered on genome information are expected to develop in the next decade, so there is urgent need to train researchers with stronger information capabilities.
- (4) In order to collect new resources in a future context of budgetary and personnel constraints, it may become necessary to discard resources that are diminished in value. It would appear that consideration of such preservation guidelines is necessary.

### *3-3. Innovation hub*

- (i) *Collaborations with industry, government, and academia*
  - The Committee offers the following suggestions for further improvement.
  
- (1) It would be advisable to make resources more visible to industry. With regard to collaboration between institutions, collaboration with research institutions of the Ministry of Agriculture, Forestry and Fisheries is advancing, and it would be a good

idea to continue this.

- *(iii) Continuous operation and attracting new users*
  - From the following perspectives, it can be evaluated as generally sufficient:
    - (1) It seems important for model plant researchers to disseminate information to crop researchers. For crop research, as well, including gene function analysis data with model plants will increase the grade of a journal.
    - (2) Innovation is a difficult issue, and it necessitates having a pipeline in readiness and especially having a network of people already created.
    - (3) In order to broaden the range of users, it is important to collaborate with the National Agriculture and Food Research Organization (NARO) and other such organizations.
    - (4) At the same time, collaboration with universities is also important. RIKEN is well situated to serve as a hub for both parties.
  - The Committee offers the following suggestions for further improvement:
    - (1) It is very much to be hoped that a website on experimental methods will be prepared.
    - (2) In order to be able to incorporate ideas in a bottom-up manner for new technology development, the possibility of issuing a public call for technology development may be worth considering.
    - (3) In order to increase the number of new users, it will be necessary not simply to provide information, but also to be ready to engage in analysis and other work together, such as through joint research.

**Committee for Cell Resource  
Evaluation and Suggestions**

**Cell Engineering Division**

**Division Head: Yukio Nakamura**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *I-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society.)*
  - From the following perspectives, it can be evaluated as meeting expectations:
    - (1) The BRC is a world-renowned hub among cell providing institutions.
    - (2) Since quality management is a major precondition for providing cells, this is the most important item. The current stance should be continued.
    - (3) Results are showing a nearly consistent upward trend. This is evaluated highly.
  - The Committee points out and makes suggestions to produce sufficiently enhanced performance in the future:
    - (1) An extremely massive number of disease-specific iPS cells have been deposited, but few of them are used. Some suggestions are provided below:
      - It is necessary to create a venue that will be appealing to many researchers and promote use of the cells.
      - The users' technology, etc., is not prepared to deal with iPS cells, which are much more fastidious than ordinary cells such as cancer cells, so it is hoped that there are established venues for dissemination of technology during university education and other training.
      - Most researchers may be hesitant to pursue this field, due to the complexity of research ethics screening in research involving disease-specific iPS cells, so it may be necessary to promote use by offering support for the creation of documents.
    - (2) It is hoped that collaboration with new teams and new locations will be conducted to establish a system in which newly deposited cells and newly developed cells can be put to use as soon as possible.
    - (3) When analyzing and evaluating performance with cell deposition and so on, it will be more convincing if not only the institution's own performance, but also data that compares the BRC's performance with the performance and characteristics of other major world-class cell banks, is added.

◎ *1-1b. Responses to previous comments and advice*

- From the following perspectives, it can be evaluated as adequately addressed:
  - (1) Infrastructure focused on disease-specific iPS cells is a move in the right direction.
  - (2) A total of 158 diseases, with 1,568 cell lines from 446 patients, have been deposited, and we believe that it will be extremely significant if iPS cells for all diseases are organized.
- The Committee points out as follows:
  - (1) It is believed that a very large budget and a large number of personnel will be needed for the ES/iPS cell infrastructure. The BRC will need further systems and infrastructures that will enable it to implement intensive resource preparation, and if this is designated as a national project, then construction of a support system that reflects the importance of the project will be essential.

○ *1-2. Is the self-analysis of strengths and weakness adequate?*

- From the following perspectives, it can be evaluated as adequately analyzed:
  - (1) It will be a major task to gather the following four types of cells: 1. ES/normal iPS cells, 2. Genome editing cells that insert disease-specific genes into them, 3. Disease-specific iPS cells, and 4. repaired iPS cells with mutated genes. Since these cells are the most basic, further hard work is expected.
- The Committee offers the following suggestions for further improvement:
  - (1) Concentration on iPS cells is in the foreground, but it would be desirable to consider promoting usage by providing a more user-friendly environment, particularly by providing technological advice.
- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) It is thought that the abundance of the BRC's resources is a strength, but it may be necessary to perform further analysis of the decrease in the number of cells provided in FY2015 and to prepare a more user-friendly environment. Moreover, the number of varieties of diseases-specific iPS cells has increased, but the number of provisions has not. This fact should be analyzed and it is required to prioritize preparation of the resources that are most needed.

(2) There is insufficient persuasive data as to why certain characteristics are defined as strengths or weaknesses. Once comparisons with similar institutions (the world's major cell banks) and the degree to which sample- incidental information is desirable, or whether it is extremely useful, are presented, only then it is possible to discuss current shortcomings and so on.

◎ *1-3. Is the plan reasonable for the medium to long term?*

- From the following perspectives, it can be evaluated as sufficiently presented:
  - (1) The Committee highly approves the orientation toward having human disease-specific iPS cells and derivative cells (derivative human ES cells, disease-specific iPS cells created through genome editing, etc.), and differentiation-marker expressed iPS cells as the main focus of activities. The Committee requests that the BRC commit people and resources to these areas.
  - The Committee points out and makes suggestions for further improvement as follows:
    - (1) ES and iPS cells are mentioned as examples of source of derivative cells, but these cells are also highly useful as function-retaining cells, such as those from primary cultures. And since it is quite possible that ES/iPS derivative cells will be used in future research, preparation of them should be considered.
    - (2) The current human resources system was mentioned, but if the mid- and long-term plans include the administrative system, in addition to collected cell materials and research, it will be necessary to consider taking a broader view, including a vision for satellite organizations and a vision for collaboration with outside organizations.
    - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
      - (1) It is reasonable to expect that human disease-specific iPS cells and derivative cells will increase sharply. However, at the same time, animal cells, including all kinds of mouse cells, will tend to decrease.

◎ *2a. Have appropriate fields been earmarked for future prioritization?*

- From the following perspectives, it can be evaluated as generally sufficient:
  - (1) These policies are reasonable because better cell incidental information greatly enhances the usability and reliability of cells for the user and also there are strong societal demands for a focus on the development of cells for drug discovery.

- (2) The Committee agrees with the idea of establishing two new teams, the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team.
- The Committee points out and makes suggestions for further improvement as follows:
- (1) The direction of emphasis, such as the increasing sophistication of incidental information about disease-specific iPS cells and the provision of differentiated cells, is correct, but user-friendliness and adaptability to cryopreservation differ greatly depending on the degree of differentiation. Since greater advances in technology development are still required in this respect, it will be important to conduct joint research and collaborate with specialized institutions. The question of how to use limited human, financial, and time resources to bring this about will be an issue.
- (2) The gene expression profiling of cancer cells can easily change, depending on factors such as the culture conditions, so it will be necessary to conduct strict analyses based on standard protocols. It would be better to profile cancer-related genes, rather than gene expressions, and use them as resource-incidental information.
- (3) When developing drug-discovery cells, incorporating researchers from companies and working together with them should be considered, instead of just offering the cells to companies (incentives such as giving priority user rights may be conceivably offered to companies that provide funds and human resources). This will make it possible for the BRC to be strongly competitive at a time when there are constraints on human resources and funding.
- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
- (1) The time frame is unclear. In order to make use of Japan's strengths, particularly in iPS cells, and to contribute to applied research in drug discovery, etc., it is essential to deal with this immediately. Riken has a major role to play.
- ◎ 3-2. *Are the policies for future resource infrastructure and technology development appropriate?*
- From the following perspectives, it can be evaluated as appropriate:

- (1) In connection with cell depositions up until now, the BRC has created a resource infrastructure that is more than sufficient, but it is also vital to make use of experiences with the cell resources to develop new cell resources. It will be necessary to put into place a strategy of proactively manufacturing resources that are often needed but have not been supplied, and plans are getting started on this kind of research and development, so the Committee definitely hopes that they will advance.
- The Committee points out and makes suggestions for further improvement as follows:
- (1) Since “it is difficult to conduct detailed differentiation capacity analysis for all cells,” the Committee suggests that consideration be given to the possibility of a “crowd sourcing” function. In other words, researchers come to the bank for a certain period (under the guidance of the bank) and analyze the differentiation capacity using standard methods, or offer cells, the details of whose differentiation capacity are unknown, and have the user share differentiation capacity analysis results with the bank.
  - (2) The Committee considers the concept of a Drug-discovery Cellular Basis Development Team to be important, so the Committee requests that this intention be conveyed to Director Yamanaka of the CiRA at Kyoto University as soon as possible, so that the direction of research can be worked out as soon as possible.
  - (3) Having no medical information or information about differentiation capacity included is rather senseless. Even if the total number decreases, the Committee requests that the BRC proceed according to the proposal.

