

Evaluation and Suggestions Form

The Director of BRC (Toshihiko SHIROISHI)

Achievements and the 4th Mid- to Long-term Plan of BRC

- (1) Is the action plan for the whole BRC in line with the RIKEN's 4th mid- to long-term plans (7 years from 2018 to 2024)? Does the plan contribute to enhancing the BRC's function as well as the development of social life and life sciences in Japan and overseas?

[Resource Committee and Review Committees of Experimental Animals]

- The action plan for the whole BRC consists of three projects: 1) bioresource infrastructure; 2) key technology development; and 3) bioresource frontier program. These projects clearly position the roles of the Divisions and Teams. Moreover, each Division and Team has defined its objectives that respond to future social and research needs, and thus, the action plan is in accordance with the 4th Mid- to Long-term Objectives and Plans. By proceeding steadily with the plans, the enrichment of the BRC's functions and contribution to development of life sciences will become possible.
- The Director intended to increase the functions of the BRC, for example, by the establishment of the iPSC-based drug discovery and development team, which will lead to the active use of bioresources in researches that aim at contribution to the society.
- The number of young PIs has increased, and they are promising.
- Experimental Animals Division and two mouse resource-related Teams have been deeply involved in the IMPC project. They should more clearly emphasize the fact that the BRC is a core member in the IMPC. It is understandable that they intend to enrich disease model mice for chronic diseases and aging, however, collaboration with practicing medical doctors is necessary for analyzing social needs more precisely.
- As model animals of human disease, why not consider the development and use of genome editing techniques for rats, hamsters, and rabbits?

[Resource Committees of Experimental Plants and Microbial Materials and Review Committee of Plant-microbe Symbiosis]

- In addition to core missions of the center, preservation, and distribution, further research has become possible to pursue. Unlike other institutions, research within the BRC seems to be limited to 1) a primary focus on the development of resources themselves, and 2) R&D that enhances the use of resources. How this kind of research project should pursue is an important future issue.
- Following an appropriate action plan, improvement to the BRC's functions is expected to eventually contribute to the development of life sciences within Japan and overseas.

- It is appropriate to adopt plant-microorganism symbiosis studies as a project which contributes to utilization of resources. However, symbiosis is highly specific to a given species, so it is not clear whether this will truly lead to practical applications. As symbiosis research develops very quickly, it is necessary to keep up with trends.
- It is important to think of new ideas for cryopreservation of stored samples using methods, which allow for continued progress, even with a lower budget and reduced staffing.
- A cross-Division/Team program for plant-microbe symbiosis research is also being implemented. Along with further enriching the functions of the BRC, its content contributes to society as well as the development of the life sciences within Japan and overseas.

[Resource Committee of Cell Engineering Division and Review Committees of iPS Cell Advanced Characterization and Development Team and iPSC-based Drug Discovery and Development Team]

- The plan is generally regarded as appropriate. In particular, establishment of the four research groups for promoting research and development for active use of bioresources is an important undertaking for enhancing the functions of BRC, and they are promising.
- It is highly appraisable that, based on the current research trend, the four new teams have been established to lead the development and incorporation of bioresources with potential necessity in the future and that they are tackling flexible and challenging projects in response to the advances of research that we feel so rapid in recent years. Moreover, it is important to distribute bioresources while maintaining high-level of research for making a contribution to various fields from basic science to innovative investigation, by making these teams collaborate with bioresource infrastructure divisions and conduct cross-sectional research within BRC.
- We expect the center to keep on contributing globally as a world leader in the management and operation of valuable bioresources. Also, it is important, as a leading research organization in Asia, to disseminate to other Asian countries the BRC's world-leading standards of QC technology and its training system for maintaining QC standards. As this can be considered as one of the activities to achieve sustainable development goals (SDGs), which the BRC can specialize in, BRC needs to propose this commitment as contribution to SDGs on behalf of Japan.
- Plans for substantive cooperation between the Kei-han-na site and the Tsukuba site are unclear. Superb researchers have at last become BRC members; accordingly, it is hoped that they will contribute to the center in the future.