### *3-3. Innovation hub*

- *(iii) Continuous operation and attracting new users*
    - It can be evaluated as generally sufficient, but the Committee points out and makes suggestions as follows for further improvement:
- (1) The Committee requests that the BRC look at case studies, including those from institutions overseas, to see whether there are any new approaches that are completely different from conventional methods.
  - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:

- (1) There will be an urgent need, not only for guidance on ES cells, but also for creating an environment that promotes the use of iPS cells. The Committee suggests that it would be a good idea to put a system in place that can offer guidance on culturing iPS cells at research base universities all over Japan.

**Committee for Genetic Resource  
Evaluation and Suggestions**

**Gene Engineering Division**

**Division Head: Yuichi Obata/ Presentation by Takehide Murata**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society.)*
  - From the following perspectives, it can be evaluated as meeting or exceeding expectations:
    - (1) The Division has actively collected resources which serves an important role supporting research in the biosciences and has managed and provided those resources in an appropriate manner while seeking improvement in quality control.
    - (2) The number of resources that have been collected and provided have met target numbers, with a significant proportion (20%) provided to overseas users.
  - The Committee points out and makes suggestions to produce sufficiently enhanced performance in the future:
    - (1) To become a “science and technology hub” and to further develop its capacity, the BRC must respond to the needs of a greater number of researchers on a worldwide basis. It must make improvements in a step-by-step manner without being bound to methods used in the past.
    - (2) For the purpose of advertising, it may be difficult for the BRC to participate in forums on its own. However, the BRC may participate in related international academic conferences and bio fairs as a member of NBRP. For this we must seek the support of MEXT and JAICA. Also, we suggest that RIKEN (through speeches by the President and the BRC Director) explains at forums, such as academic conferences, the benefits of a national project for depositing and using resources, while seeking sufficient funding for this purpose.
    - (3) To make sure an incident does not recur involving infringement of laws controlling export of certain microorganisms, measures need to be put in place. In addition to internet searches for the latest revisions of the relevant laws, routine contact with government ministries and agencies need to be enhanced so that the information is received beforehand.

- (4) To maintain high-quality resources which supports technology that is becoming increasingly diverse, the Division needs to promote research in genomic analysis and to develop the resources and the latest storage technology. Also, we expect that the importance of resources receive greater attention by increasing our collaboration with other institutes, users and the community.
- (5) The BRC's global ranking is likely to improve when sequencing and genomic analysis services are provided together with the resources by the Gene Engineering Division, including collaborative projects with other institutes.
- (6) Further reductions are expected in management, maintenance and supply costs.

◎ *1-1b. Responses to previous comments and advice*

- In the following respects, we have rated our response highly.
- (1) Use of English has increased; further effort is expected.
  - (2) Active research leading to collection of resources that involves clones related to CRISPR/Cas9 for genome editing, and vectors emitting visible fluorescent proteins, are commendable. Specific plans are needed for expanding the applications for use of resources.
- For further improvements, the committee recommends the following.
- (1) For further expansion into the international resource market, the following suggestions are made.
    - i. Until now resource operations have been regarded as a “RIKEN project”. Transformation to a “national project” or a “project supported by national policies” will serve to reposition the operation as an activity benefiting the research community as a whole. For this, we need to consider changing the name of the BRC (candidates include “Bio-resources Community Center” and “Community Center for Bioresearch Materials”), with the possibility of starting a new organization independent of RIKEN, or changing the organizational structure so that RIKEN is no longer appears in the forefront.
    - ii. At the least, provide leadership so that all biomaterials used for research in Japan are focused into one organization. For this purpose:
      - A) Convene a gathering of editors of relevant domestic journals attended by the center director and president (as well as MEXT officials). The purpose of the gathering will be to make sure that manuscripts of submitted papers contain correct citations on all deposited biomaterials used in the research.
      - B) In a manner similar to a) above, request that institutes and academic societies

appoint officers in charge of deposited biomaterials. Take further measures, such as offering incentives to the officers.

- C) Have researchers give citations in their papers stating that the biomaterials will be provided by XX (new organization's name). Also whether or not deposited biomaterials will be used is to be added as a category in applications for Grants-in-Aid for Scientific Research (Kakenhi) proposals.
- (2) Strategic measures currently in place should be continued by all means. On the other hand, decisions need to be made regarding obsolete resources.
  - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
    - (1) With respect to overseas resource organizations, specifically Addgene, there is a need to demonstrate our superiority, or at least coexist on equal terms (the former is more desirable). This should be considered the top priority of the BRC in the future.
    - (2) With respect to expansion into new fields, a high priority is given to the development of a reliable differentiation marker.
  - 1-2. *Is the self-analysis of strengths and weakness adequate?*
    - From the following perspectives, it can be evaluated as adequately analyzed. The Committee points out and makes suggestions for further improvement as follows:
      - (1) An action plan is necessary, taking into account the strengths and weaknesses.
      - (2) By holding technical lectures on a more regular basis, information on the effective use of resources may be more widely publicized. Follow-up surveys are necessary to find out if lecture attendees used the services afterwards. In addition to targeting researchers presenting their papers, writers of experimental protocols and procedures should be contacted so that they can be introduced to the BRC.
    - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
      - (1) Concerning a problem that has been given as a “weakness”, i.e. that the Division is not well known by the domestic research community, it is necessary to extend our analysis to problems in our organizational structure. That is, RIKEN is one of many scientific institutes in Japan, and the BRC provides a service by storing and providing material for RIKEN. However, Japan's (and the world's) research community does not consider the BRC a service that is available to them for storing and providing the material. This does not follow the government's recent initiative

to strengthen Japan's science and technology and we need to publicize the fact that our services are broadly available for use by the scientific community. For this publicity, in addition to action by RIKEN and the BRC, we need the funding organizations, including MEXT, to cooperate by providing guidance for the research community.

◎ *1-3. Is the plan reasonable for the medium to long term?*

- From the following perspectives, it can be evaluated as generally reasonable:
  - (1) The plan focuses on quality and ease-of-use. With regard to provisions on the direction to take, flexibility is the key.
  - (2) With respect to adjustment and collection of cancer cell genome stock DNA, it is necessary to clarify who is doing what research, and for what purpose.
  - (3) We recognize that there is a need to engage in R&D with an appropriate partner in a strategic manner. Also, to ensure the quality of clones, there is a need to post on our website precautions for handling and anticipated problems in words that are easily understood by beginners.
- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) The BRC needs to decide on its area of focus, and avoid dispersing its activity. Are we a research institute? Or are we primarily a science and technology hub?
  - (2) In order to surpass Addgene functionally as well as operationally, we must operate very successfully as a hub. For this, we need to rebuild our organization, manage our priorities, and set a division of duties with partnering organizations in a clear manner. Funding and human resources must be secured.

◎ *2a. Have appropriate fields been earmarked for future prioritization?*

- The direction chosen is appropriate, in general. The committee gives the following suggestions for further improvement.
  - (1) When handling material derived from humans, ethical issues and ensuring source confidentiality are the biggest concern. We need to differentiate our services from those of biobanks, while also collaborating with them.
  - (2) With respect to genomic resources (especially metagenomics research) it is difficult to know what researchers really require. (We need to know, in specific terms, how the Division conducts market research.) Also, the purity and fragmentation of their genomic DNA varies. Therefore disclosure of data on the variation found in the

methods and conditions of extraction for their DNA sources would be considered sufficient.

- The following area was found inadequate and this suggestion is made.
- (1) Technologies employed for genome editing will advance quickly. Therefore methods that take this into consideration (especially for gene knock-in techniques) are desirable.
- *3-2. Are the policies for future resource infrastructure and technology development appropriate?*
  - From the following perspectives, it can be evaluated as generally appropriate:
    - (1) There is a need to clarify selection criteria for collecting of resources.

### *3-3. Innovation hub*

- *(i) Collaborations with industry, government, and academia*
    - It can be evaluated as generally sufficient, but the Committee points out and makes suggestions as follows for further improvement:
- (1) As resource facility development and storage - and supply services - are becoming increasingly important, collaborations within the BRC need to be enhanced, especially among those involved in infrastructure-related work.
- *(iii) Continuous operation and attracting new users*
    - From the following perspectives, it can be evaluated as sufficient:
- (1) Looking at the characteristics of the users (such as purpose of use and possible ripple effects), and actively promoting exchange with the community and within RIKEN, will allow better prioritization of resources provided (leading to smooth operations) and an expansion of the user base. The Gene Engineering Division is requested to consider methods of optimal utilization for the resources currently in use. Furthermore, collaborations between locations and disciplines, and support services after provision of genome resources (such as sequencing and analysis), need to be promoted, which will lead to expanded use of resources and assessment of research patterns and problem areas. (Joint research is also possible, but fees must be charged to beneficiaries.)
- The following area was found inadequate and this suggestion is made.
- (1) For our facilities to develop into a “science and technology hub” it is likely that we

will need to radically change our current method of operation and devote our energy to refining our function as a hub. We think that the BRC needs to concentrate on a new initiative to develop resource platforms based on the research results of other institutes, which may involve joint projects with other institutes. Without such efforts it is unlikely that the BRC will be able to transform into a science and technology hub.

**Committee for Microbe Resource  
Evaluation and Suggestions**

**Microbe Division (Japan Collection of Microorganisms-JCM)**

**Division Head: Moriya Ohkuma**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *I-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)*
  - From the following perspectives, it can be evaluated as meeting expectations:
    - (1) Performance above the target values in both collection and distribution, and yielding world top-class results in the number of research papers published by users, quality management, and preparation of genome information.
    - (2) An increase in the number of depositions, appropriate response to the increase in depositions, and JCM's ranking as second best in the world demonstrate the deep level of trust it has earned from the microbial research community both in Japan and overseas.
    - (3) An increase in the number of research papers by users indicates project results themselves have been passed on to society.
    - (4) JCM made obvious contributions to microbial research in Asia, and that clearly states its strategies as a research infrastructure. It is hoped that contributions will be extended to the nations of Africa and South America.
  - The Committee points out and makes suggestions to produce sufficiently enhanced performance in the future:
    - (1) A system for gene sequence check of all available strains should be continuously maintained. It is hoped that new quality check methods will be developed and further extensive efforts will be made with respect to quality management.
    - (2) Genomes for yeasts and fungi have been sequenced. It is hoped that methods of publishing genome information will be derived for increasing use and that explanations will be provided next year saying that favorable results have been obtained.
    - (3) Judging from the current systems, inconclusive results may occur unless priorities are made clear at every given moment. With limited human resources, it is

necessary to decide whether to get rid of something, and if not, to aim for greater efficiency.

- (4) To the greatest extent possible, new resource developments should not be directed just at new taxonomic knowledge, but also at microbes related to the environment and health.

◎ *1-1b. Responses to previous comments and advice*

- It can be evaluated as adequately addressed, but for some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:

  - (1) The BRC has carried on enthusiastically in the face of various constraints. It is commendable that previous remarks have been dealt with seriously and appropriately, including pre-distribution testing of strains that have not undergone gene sequence check and speedy distribution in response to needs.
  - (2) Concerning the introduction of MALDI-TOFMS and the genome sequencing, continuous efforts should be made to obtain a budget for these. MALDI-TOFMS has even been introduced into laboratories in developing countries and is producing positive results. This fact can be added to the budget request as a reference. The possibility of constructing a system in which this kind of mass spectrometry is used in conjunction with another institution should be considered.
  - (3) The collection strategy is insufficiently proactive. The supplementary budget for FY2015 includes nothing but requests for purchasing replacements for old equipment, and the Committee hopes that a proactive strategy is implemented in the future.

○ *1-2. Is the self-analysis of strengths and weakness adequate?*

- It can be evaluated as adequately analyzed. The Committee offers the following suggestions for further improvement:

  - (1) The analysis of strengths is sufficient. The items that are mentioned as weaknesses are difficult to deal with, but since the analysis shows that JCM has many employees who are close to retirement, the Committee requests that the BRC make plans for technological continuity so that transitions go smoothly.
  - (2) It is necessary to analyze any weaknesses, because the focus is changing from taxonomy, the previous field of expertise, to microbes in the areas of the environment and health, and because this is happening during a period of constraints.

◎ 1-3. *Is the plan reasonable for the medium to long term?*

- From the following perspectives, it can be evaluated as generally reasonable, but the Committee offers the following suggestions for further improvement:
- (1) Specific fields to emphasize have been determined and specific policies when executing the plans have been fully considered, and it is expected that the plans will be adequately realized.
  - (2) It is hoped that specific methods will be presented for the stated orientation of “Resources for Accelerated Research Aimed Solving Issues Related to Society’s Urgent Needs” and that systems to achieve it will be created.
  - (3) It is hoped that there will be specific strategies to develop technologies for fastidious microbial resources.
  - (4) The Nagoya Protocol should be dealt with appropriately by solidly grasping the status of the domestic measures related to it, exchanging opinions with WFCC and other overseas institutions, and learning about trends there. Rights of ownership for genome information of resources could become controversial in developing countries, and it is assumed that this will affect academic use.

◎ 2a. *Have appropriate fields been earmarked for future prioritization?*

- It can be evaluated as generally adequate, but for some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
- (1) Current research on microbes has reached a turning point. This is a shift from pure cultures to symbiotic systems, as expressed in the spread of the word “biome.” Mentioning symbiotic microbes as an area of emphasis is extremely appropriate. Given systems for implementation of these plans and the specificity of the research themes, it is anticipated that positive results will be obtained.
  - (2) Regarding the coming “Plant Symbiosis Research Team (tentative name),” the plan to have every step coordinated with JCM operations should be reconsidered, and the plan should include questions such as “How are the proposals based on society’s needs?” “Why will it be concerned only with symbiosis with plants?” “What resources will be developed and, specifically, in anticipation of what kinds of users?” “What results can be expected?” The proposal should be attractive enough that anyone would agree to it.
  - (3) There will be a high level of demand for additional information and research results concerning complex microbial systems and consortium microbes. It is not a bad idea to offer genome information about complex and symbiotic microbes as new

resources, and it is possible to develop this with a strong point of JCM, but the process to present them as a new JCM resource is unclear.

- ◎ *3-2. Are the policies for future resource infrastructure and technology development appropriate?*
- From the following perspectives, it can be evaluated as generally adequate, but for some portions that are deemed to have room for improvement, the Committee points out and makes suggestions as follows:
  - (1) Based on highly persuasive previous results, human indigenous microbes are an appropriate resource to prepare. Preparation of genome and omics information is also something that is growing along with developments in microbiology, and it is judged that there is great potential for making a contribution in this regard. Creating resources from fastidious microbes is a cutting-edge issue, and there are actual research results in this area, so JCM should be able to become a world leader. It is anticipated that synergistic results will be gained in the various subjects that are linked to this field.
  - (2) The orientation is appropriate, and several results have been achieved, but it would be a good idea to indicate a bit more clearly which aspects will be emphasized.
  - (3) It would be ideal to present specific plans for resource infrastructure and technology development plans with respect to the preparation of microbes that can accelerate problem-solving type research in the environmental fields.

### *3-3. Innovation hub*

- It can be evaluated as generally sufficient, but for portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) Concerning the fact that many type strains are distributed, it is hoped that this will be mentioned more clearly in the “Search for users” and responses or plans based on that will be worked out.
  - (2) Increased exposure for databases should be a goal, so that the JCM number can be reached using keywords, and it is recommended that when being requested to distribute the strain, clients should be asked their reasons for choosing that particular strain.
  - (3) It is anticipated that collection of resources will continue to increase given appropriate efforts. On the other hand, once a resource has been distributed, it can be stored continuously, so the same resource is not used repeatedly. In order to

increase the number of new users and expand projects, it is necessary to strive to cultivate new users through open invitations to unexplored foreign countries.

● *(i) Collaborations with industry, government, and academia*

- It can be evaluated as generally sufficient, but for portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) It would be ideal to indicate strategies for the involvement of resource infrastructure in ties with the industrial sector.
  - (2) It would be desirable to go one step farther in plans for collaboration with the industrial sector so that the collaboration involves not only the use of resources but also the ability to acquire any leftover resources. It is necessary to consult carefully with partners and propose plans that take the future into consideration.