[Resource Committee of Genetic Materials]

- The action plan of the whole BRC is in line with the RIKEN's 4th mid- to long-term plan. The plan is enhancing the BRC's function as well as the development of society and life sciences in Japan and overseas.
- The BRC has been raising the efficiency in research activities in Japan and the world by providing research resources, which are difficult for individual universities to manage. BRC has carried out collection, QC, and distribution of world-class research resources, and moreover, BRC is

conducting R&D to promote active use of resources and striving to raise technological levels, in line with the RIKEN 's 4th mid- to long-term plan.

[Resource Committee of Integrated Bioresource Information Division]

- The BRC's overall action plan is considered to be in line with RIKEN's Fourth Mid- to Long-Term Plan and goals. It responds to societal and research needs for example by contributing to genome medical research of rare diseases. It is contributing to the development of society and the life sciences within Japan and overseas.
- International data sharing of human genetic variation, such as GA4GH, is rapidly expanding and has become important in the studies of iPS cells and disease models. Under the leadership of the director, the center should take initiative as a Japan's leading resource center by the collaboration with AMED.

International collaboration

- (1) Is the international exchange being actively addressed, and are they functioning as a hub of international scientific technology?

[Resource Committee and Review Committees of Experimental Animals]

- The (former) Director is leading the activities to promote international collaboration.
- The BRC is promoting international sharing and collaboration among resource centers, and promoting internationalization appropriately.
- Specific initiatives to promote international collaboration include:
 - As the varieties and quantities of bioresources produced by or required for research and development (R&D) have far exceeded the capacity of any single country or center, international sharing and collaboration among resource centers is necessary. In addition, international standards of bioresource quality are required. To achieve this, international network activities are being carried out in the following areas:
 - 1) bioresources: the Asian Network of Research Resource Centers (ANRRC)
 - 2) mouse strains: the International Mouse Strain Resource (IMSR), the International Mouse Phenotyping Consortium (IMPC), and the Asian Mouse Mutagenesis Resource Association (AMMRA)
 - 3) human and animal cells: the International Stem Cell Banking Initiative (ISCBI) and the International Cell Line Authentication Committee (ICLAC)
 - 4) plants: Multinational Arabidopsis Steering Committee (MASC)
 - 5) microorganisms: the World Federation for Culture Collections (WFCC)

- Through the training and development of young scientists and technicians, international collaboration has been conducted. For example, the Summer Mouse Workshop involving the RIKEN BRC, Nanjing University Model Animal Research Center (MARC), and Seoul National University has taken place seven times. Moreover, they are also striving to accept and train 121 students, researchers, and technical staff from overseas. These activities are important in creating a place for the exchange of human resources who will play an active role in both countries in the future.
- The committees recommend international activities, in particular, public relations inside and outside Japan. It is necessary that BRC make a unique appeal on its international collaboration with external organizations and the academic conferences it organizes.
- The BRC's position in the IMPC project must be clearly explained.

[Resource Committees of Experimental Plants and Microbial Materials and Review Committee of Plant-microbe Symbiosis]

- The talent development initiative (focusing on researchers, technical staffs, and students) is praiseworthy. These efforts are being carried out internally as well as externally, and even include training overseas researchers and technical staffs.
- It is laudable that the Director leads each international collaboration, either as chairman or director, and is expanding the promotion of internationalization. It is anticipated that further globalization efforts will take place.

[Resource Committee of Cell Engineering Division and Review Committees of iPS Cell Advanced Characterization and Development Team and iPSC-based Drug Discovery and Development Team]

- It is necessary to further improve the international presence of BRC by creating more specific action plans and clearer strategies for international sharing and collaboration and assuming the leadership.
- International collaboration in the field of information is considered to be particularly important and it is necessary that it should play an important role as a bioresource center that consolidates the resources and the accompanying information.
- Promotion of robust and substantial collaboration with Asian countries that have high rates of both young population and economic growth, such as Indonesia, will yield great benefits in the mid to long-term.
- “Standard forms for basic requirements of biobanks for research purposes” are currently published in ISO/TC276. It is necessary for BRC to make its opinion on the position of RIKEN BRC in relation to this international standard.