● *3-5. Training of global human resources*

- It can be evaluated as generally sufficient, but for portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) Training of curators from major Asian countries at JCM is a valuable activity. It makes a major contribution to building up networks. Even though staff members are pressed for time, they are judged to have dealt with this well. In particular, training in the management of the BRC and training in taxonomy for quality control are important steps in the establishment of the BRC in developing countries.
  - (2) Opportunities within the framework of international collaboration among Asian countries can be proactively used. At the moment, a heavy burden is being placed on employees, but taking in trainees is effective in fostering global human resources. The ripple effect of this training is huge, and viewed in the long term, it will be even more valuable in the future.

● *4. Collaborations among the RIKEN Centers*

- It can be evaluated as generally sufficient, but for portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) These collaborations seem to be based on actual performance, but it is better to establish issues with greater freedom by involving outside RIKEN, instead of collaborating with familiar parties.

**Review Committee  
Evaluation and Suggestions**

**Bioresource Engineering Division****Division Head: Atsuo Ogura**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society.)*
  - It can be evaluated as generally overwhelming expectations:
  - (1) The Division receives high marks for many significant successes, including developing a new superovulation method, improvement of the methods for generating cloned mice, and establishing high-quality TS (trophectoderm Stem) cell lines. All of them contributed to foundation for bio-resource projects, such as efficient maintenance of existing resources and establishment of new resources. In addition, this Division has made marked achievements in the field of basic biology including epigenetic regulation of mouse development.
- ◎ *1-1b. Responses to previous comments and advice*
  - From the following perspectives, it can be evaluated as adequately addressed:
  - (1) It is admirable that the Division is selectively culling research topics in order to maximize research results.
- *1-2. Is the self-analysis of strengths and weakness adequate?*
  - From the following perspectives, it can be evaluated as adequately analyzed:
  - (1) According to Division's self-evaluation, one of the weaknesses is that the Division is working on a variety set of issues, but the Division is currently achieving good results in almost all areas, so it looks as if this is a strong point rather than a weakness.
  - (2) It is important to narrow down topics in accordance with division's number of personnel.
- The Committee offers the following suggestions for further improvement:
- (1) It is stated that the introduction of next-generation sequencing technology is an issue, but this is not an issue that one division can deal with alone. The Center as a

whole ought to look at guidelines for this project, including collaboration with other Centers within RIKEN.

● *1-3. Is the plan reasonable for the medium to long term?*

- From the following perspectives, it can be evaluated as reasonable:
  - (1) Analysis of TS cells and attempts to create higher-quality TS cell lines are progressing. Good results in this area are highly likely to lead to breakthroughs in developmental biology.
  - (2) Classification of issues into those that are essential for the resource infrastructure project and those that are challenging, that is, difficult to achieve but likely to have an impact, is effective. Live-imaging technology for eggs and embryos, such as FRET, search for genome plasticity factors in the 129 strains, establishment of primordial germ cell lines and others are challenging areas of research.
  - (3) Rescuing eggs from aged female mice will have an impact as a practical method, and the Committee anticipates that it will gain visibility in society.

● *2a. Have appropriate fields been earmarked for future prioritization?*

- From the following perspectives, it can be evaluated as appropriate:
  - (1) This Division is an appropriate location for developing new genetic engineering technology in the Center, and its importance will not change in the future.
- The Committee offers the following suggestions for further improvement:
  - (1) The introduction of epigenome analysis for resource quality control is an important effort for ascertaining the factors underlying fluctuations in phenotypes and for fully establishing a high degree of resource homogeneity by preventing the fluctuation. The significance of this research is well recognized. Note, however, that the research methodology is a bit lacking in specificity.

● *3-2. Are the policies for future resource infrastructure and technology development appropriate?*

- From the following perspectives, it can be evaluated as appropriate:
  - (1) All of the technological developments that form the foundation for bio-resource projects are important, and it is expected that they will make a major contribution to the activities of the BioResource Center.

*3-5. Training of global human resources*

● (ii) *External*

- From the following perspectives, it can be evaluated as sufficiently presented.
- (1) This Division receives especially high marks for continually training young human resources and preparing them to move on to other research laboratories outside the BRC.
- (2) The Committee also gives high marks for offering technological trainings that are possible only in this Division.

● 4. *Collaborations among the RIKEN Centers*

- From the following perspectives, it can be evaluated as sufficiently presented:
- (1) Sufficient collaborations among the Centers have been formed. Cross-disciplinary research is taking place in the “Epigenetics Project”.

**Review Committee**  
**Evaluation and Suggestions**

**Technology and Development Team for Mammalian Genome Dynamics**

**Team Leader: Kuniya Abe**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *I-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)*
  - It can be evaluated as generally meeting expectations:
    - (1) The establishing the EpiSC (Epiblast Stem Cell) line by means of Wnt signaling inhibition has had a major impact as a foundation of stem cell resource development. The discovery that the transitions of stem cell naïve states and primed states can be accelerated by Wnt inhibition will contribute to basic stem cell biology. In addition, it is also expected to make a major contribution to resource development in the future.
    - The Committee offers suggestions to produce sufficiently enhanced performance in the future:
      - (1) The plan appears to be progressing toward achievement as anticipated, but the appeal of the achieved portion appears to be modest. This is an issue that also relates to the connection with joint research; if the appeal is more attractive, it would enable even further vitalization of the field/technology through joint research with a variety of researchers. Specifically, it would be a good idea to make collaborative effort, in which the naïve-primed conversion system will be used widely through the support from this team. If successful cases come out, it will be a great appeal.
- ◎ *I-1b. Responses to previous comments and advice*
  - From the following perspectives, it can be evaluated as adequately addressed:
    - (1) Last time it was pointed out that there was insufficient differentiation from research conducted at universities. This time, the team presented technology development with more emphasis on cellular resources, the better method for establishing stem cell resources, for example. This is a field that can be advanced advantageously for RIKEN, including collaboration with other Centers and organizations within

RIKEN. In that sense, it is considered that the team addressed very well the issue identified last time.

- *1-2. Is the self-analysis of strengths and weakness adequate?*
  - From the following perspectives, it can be evaluated as adequately analyzed:
  - (1) Both analysis of cells and improvement of imaging technology are important parts of the BRC's function. It is commendable that these are being pursued as projects of RIKEN as a whole (4D imaging project).
  - The Committee offers the following suggestions for further improvement:
  - (1) It is fully clear that a contribution is being made to the advancement of science, but it would be preferable to provide an explanation of how a contribution is also being made to the BRC mission, one that is more readily understandable to third parties.
- *3-2. Are the policies for future resource infrastructure and technology development appropriate?*
  - From the following perspectives, it can be evaluated as generally appropriate:
  - (1) The aim to provide new gene editing methods in relation to the CRISPR method is a desirable direction to take. However, the competition is correspondingly intense. This is a field where research of the originality and creativity characteristic of RIKEN is most wanted, and it is to be hoped that research will be carried out in an increasingly challenging manner. It is anticipated that research will produce results that lead the rest of the world.
  - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) The development of CRISPRa and CRISPRi is very interesting, but the development of manipulation system for gene expression using a CRISPR system is being undertaken at many laboratories around the world, and it seems unnecessary to direct effort into anything other than resources that are to be used by this team itself.

### *3-3. Innovation hub*

- *(i) Collaboration between industry, academia, and governments*
  - From the following perspectives, it can be evaluated as sufficient:
  - (1) Joint development with corporations is commendable.

● *(iii) Continuous operation and attracting new users*

- From the following perspectives, it can be evaluated as sufficient:
  - (1) EpiSC cells and 4D observation technology are important key technologies, so their use, both directly and indirectly, can be expected to increase in the future.

● *4. Collaborations among the Riken Centers*

- From the following perspectives, it can be evaluated as sufficiently presented:
  - (1) The approach of characterizing bioresources using new image-analysis technology appears to be optimal for projects within RIKEN.
  - (2) Participation in the single cell project and other such activities are producing a record of performance.

**Review Committee  
Evaluation and Suggestions**

**Technology and Development Team for Mouse Phenotype Analysis: Japan Mouse Clinic**

**Team Leader: Shigeharu Wakana**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)*
- It can be evaluated as meeting expectations:
- (1) This Team has constructed Japan's largest systematic mouse phenotyping pipeline, which measures up to international standards. Providing the research community with its foundations is making wide-ranging contributions to the growth and development of the life sciences. In addition, its participation in the IMPC since its early stages has made Japan's presence known in this field. Based on these points, the importance of this project and its contribution to society are obvious. The Committee also gives high marks for conducting training sessions on methods of phenotyping to disseminate these techniques to the research community in Japan and overseas.
- The Committee offers suggestions to produce sufficiently enhanced performance in the future:
- (1) Participation in the IMPC is highly commendable, and is one of Japan's major contributions to the international community. It will be desirable to guarantee stable project expenses and convert your platform to a sustainable form, including updating equipment on a limited budget.
- ◎ *1-1b. Responses to previous comments and advice*
- From the following perspectives, it can be evaluated as adequately addressed:
- (1) The team is making efforts to increase the number of users, and it is hoped that its own income will increase based on user fees.
- The Committee offers the following suggestions for further improvement:
- (1) Despite the importance of the collaboration with the IMPC, it is regrettable that

direct budget for participation in IMPC is not allocated by government. Some sort of scheme or a change in perspective, including consideration of budget problems, might be necessary to continue.

- *1-2. Is the self-analysis of strengths and weakness adequate?*
  - It can be evaluated as adequately analyzed, but the Committee offers the following suggestions for further improvement:
    - (1) The JMC is the foundational for mouse phenotyping in Japan, and the Committee requests that the JMC consider not only maintaining it, but improving it. The revision of the “Labor Contract Act” in April 2014 has made the continuous employment of experienced personnel more difficult, but this is probably something that RIKEN as a whole should deal with.
- *1-3. Is the plan reasonable for the medium to long term?*
  - From the following perspectives, it can be evaluated as reasonable:
    - (1) Age-associated phenotype screening for dementia and autophagy-related diseases, construction of an RDoC-based platform for mouse behavioral analysis, and imaging analysis of mouse fetuses, are international trends in research, and as such, these plans are appropriate.
- *2a. Have appropriate fields been earmarked for future prioritization?*
  - From the following perspectives, it can be evaluated as appropriate:
    - (1) The Committee commends the team for including phenotyping of aging-related traits in the next IMPC.
      - The Committee offers the following suggestions for further improvement:
        - (1) RIKEN BRC will inevitably choose to continue cooperating with the IMPC. However, collaboration on an equal basis will be difficult, due to factors such as the size of their budgets, and it would be desirable to strive to include the formation of uniquely Japanese views.
- *3-2. Are the policies for future resource infrastructure and technology development appropriate?*
  - Generally being appropriate is commendable, but the Committee offers the following suggestions for further improvement:
    - (1) The expansion of the Mouse Clinic into an on-demand mouse clinic will not be

necessary. It will be more important to improve the completeness of the standardized phenotype analysis (more mutant mice should be analyzed). Moreover, the Committee (one reviewer) did not entirely understand the significance of the nature of the next IMPC age-associated diseases phenotype screening, especially screening for autophagy-related diseases.

- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) Given the current decrease in funds for operations at Japanese universities, the current situation does not make it easy for individual researchers to analyze mouse phenotype adequately. RIKEN BRC ought to enhance the size of its institutions and support staff so that it can take a more proactive approach to meeting these needs.
  - (2) Research on the interaction of genetics and environment during the gestation period has become a worldwide trend and is increasingly competitive. Therefore, the team should try to distinguish themselves from other research groups in Japan and overseas in the field of epigenetic analysis of offspring exposed to maternal nutritional or metabolic abnormalities during the gestation period.

### *3-3. Innovation hub*

- (i) *Collaborations with industry, government, and academia*
  - From the following perspectives, it can be evaluated as generally sufficient:
    - (1) A comprehensive pipeline gives the team the latent ability to become a hub. The plans to move from being merely an investigative institution to one that emphasizes data interpretation (analysis) are appropriate. Moreover, stronger ties with the clinical research groups would be an appropriate policy.
- (ii) *Collaborations within the BRC*
  - From the following perspectives, it can be evaluated as generally sufficient:
    - (1) It is hoped that the collaboration with the Technology and Development Unit for Knowledge Base of Mouse Phenotype will be developed and expanded.

**Review Committee**  
**Evaluation and Suggestions**

**Team for Advanced Development and Evaluation of Human Disease Models**

**Team Leader: Tetsuo Noda**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)*
  - It can be evaluated as generally meeting expectations:
    - (1) This team pursued projects on the following three issues. i) Phenotype analysis of mutants and identification of causal genes was completed in eight cases, research papers were published or are in preparation, indicating the large part of operations have been done. ii) A patient-derived xenograft (PDX) evaluation system for human cancer cells was generated in collaboration with the JFCR (The Cancer Institute of Japanese Foundation for Cancer Research) and its use value has been established. iii) A metabolomic analysis system using the NMR method was constructed. In summary, the performance that was initially anticipated is achieved.
    - The Committee offers suggestions to maintain the performance sufficiently in the future:
      - (1) Evaluation systems that used patient-derived xenograft (PDX) are expected to serve as important foundations for future translational research on cancer. Furthermore, it will be of great value if PDX and cell lines established at the JFCR could be provided through the BRC as a part of bioresource project.
      - For some portions that are deemed lower than expected, the Committee points out and makes suggestions as follows:
        - (1) The team is yielding considerable research results, but due to the experimental difficulties in the analyses of various different types of disease models, the whole procedures are not efficient enough. As pointed out last time, they are very useful resources, and it would be desirable to provide them to public as soon as possible to promote joint researches.
- ◎ *1-1b. Responses to previous comments and advice*

- From the following perspectives, it can be evaluated as adequately addressed:
    - (1) Response regarding the items pointed out appears to be steadily underway with the publication of research results and other such measures. There is a possibility, however, that the development of successor personnel is an issue.
  - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
    - (1) The research papers on mutant mouse analysis are of high quality and the way they are steadily being made public is commendable. However, the question is whether these have sufficient necessity as RIKEN BRC research themes. This time, again, the published content includes important concepts and can also be rated positively for its high level in academic terms, but the distinction from results achieved at the JFCR was unclear.
    - (2) As regards the necessity for changing to another team leader and the timing for that change, the explanation stated that this had not been done. The matter of the share of burden for cooperative activities with the Mouse Clinic is also unresolved.
- *1-2. Is the self-analysis of strengths and weakness adequate?*
- From the following perspectives, it can be evaluated as adequately analyzed:
    - (1) The explanation from this viewpoint was not clear, but where the strengths are concerned, it is easy to infer overall.
  - The Committee offers the following suggestions for further improvement:
    - (1) An explanation was given of the connection with the BRC as a part of the broader research as a whole, and it was made clear that there is great potential overall. However, the impression was given that the part of research that constituted collaboration with the BRC was not positioned as central to the research as a whole.
- *1-3. Is the plan reasonable for the medium to long term?*
- From the following perspectives, it can be evaluated as generally reasonable:
    - (1) This team has been a driving force for cancer research in Japan, and its presence serves as a major motivating force that enhances the added value of resources in the BRC. It should continue to be supported even after the comprehensive reassessment in fiscal year 2018.
  - For some portions that are deemed insufficient, the Committee points out and

makes suggestions as follows:

- (1) Evaluation systems using PDX, which were furthered under operation of the support foundation for “the program for strategic cultivation of next-generation cancer research seeds”, are considered useful. However, it was not clear how they would be tied in with bioresource projects as an outlet for results.
- (2) A continuous explanation regarding the necessity for implementing this at the BRC is to be hoped for.

◎ *2a. Have appropriate fields been earmarked for future prioritization?*

- Some portions are adequate, but the Committee points out insufficient portions as follows:

  - (1) An explanation of how they are to be connected to bioresources projects as an outlet for results and whether or not the BRC should be the implementer is what is needed next.

*3-3. Innovation hub*

● *(iii) Continuous operation and attracting new users*

- From the following perspectives, these can be evaluated as being generally sufficient, but for portions that are deemed insufficient, the Committee offers the following suggestions:

  - (1) There is no indication of plans aimed toward expansion of the number of users of related resources.

**Review Committee**  
**Evaluation and Suggestions**

**Mutagenesis and Genomics Team**

**Team Leader: Yoichi Gondo**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)*
  - It can be evaluated as meeting expectations:
  - (1) This team made scholarly significant achievements, which meet expectation. They include development of a mutation detection system using whole-exome sequencing of the ENU-induced mouse mutants; the estimation of spontaneous mutation rates using a next-generation sequencing of the C57BL/6 strain. There is also the initiative attempting to determine platinum genome sequences using PacBio single molecule sequencing of the C57BL/6 reference genome, which will provide a useful foundation for future mouse genome and genetics analyses.
  - (2) The creation of a mutation detection system using whole-exome sequencing analysis and the development and cataloguing of the single base replacement allelic series can be commended as contributions to the qualitative improvement of resources provided by the BRC. As to other scholarly results, their direct contribution to BioResource Center operations is rather tenuous.
  