<https://www.iso.org/committee/4514241/x/catalogue/p/1/u/0/w/0/d/0>

[Resource Committee of Genetic Materials]

- The whole center is actively promoting internationalization by implementing collaboration, sharing, and human resource development.
- The Center has been actively accepting many foreign researchers and technical staff as trainees,

providing them with education and technical guidance. It is important to enhance the presence of Japan's bioresource research center, disseminate the international criteria of quality controls (QC) and standard protocols as a world leader to raise technological levels of the bioresource centers in other countries and to unify the protocols through such an international exchange. It is hoped that international network of bioresource centers will be established in the future by cooperating with other countries' centers and that such network will contribute to the activation and improving the efficiency of various research fields. Moreover, international exchange in the laboratory is also desirable.

[Resource Committee of Integrated Bioresource Information Division]

- It is being operated properly.
- The center is being operated to promote international sharing and collaboration with resource institutions in the world. Some efforts in this respect include participating in the IMPC, and creating and leading an Asian network through the Asian Network of Research Resource Centers. From these viewpoints, the center is highly appreciated.

Advice for further improvement of the activity of BRC

- (1) What are R&D and technical development that should be commenced immediately (within 2-3 years)?

[Resource Committee and Review Committees of Experimental Animals]

- With the development of genome editing technology, researchers have become able to produce the mouse strains they need with reduced cost, which lowered the hurdle. In order to make the researchers feel that they had better order BRC resources than produce the materials by themselves, the Experimental Animal Division needs to simplify the procedures for ordering, improve the efficiency of collection and distribution for cost reduction. Besides the current Tg testing for general purposes, the Division needs to consider developing and promoting test kits for genotyping background strains as well as accepting commissioned analysis.
- Quality test as well as quality control systems should be established for improving the authenticity in resources using genome editing technology.
- Development of imaging technology for the whole body is essential for future development of life sciences and clinical research, and must be advanced rapidly.
- R&D of mouse strains with high versatility such as mouse strains that can be used for optogenetics should be prioritized.
- Development of consolidated database for the BRC's unique bioresources, including the integrated information on similar mouse strains and linking to bioresources other than mice such as iPS and ES cell lines as well as DNA/cDNA clones.

- Development of genetically engineered (GE) mice, using cutting-edge R&D should be carried out, based on CRISPR/Cas9 genome editing technology. Specifically, the following R&D of GE animals on joint research bases, in response to researchers' needs in fulfilling their own research proposals:
 - 1) A method that directly targets using fertilized eggs
 - 2) A method that targets ES/iPS cells
 - 3) A method for conditional gene modification
 - 4) Methods using various CRISPR/Cas9 systems
 In addition, the center should consider the following:
 - 5) For evaluating characteristics of GE mice, the BRC should conduct R&D of assessment for expression patterns of target genes (or marker molecule expressed under the control of target gene) by expression analysis with tissue-clearing technique (e.g., the clear, unobstructed brain imaging cocktails and computational analysis (CUBIC) method)
 - 6) To train staff with basic R&D techniques
 - 7) The BRC should deal with bioresources with CRISPR/Cas9-related patents and prepare MTA that corresponds to industrial use of such resources.
- Public relations should be strengthened for promoting effective use of resources.
- Technical courses are a major contribution for external researchers, leading to increase of the number of users. It is desirable to host courses in Kansai area to provide easy access for local researchers and technical staff.

[Resource Committees of Experimental Plants and Microbial Materials and Review Committee of Plant-microbe Symbiosis]

- The accumulation of mutant resources is important to the creation of *Brachypodium distachyon*. Moreover, it is also important that usage techniques are simple. It is an urgent task to create users with a great affinity for *Brachypodium distachyon* as a material. Simultaneous use of this material will allow us to bring their disparate proficiencies together.
- Throughout the Experimental Plant Division, the time has come to reconsider both the research potential and limitations of experimental plants. With the rapid development of genome research techniques, an increasing number of researchers are carrying out analysis of target crops from the outset. This contrasts with the conventional method of applying analysis to individual target crops based on model plant research. We would like to see further work with the research community, and appeal to the needs that cannot be fulfilled without model plants.
- Through the framework of international cooperation (e.g., JSPS and SATREPS (JST and JICA)), it would be desirable to attempt creation of international RIKEN BRC sites. Such locations could introduce a management system for the storage, assessment, and distribution of technologies developed in Japan.
- Collection of difficult-to-culture microorganisms associated with animals such as humans and livestock, and those within plants and rhizospheres, ought to be prioritized from the perspectives

of food, health, and environmental sciences. To this end, it is necessary to develop single-cell technology that does not involve culturing. Of course, single-cell technology entails single-cell genome analysis. However, it is also important to develop technology for cellular evaluation (i.e., identification at genus and species levels, function) using single-cell imaging.

[Resource Committee of Cell Engineering Division and Review Committees of iPS Cell Advanced Characterization and Development Team and iPSC-based Drug Discovery and Development Team]

- It is necessary not only to ensure simple expansion of bioresources in quantity but to conduct research and develop technology based on the needs of researchers in the fields of oncology, immunology, and stem cell research, and therefore, efforts to gather such information of the needs should also be made.
- In regard to resource information, it is considered of great significance to combine resources and information together, and manage and maintain this combination as a set. Therefore, the role of a specialized department that can collate highly abundant information efficiently and organically with resources and disseminate them to users is considered to be highly important.
- BRC should begin to construct a platform that integrates bioresources with their omics data such as genome sequences and transcriptomes as well as clinical data. Particularly, It is suggested that BRC should give priority to the fields Japan has great advantage in. What about the transcriptome data obtained with Japan's technical strength, i.e. the CAGE technology by the FANTOM team? BRC could also combine bioresources with HLA information which is not technically unique but will definitely give BRC resources unique characteristics that those of Europe and the USA do not have. It is also important to propose such measures to promote the active use of these data, which should be implemented not only by BRC but as national projects, to the AMED and other related organizations.
- BRC should efficiently promote research and development that enhance the active use of bioresources in collaboration with external parties. To achieve this, it is considered necessary to review the existing projects for outsourcing routine tasks.
- BRC should identify global research trends and reflect them for the operation. The higher the usefulness of cell resources is, the more it will be demanded both domestically and internationally. It is necessary to keep on improving the system to smoothly provide cell materials overseas, e.g. to make the English version of the official homepage user-friendly.
- Research using organoids is advancing in some countries, and the development of technical infrastructure for organoids banking will be required.

[Resource Committee of Genetic Materials]

- The fusion of imaging and omics analysis is ongoing. Along with this, there is a high likelihood that new types of genetic materials will emerge. Therefore, it is necessary for the BRC to be ready when it occurs.
- Stable storage and provision of research resources which genome and meta-information are

accompanying with regularly updating the latest information.

- Research on healthy longevity and age-associated diseases in the aging society.
- Technology for stable and efficient storage of increasing research resources.
- New cell culture methods.
- Visualization technology for biological systems.
- Technology for metagenomic analysis.

[Resource Committee of Integrated Bioresource Information Division]

- Technical development of automatic system to prevent violation of laws when use resource provision system of the Center.
- Measures relating to security and tampering-prevention.
- To examine the followings for information infrastructure development:
 - Establishing a bioresource annotation and curation center.
 - Computer-related cloud usage.
 - Centralized processing system to support individual researchers and universities, such as preparation of MTA and payments for use of bioresources.
- Collaboration with DBCLS and DDBJ/INSDC.

(2) What are novel resources to be developed and prepared and R&D to be required from a long-term perspective toward the next Mid- to Long-term Plan?

[Resource Committee and Review Committees of Experimental Animals]

- Use of AI technology in the analysis of phenotype (image analysis, in particular).
- Establishment of the searching platform enabling easy access to domestic bioresources, where users can search for both plant and animal resources.
- Development of advanced experimental techniques and advanced measurement technology. To be more specific, R&D specializing in the analysis of cellular states (dynamics) for comprehensive understanding of the relationships between cellular dynamics and phenotype such as mouse behavior.
- Continuation of the Bioresource Engineering Division engaged in the development of key technology or the establishment of an alternative laboratory that can make a new achievement.
- Development and maintenance of mouse resources for forward genetics. New recombinant inbred (RI) strains, including Japanese wild mouse strains, are considered useful in clarifying disease causes. Moreover, when new RI strains are established, they can be used as hybrid mouse diversity panel by combining the RI strains with inbred lines of mice that are deposited to the BRC.
- Creation of model mouse with non-coding variants is important. However, as it is anticipated to be difficult, it is necessary to have deep discussions within the BRC and work with a long-term strategy.
- Building human disease database (including X-ray CT, MRI etc.) linked to RIKEN BRC's collections of genetic materials, cell lines, and disease-specific iPS cell lines and to the materials

in Japan and overseas for drug discovery. This database is expected to form main database consolidated across administrative borders among ministries and agencies and serve for active use.