- ◎ *1-1b. Responses to previous comments and advice*
  - From the following perspectives, it can be evaluated as adequately addressed:
  - (1) A large contribution has been made toward improving the quality of the library of ENU-induced mutant mice.
  
  - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) The last time it was pointed out that nowadays CRISPR/Cas9 genome editing has dramatically raised the efficiency of target gene destruction so that it will be necessary to reconsider what kind of value there is in the ENU-induced mutants. With regard to this point, the team stated that the two are complementary and useful, for example, for analyses of gene-to-gene interactions, but this explanation is not

sufficient.

○ *1-2. Is the self-analysis of strengths and weakness adequate?*

- From the following perspectives, it can be evaluated as adequately analyzed:
- (1) The results from this team have reached a “goal” point, and it appears necessary to examine what kind of new contribution should be made in RIKEN BRC in the future.
  
  - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
- (1) As a shortcoming, there was the self-analysis stating that the development of a model mouse for gene-to-gene interactions has not yielded any actual results. Taking the genomic mutation density in the ENU-induced mutant library into consideration, the likelihood that genes in particular genetic pathways or networks will also simultaneously have mutations is probably not very high. Therefore, development of a multifactorial disease model using the present library has a low theoretical probability.

● *1-3. Is the plan reasonable for the medium to long term?*

- From the following perspectives, these can be evaluated as being generally reasonable:
- (1) The basic mutation rates per generation and the differences between strains have been overlooked so far, even though these are basic genetic information. Work to discover related information about these matters by re-sequencing is an important task that can only be performed by RIKEN BRC, and this has the potential power to give rise to new directions in genetics.
  
  - For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
- (1) It was difficult to tell from the explanation given what output is expected in advance of visualizing the gene variations in experimental animals.

● *2a. Have appropriate fields been earmarked for future prioritization?*

- From the following perspectives, it can be evaluated as generally adequate, but for some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:

- (1) For the reasons cited in section 3, an effort to clarify gene-to-gene interactions by the use of material from the ENU-induced mutant library appears to present methodological problems.

### *3-3. Innovation hub*

#### ● (ii) *Collaborations within the BRC*

- From the following perspectives, it can be evaluated as sufficient:
  - (1) Projects that are only feasible through collaboration with other units within RIKEN BRC, such as the Experimental Animal Division, the Bioresource Engineering Division, and the Technology and Development Team for Mouse Phenotype (Japan Mouse Clinic), are being pursued, which is commendable.
- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
  - (1) Explanations of the record of results from use of frozen sperm of mice with ENU mutations and of the outlook for the future appeared to be insufficient. Perhaps it would be better to step up the promotion activities for the database that has been disclosed.
  - (2) It is possible that discovering users of point mutations in genes that resulted in lethal from knockout mutations will lead to discovering additional users. On the other hand, plans to screen for modification genes and to develop a multifactorial disease model are not clear, and the probabilities of achieving the objectives are not yet apparent.

**Review Committee**  
**Evaluation and Suggestions**

**Technology and Development Unit for Knowledge Base of Mouse Phenotype**  
**Unit Leader: Hiroshi Masuya**

◎: Compulsory report items ○: Major report items ●: Optional report items

- ◎ *1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)*
- From the following perspectives, it can be evaluated as meeting expectations:
- (1) In order to expand the use of bio-resources, phenotypes and other mouse trait information, which is expected to be even more important in the future, this Unit has developed a user-friendly and integrative mouse phenotype database. In addition, the Unit has developed softwares for other resources of the Center (for example, the Disease-Specific iPS Cell Bank) and has developed a web system for resource deposition for the entire BRC. The results have exceeded expectations in improving the information infrastructure in BRC as a whole. Furthermore, the Unit has made a notable international contribution by taking the data from International Mouse Phenotype Consortium (IMPC) and converting it to the Resource Description Framework (RDF) format, which is essential for semantic web technology.
  - (2) In the presentation, three barriers that impeded the information infrastructure project were pointed out, but this indicates that the problems inherent in these fields have been sufficiently analyzed. The Committee would like the unit to continue steadily trying to surmount these three issues.
- The Committee offers suggestions to produce sufficiently enhanced performance in the future:
- (1) There is an impression that international standardization has required many human resources, but it can be said that this is due to society's demands. Therefore, it would be desirable to accelerate the Unit's own unique knowledge-base research. For example, the importance of the text mining is clear, so the Committee definitely wants the unit to flesh out work in that area.
- ◎ *1-1b. Responses to previous comments and advice*

- From the following perspectives, it can be evaluated as adequately addressed:
  - (1) The previous Committee asked how the Unit manages all projects under the condition of insufficient funds and personnel. The fact that the Unit has received funding from the NBDC project of JST indicates that one of the items that we pointed out was dealt with. Also, good international collaborations, like those with the IMPC, the OBO, and the CLO, were performed, so the Committee commends the Unit for dealing with this item.
  
- The Committee offers the following suggestions for further improvement:
  - (1) The group has dealt with issues in a satisfactory manner, but because significant results are expected to be produced, the issues previously pointed out have not been assimilated sufficiently. One factor to be mentioned is insufficient personnel resources, and this Unit is not solely responsible for it, but the problem remains.
  
- *1-2. Is the self-analysis of strengths and weakness adequate?*
  - From the following perspectives, it can be evaluated as having been adequately analyzed:
    - (1) Self-analysis is reasonable. In particular, the lack of technological strength in data analysis is pointed out as a shortcoming, but this is an issue common to the entire field of data science in Japan. This problem, including the training of human resources for statistical analysis, text mining, and other areas, has to be dealt with in the future.
  
  - The Committee offers the following suggestions for further improvement:
    - (1) The problematic areas were sorted out well, but specific plans should have been indicated for preparing an economic foundation (including human resources) in order to overcome problems.
  
- *1-3. Is the plan reasonable for the medium to long term?*
  - From the following perspectives, it can be evaluated as reasonable:
    - (1) These are appropriate medium- to long-term plans for collecting relevant genetic pathway and phenotype data for aging and specific incurable diseases, integrating the information with BRC resources, and using RDF technology to drive an expansion of resource information users.
  
- *2a. Have appropriate fields been earmarked for future prioritization?*

- From the following perspectives, it can be evaluated as appropriate:
- (1) The Unit is commended for taking the initiative in using RDF for the purposes of standardization.

*3-3. Innovation hub*

- *(iii) Continuous operation and attracting new users*
- From the following perspectives, it can be evaluated as generally sufficient:
- (1) Trying to expand the number of resource users by integrating information with RDF technology will be an important issue, and it will be vital not only for operating the technology in a stable manner, but also for expanding the number of new users in the future.

*3-5. Training of global human resources*

- *(ii) External*
- From the following perspectives, it can be evaluated as sufficiently presented.
- (1) High-quality joint researches, such as NBDC and IMPC, are being carried out.

## **Evaluations and Comments on the Proposal of the Four New Projects by BRC Resource Committees and Review Committee**

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## **General evaluation and comments on the proposal of the four new projects**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- The four proposed teams are backed by the precision and highly reliable quality management with respect to BRC activities up to now in experimental animals, experimental plants, cells, microorganisms, and genes, as well as by their phenotype analysis, and they are commendable as a medium- to long-term plan based on fundamental revision with this foundation.
- The proposal calls for the creation of four new teams in bioresource-related research development programs and for steps to be taken to prioritize them and it is appropriate in terms of field and theme. However, as to the question of what individual themes will become the focus, it will be necessary to engage in thorough information exchange with the various research communities involved and on that basis to give close and careful consideration to approaches capable of highlighting Center characteristics.

Committee for Cell Resource

- The plan takes the current four teams and one unit in the BioResource Frontier Programs and reorganizes them into five to six teams, but it will be necessary to explain sufficiently that the objects of each team's development activities are closely linked to the needs of resource operations.
- Partly for historical reasons, this Center's BioResource Frontier Programs have, until now, been composed mainly of teams that use mice as their subjects. The current radical reform includes launching four teams: 1) Symbiosis Research Team, 2) Next-generation Human Disease Model Development Team, 3) Higher-order Cell Characterization Team, and 4) Drug-discovery Cellular Basis Development Team. In particular, Teams 2) to 4) must be strongly promoted.
- Generally, the emphasis is appropriate. Even though the direction of emphasis in the cell resource projects is correct, when reorganizing the program teams, it will be important to look at the other resource projects and make careful decisions about whether the distribution of human, financial and time resources is appropriate

throughout the Center.