- Enhancement of organizational capacity for the public relation.
- Human resource development of the next generation to support the BRC. It is necessary to evaluate whether young staff can proceed with their current duties and research independently to some extent.

[Resource Committees of Experimental Plants and Microbial Materials and Review Committee of Plant-microbe Symbiosis]

- Considering their specialization in plant materials, emphasis on application aspects is mainly in line with the goals of agricultural and biotechnological sciences. However, this raises the question of how cooperation and compartmentalization should be performed with the Ministry for Agriculture.
- The preservation and development of liverwort (a model plant developed in Japan) and other culture cells should be considered. For this end, it is necessary to secure additional staff.
- The center should examine development and preparation of necessary resources for taxonomy based on genome sequence and the organizational strengthening for it.
- Further improvement of the quality of BRC's bioresources results in the creation of trust and credibility, becoming an advantage in international competition. Therefore, the technical development and research for quality control should be advanced continuously.
- In terms of quantity, the strengthening of symbiotic microorganisms and/or difficult-to-culture microorganisms is expected. Novel technical development and research such as single-cell imaging technologies (including new search and discovery, as well as AI technologies) should also be promoted. The advantage of single-cell imaging technology is that it enables identification of the genus and species of difficult-to-culture microorganisms and making evaluation of their functions and selection possible without cultivation.
- The development of highly-efficient isolation techniques for microbes that are difficult to be cultivated from the field, and the development of technology for the genetic transformation of AMF.

[Resource Committee of Cell Engineering Division and Review Committees of iPS Cell Advanced Characterization and Development Team and iPSC-based Drug Discovery and Development Team]

- In regard to iPS cells, for example, the “personal iPS” era will come in the near future, and it will be necessary to respond to it. The adoption of AI technology for cell evaluation and robot technology for cell preparation will be indispensable.
- BRC should take advantage of the knowledge gained as the biorepository so far and to prepare a backup system for these biobanks, and to play a pivotal role as the national center with abundant storage of medical information.
- Concerning single-cell genome and transcriptome analyses by next generation sequencing (NGS), BRC should develop world’s cutting-edge NGS technology by collaborating closely with other

teams within RIKEN. This will not only produce cutting-edge analytic technology but enable cutting-edge characteristic analysis and QC of bioresources. Moreover, advancement in analytic technology will also directly lead to contribution to clinical medicine. BRC should aim at developing technology of higher level than that of the Sanger institute in the UK.

- BRC should take up unique challenges that are not addressed by other biobanks, such as accumulation and integration of genetic parts and biological devices that contribute to microbiome analysis and synthetic biological approaches.
- In the next mid- to long-term plan, BRC should further promote the collection, preservation, and provision of bioresources, as appropriate in light of social circumstances. Moreover, it is necessary for RIKEN BRC to present guidelines setting forth what constitutes appropriate use. Within Japan specifically, it is necessary to establish a system enabling all researchers to make use of human sample material e.g., pluripotent stem cells, mesenchymal stem cells, and various organ cells promptly and properly.
- BRC should promote the collection of cells/tissue/samples with various reporter systems and conducting user surveys. BRC should also examine research and development of resources for bioassays, corresponding to needs.

[Resource Committee of Integrated Bioresource Information Division]

- Development and maintenance of technologies necessary to link and operate hardware both within the center and externally.
- With the worldwide spread of data-driven science, it is important to further expand the activities of the Integrated Bioresource Information Division.
- Provision of experimental animals and cell materials for genomic medical research study.
- Collaboration with human biological sample and biobanks supported by the AMED.
- Promoting the maintenance of an unbiased approach which contributes to basic biology.

End