- The content of the proposal is basically appropriate, but the time frame is unclear. (Obata: we need to start in 2018, at the beginning of the next five year plan) Instead of dealing with this over a five-year period, it is essential to respond to this as rapidly as possible.
- The collaboration between iPS cells and model animals is extremely important, so this should be strongly promoted. However, the current explanation feels a bit weak.

#### Committee for Genetic Resource

- With regard to Next-generation Human Disease Models and Higher-order Cell Characterization, it will be important to build stable systems for cooperation with medical institutions as well as to further investigate the diseases and related matters that are to be designated as the objects of research.
- With regard to Drug Discovery and Symbiosis, the plan is based on appropriate collaboration and actual results. With regard to human disease models, it will be necessary to take advantages of completion of the mouse genome sequence (reference sequence) in collaboration with industry, academia, and government, as well as to start this plan.

#### Committee for Microbe Resource

- Of the four new teams planned, those other than the Symbiosis Research Team have actual performance results and are judged to be easy for the Japanese people to accept, due to their links to medical treatment. The Next-generation Human Disease Model Development Team, which is developing a model mouse for designated incurable diseases and age-related diseases, and the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team, which both use the iPS cell platform, are appropriate.

#### Review Committee

- The idea of drastically restructuring the present bioresource-related research development program and establishing a Symbiosis Research Team, a Next-generation Human Disease Model Development Team, a Higher-order Cell Characterization Team, and a Drug-discovery Cellular Basis Development Team that are responsive to demands from society, is readily understandable, and this is reasonable as a medium- to long-term plan.

- It would be desirable to reconfigure this project from the perspective of why the project will be in the interest of the Japanese people, who are stakeholders. With regard to fields that are being prioritized, it is considered essential that projects be carried forward by researchers who are at the forefront of the field concerned. However, there is no explanation of policy with regard to personnel recruitment, so evaluation is difficult. Of four themes, two have to do with iPS cells and one has to do with resources involving individual mice, and this appears to be lacking in balance. It does not appear necessary for the BRC to pursue research on resources that are specialized in iPS cells.
- Tie-ups with corporations can be expected in drug-discovery cellular target basis development, but there is some doubt about symbiosis and designated incurable diseases.

## 1. Evaluation and comments on the proposal of the Next-generation Human Disease Model Team

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Animal Resource

- The preparation of mouse resources to serve as models, in particular for designated incurable diseases that impose a major burden on the patient and caregiver, and for lifestyle-related diseases that become an increasing risk with senescence and aging, is the correct course to take and one that is in accordance with society's demands. It is important to proceed with this while also collaborating with outside organizations. With regard to the senescence model, there are still some reasons to examine the choice of genetic background of disease mouse models.
- The Next-generation Human Disease Model Team will be important in developing next-generation resource infrastructure. Contributing to international public relation activities and obtaining the international recognition and positive evaluation of these resources can also be considered important roles. Therefore, a team leader should be chosen who can collaborate closely with the Experimental Animal Division and Engineering Divisions. The leader should be recognized in other countries and should receive the support of researchers in Japan. The leader must be able to select and produce next-generation human disease models. It is to be hoped that the next generation human disease model development team will be created by a leader who possesses these capabilities.
- The creation of a Next-generation Human Disease Model Team is movement in an appropriate direction, and it is an initiative that responds to the growing need in research communities. However, the outlook for the extent to whether model animals of designated incurable diseases will satisfy BRC user demands should be examined in specific detail on the basis of fact. In other words, it is necessary for the BRC to explicitly explain its basic policy related to mouse collection and development. Furthermore, it is not necessarily guaranteed that genetic mutations that induce disease phenotypes in humans will produce similar phenotypes in mice. It is necessary to develop disease models for which there are greater needs. Most rare diseases models may risk having only limited number of users.

- Production of disease models overlaps in many parts with basic research. The question of whether this kind of project should be carried out by a resource center must be given careful consideration. As experienced experts in that field see it, there is a possibility that the models will not be usable. Projects with stronger technology development aspects are better.
- In order to prepare model mice for designated incurable diseases, lifestyle-related diseases, and so on, it will be necessary in future to take steps for collaboration with researchers in clinical fields.
- From what perspective was the theme of "development and expression analysis of next-generation mouse for visualizing autophagy and mitophagy" adopted? Also, was discussion conducted within the BRC as to whether or not this theme was to be of great importance to the BRC in the future? These points require explanation.

#### Review Committee

- With regard to next-generation human disease model development, the plan is to use genome editing and other up-to-date methodologies to create a model mouse for diseases designated incurable by the Ministry of Health, Labor and Welfare, for diseases of aging, and so on. The model mouse with added characterization information obtained by the characterization platform will then be provided under the plan. This is based on the record of collaboration within the BRC up to now, and the plan covers issues with a high degree of novelty.
- On the point of how to pursue research in diseases of aging, however, it will be necessary to do more than simply experiment with long lived animals. More distinctive research needs to be planned, given RIKEN's standing in leading-edge research.
- Next-generation Human Disease Model can be considered reasonable as a project, but it will need to develop pathological models for which there is greater need. Most rare diseases have a limited number of users.
- Regarding the Human Disease Model Development Team plan, there is some doubt about its reasonability. Mutant mice are important in disease model mice, but that importance is thought to vary with the field. In cancer research, for example, models that recreate human disease at the tissue level and genetic mutation level are important, such as in the case of patient-derived xenograft (PDX), as shown by Team Leader Noda. Degenerative diseases were cited as an example of where disease model animals should be developed, but the creation of mice with mutations of well-known association with ALS or Alzheimer's disease should

not be made the central focus of resource-related research. More important than that might be the development of models that recreate the degenerative disease mechanism of mutation at the protein level by injecting samples from the brains of human patients directly into mouse brains. In any event, the participation of researchers who are on the leading edge, as Team Leader Noda is in cancer research, is essential in the various individual disease areas.

- When proceeding with the preparation of model mice for designated incurable diseases, lifestyle-related diseases, and so on, in the future, it will be necessary to seek even more extensive collaboration with researchers and institutions in clinical fields.

#### Committee for Genetic Resource

- In the Next-generation Human Disease Model Development, it will be essential to collaborate on designated incurable diseases and diseases of aging with medical research fields (laboratories, universities, and other such academic institutions), and a strategy for that purpose is necessary. Candidates that have been proposed include not just genes, but also (which is better) the creation of model mice in response to requests from academia.
- The Next-generation Human Disease Model Development is expected to become a beneficial project given the context of mouse resources at the BRC, but it will be necessary to leave the diseases to be addressed unspecified at present, and instead retain the flexibility to aim at topics that arise at any given time.
- As genome editing technology advances, the time will probably come when disease mice for single-gene defects can readily be produced. Readiness to support such activity and the development of suitable technology will be required. It would seem that supplying mice with expressions reduced to the point of a difference, even in the case of single gene defects, or the technical innovation in a method of producing such mice, is important. Since the number of mice required cannot be managed by a single researcher, the value of the BRC is likely to be enhanced.

## **2. and 3. Evaluation and comments on the proposal of the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Cell Resource

- Supplying differentiated cells will be very attractive to users, but it is believed that user friendliness and adaptability to cryopreservation differ greatly depending on the degree of differentiation. Since greater advances in technology development are still needed in this respect, it will be important to conduct joint research and proactively pursue collaboration with specialized institutions.
- It is necessary to provide sufficient explanations of how each team's objects of development are closely linked to research needs. On that point, it was easily possible to understand the relation to operations of the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team.
- The Committee agrees that the four newly developed teams should play an active role in the BRC. The launch and development of the Next-generation Human Disease Model Team, the Higher-order Cell Characterization Team, and the Drug-discovery Cellular Basis Development Team are especially important.
- Since other research institutions and consortia are also considering the development of teams for drug-discovery cellular resources, enhancing collaborative ties and cooperation with them should be considered in order to contribute to the establishment of many drug discovery platforms.

Committee for Experimental Animal Resource

- Regarding the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team, the BRC position appears to have been made clear. That is, in other words, to proceed on the basis of rigorous, close examination of the basic nature of iPS cells (with confirmation of differentiation capacity, total genome sequence, and genome editing as the three key supports). On this point, the BRC appears to assure its own unique identity, which is unlike other institutions. The question of what kind of iPS cells to be selected appears likely to be most important, and it appears that the evaluation will differ by whether (1) the BRC will

conduct a close examination of the basic nature of iPS cells selected by CiRA, or (2) the BRC will have its own unique selection criteria. If (2) is the case, then how to divide up the territory with the CiRA will become important. It will be necessary to clarify this issue.

#### Review Committee

- Regarding the two teams concerned with iPS cells both have plans to further heighten the predominance of these original resources that are founded in unique research originating in Japan. Both teams should be prioritized in the future, and the plans are appropriate and commendable.
- With regard to the Higher-order Cell Characterization Team and the Drug-discovery Cellular Basis Development Team (differentiated cell provision system), it is necessary to clarify the mission definition and the allocation of roles for each.
- With the exception of the Higher-order Cell Characterization, the names of the themes alone will be able to communicate their importance to the public. In that regard, Higher-order Cell Characterization will require full explanation.
- Including iPS is in line with the flow of the times, but it will probably be necessary to set up arrangements to enable demonstrations of the BRC's uniqueness so that the BRC does not end up in the role of a subcontractor to the CiRA. In terms of providing bioresources, this is entirely commendable, but personally, from the perspective of supporting bioresources with pioneering research, the innovative nature of the direction taken would become clearer if it included areas that do not present prospects for immediate results, such as three-dimensional organ formation utilizing animals, rather than just mass culturing.
- iPS is a field in which it is easy to see prospects for industry-academia collaboration. It should be possible to freely configure the allocation of roles and so on with the CiRA. It is easy to understand the necessity for providing bioresources and the contribution, but there was little explanation of the fundamental innovations involved.

#### Committee for Genetic Resource

- With regard to the application of iPS cells to drug discovery, higher-order cell characterization is extremely appealing, but there is some doubt as to how many disease traits can be reproduced at the cellular level for use in drug screening.
- Higher-order Cell Characterization and Drug-Discovery Cellular Basis Development are important, and the intent in them is understood to signify that the

BRCA bears crucial responsibility for a key element in national government projects. This will bring about the implementation of a large-scale joint system with core research institutions in Japan, including the CiRA.

- In Drug-Discovery Cellular Basis Development, cell differentiation technology and differentiated cell quality management technology will be necessary. Establishing these technologies will require the allocation of considerable resources as well as experience. It will be necessary to clarify the BRCA's roles in this large-scale joint project as well as its budget.
- In fields where new initiatives will be undertaken in the future, coordination with the RIKEN Center for Developmental Biology will be a key. Implementation in the new priority fields of Higher-Order Cell Characterization and Drug-Discovery Cellular Basis Development will require further full examination of the substance of cooperative systems, taking the new functionality of this center. In this case, it will be necessary not only to clarify the positioning of the BRCA in terms of bioresource projects, but also to significantly expand the personnel and funding required for initiatives in the new fields.

#### **4. Evaluation and comments on the proposal of the Symbiosis Research Platform Team**

**Conclusion: It can be evaluated as appropriate and reasonable.**

**The Resource Committees and the Review Committee offered the following comments and suggestions for further improvement:**

Committee for Experimental Plant Resource

- It is anticipated that the symbiosis research platform will undergo major growth in the future.
- Apparently a symbiosis research platform is to be set up, but there are already numerous institutions and researchers around the world that are moving ahead with large-scale analyses related to symbiosis. It will be important to consider how to highlight the uniqueness of efforts of BRC. RIKEN is fully equipped with analysis platforms of every type in its laboratories, and it is to be hoped that collaborative efforts will be pursued. It can also be anticipated that different materials from different sources and using different soil will produce different results, so it will also be necessary to give careful thought to sample materials.
- In terms of symbiotic systems, *Arabidopsis thaliana* does not have a symbiotic relationship with mycorrhizal fungus, so there is a question as to whether it is appropriate for symbiosis research. Symbiosis research is most advanced in *Lotus japonicus* and other leguminous plants, and perhaps these could be newly introduced for this purpose.
- Research teams for the purpose of promoting collaborative research are being considered, and it would be a good idea if this could be realized in a way that helps to acquire a budget for it. A symbiosis research team with plant-microorganism collaboration would fit with trends in research.

Committee for Microbe Resource

- The plan to reassess the research and development teams that have achieved their objectives and to launch new research and development teams concerned with microbes and plants is reasonable.
- Sophisticated research using model life forms can be performed for microbe and plant symbiosis, but the results are self-contained, and it is unknown when and what kind of users are assumed during this resource development. If this is

considered to be research aimed at supplying resources, that idea should be reconsidered.

- Concerning the Symbiosis Research Platform, the Committee can understand the judgment of the Center Director that, in the mid- and long-term view, new research and development teams related to microbes and plants should be launched. Among the fields that should be emphasized, the Microbe Division and Plant Symbiosis Platform has positive prospects, but it would be desirable to declare more specifically what results can be expected. In particular, it is necessary to explain the role of the Microbe Division and the significance of using fastidious microbes.
- The Committee can understand wanting to take advantage of the respective strengths (internal factors) of the Experimental Plant Division and the Microbe Division, but quite a few resources are needed. Some doubt remains whether “More Efficient Use of Fertilizer and Establishing Agricultural Methods without Excessive Use of Chemicals,” which has been mentioned as an “exit point” for this research, is an issue that the RIKEN BRC ought to deal with. Further discussions about which issues the RIKEN BRC should deal with should be held.
- The plan coordinating every step with JCM operations should be made, including the consignment to JCM and the publication of the microbes separated in the midst of the Symbiosis Team’s research, etc. The Committee’s suggestion is to formulate the ways in which the recently presented expanded genome information is made use of for promoting the use of JCM resources, and to show it together with the short- and mid-term output.

#### Review Committee

- In the project to prepare a platform for symbiosis research, analysis of the interaction between plant and microorganism genomes can contribute to elucidation of the genomic mechanisms of environmental response, disease and pest response, and so on. These are important research issues with promise for the future.
- Bioresource infrastructure projects within the Center should extend further these themes in ways that increase the already close collaboration between the Experimental Plant Division and the Microbe Division, as well as with the RIKEN Center for Sustainable Resource Science and other such centers and units.
- Symbiosis research is a theme with a large degree of novelty and a wide range of fields, and as with the other themes, it can be expected to be capable of responding to strong worldwide demand. This research is also viewed as having the potential to suggest new concepts for ecology and numerous other research fields.

- With regard to the Symbiosis Research Platform, proposals are being made for plans based on the actual record of collaboration between the BRC and the RIKEN Center for Sustainable Resource Science (CSRS).

#### Committee for Genetic Resource

- The symbiosis research platform is unique and is anticipated to yield unexpectedly significant results.
- With regard to the preparation of a symbiosis research platform, the future understanding of plant symbiosis in agriculture and forestry and its active application will be of importance to Japan, which faces the fundamental issues of limited land and difficulty in providing its own food supply. The significance of plans to realize groundbreaking agricultural technologies is understandable. However, careful investigation is required to determine whether or not research results obtained using model plants and model soil can truly be applied in practice to industrial crops. It is also necessary to keep this model research from falling into complacency. A good approach may be to pursue joint research with expert farmers so as to convert the experience of the expert farmer into theory.
- Select a number of industrial crops that are high in order of priority for usefulness in improving the future food situation in Japan (and the world).

#### Committee for Experimental Animal Resource

- The Symbiosis Research Platform is extremely attractive in the way that it has taken a step forward in analyzing the relationship between the individual plant and the resident bacteria in that plant in terms of the individual plant and the environment, so that analysis should be more specific, more comprehensive, and founded in genome science. It is also indicated that the multiple development divisions at the BRC will engage in cooperative work. Similar things could be said of the experimental model animals. The individual animal and its intestinal flora, skin surface microbiotas exert significant influence on the individual animal's phenotype. In light of the above circumstances, it appears that this team's results and future developments with regard to experimental animals will be also something to look forward to.

## **The List of BioResource Center Resource Committees and Review Committee Members**

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## **Dates of Resource Committees and Review Committee**

### **Resource Committees**

April 4, 2016

Experimental Animal Division  
Experimental Plant Division

April 11, 2016

Gene Engineering Division

April 12, 2016

Cell Engineering Division

April 13, 2016

Microbe Division (Japan Collection of Microorganisms-JCM)

### **Review Committee**

April 8, 2016

Bioresource Engineering Division  
Technology and Development Team for Mammalian Genome Dynamics  
Technology and Development Team for Mouse Phenotype Analysis: Japan Mouse Clinic  
Team for Advanced Development and Evaluation of Human Disease Models  
Mutagenesis and Genomics Team  
Technology and Development Unit for Knowledge Base of Mouse Phenotype