



The Report

The Seventh Advisory Council Meeting of the RIKEN BioResource Research Center

July 3 – 5, 2019



*Foundation for Discoveries
and
Access to the Future*



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Dr. Ohkuma, Dr. Murata, Dr. Hayashi, Dr. Ichihashi, Dr. Inoue
(The 2nd row, left to right)**

[Black: AC members / Gray: BRC members]

July 3 – July 5, 2019

**RIKEN BioResource Research Center
and
Okura Frontier Hotel Tsukuba**

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I. The Members List of the RIKEN BioResource Research Center Advisory Council

[International members]

Dr. Martin Hrabě de ANGELIS (Chairperson)

Director, Institute of Experimental Genetics, Helmholtz Zentrum München
German Research Center for Environmental Health (GmbH), Germany

Dr. Kent Lloyd

Professor, School of Veterinary Medicine
University of California, United States of America

Dr. Sean May

Professor, Division of Plant and Crop Sciences, School of Biosciences
University of Nottingham, United Kingdom

Dr. Nadia Rosenthal

Scientific Director, The Jackson Laboratory for Mammalian Genetics
United States of America
(Mail Review)

Dr. Stephen D. M. Brown

Director, Mammalian Genetics Unit, Mouse Genome Centre
Medical Research Council, United Kingdom
(Mail Review)

[Domestic members (Alphabetical order)]

Dr. Masahito Ikawa [Chairperson of Resource Committee of Experimental Animal Division and Review Committee of Experimental Animals (A)]

Professor, Research Institute for Microbial Diseases
Osaka University, Japan

Dr. Tetsuro Mimura [Chairperson of Resource Committee of Experimental Plant Division]

Professor, Department of Biology, Graduate School of Science & Faculty of Science
Kobe University, Japan

Dr. Satoru Miyazaki [Chairperson of Resource Committee of Integrated Bioresource Information Division]

Dean/Professor, Department of Medicinal and Life Sciences
Faculty of Pharmaceutical Sciences
Tokyo University of Science, Japan

Dr. Hiroyuki Ohta [Chairperson of Resource Committee of Microbe Division and Review Committee of Plant-microbe Symbiosis]

Director/Vice President (Education) /Professor, College of Agriculture
Ibaraki University, Japan

Dr. Sumio Sugano [Chairperson of Resource Committee of Gene Engineering Division]

Adjunct Lecturer, Medical Research Institute
Tokyo Medical and Dental University, Japan

Dr. Satoru Takahashi [Chairperson of Review Committee of Experimental Animal (B)]

Professor, Faculty of Medicine
University of Tsukuba, Japan

Dr. Junya Toguchida [Chairperson of Resource Committee of Cell Engineering Division and Review Committee of iPS Cell]

Professor, Institute for Frontier Life and Medical Sciences
Kyoto University, Japan

II. Terms of Reference to the BRAC from the BRC Director

The 7th BRAC is asked to evaluate following item 1 to 4, and to propose ideas and advices for further improvement of the activity of BRC (item 5).

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

- (1) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?
- (2) Have the current achievements reached the standards of other major international bioresource centers?
- (3) Is the action plan for the whole BRC in line with the RIKEN's 4th Mid-to Long-term Plan (7 years from FY2018 to FY2024)?
- (4) Is the plan contribute to enhancing the BRC's function in Life Science including Health, Agricultural and Environmental Sciences, and ultimately to returning the benefits of research to society in Japan and the world?

2. SWOT analysis of BRC by the Director

- (1) Is the result of the SWOT analysis valid?
- (2) Are the countermeasures for the result of the SWOT analysis appropriate?

3. International collaboration

- (1) Is BRC conducting the international collaboration actively, and functioning as an international hub?

4. PI assessment

- (1) Is the PI fulfilling the role in line with the BRC's mission?
- (2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?
 - (i) Output and impact
 - (ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories
 - (iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution
- (3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

5. Advices for further improvement of the activity of BRC

- (1) What are R&D and technical innovation that should be commenced immediately (within 2-3 years)?
- (2) What are novel resources and new research fields to be developed from a long-term perspective toward the next 5th Mid- to Long-term Plan?

III. Recommendations from BRAC to President Hiroshi Matsumoto

TOR 1

[Achievements and contributions to society]

The BRC has made significant and noteworthy achievements within each of three major missions, operation of Bioresource Infrastructure, Key Technologies Development and Bioresource Frontier Program, thereby significantly contributing to society and the research community both domestically and internationally.

[Consistency with 7-year plan]

Maximization of R&D achievements and improvement in the quality of other operations serves as an overarching theme in RIKEN's 4th Mid-to-Long-term Plan. The BRAC is very confident that the action plan of the BRC is fully in line with the 4th Mid- to Long-term Plan of RIKEN.

TOR 2

[Strengths (internal/positive)]

- Five different bioresources in the same campus in tight collaboration with MEXT-AMED NBRP.
- Collections of unique bioresources developed in Japan.
- High Quality Control: QMS with certification of ISO9001:2015 and quality test by DNA Barcoding etc.
- Research adding value to the bioresources with four new groups under the Frontier Program and one under Infrastructure Division.

[Weaknesses (internal/negative)]

- Limited laboratory management experience of the five recently appointed PIs.
- Shortage of highly qualified and recruitable candidates in Japan to succeed retiring core faculty.
- Imbalance in the diversity within the ranks of scientific faculty, particularly the lack of female PI scientists.

[Opportunities (external/positive)]

- Resources that could be deposited from distinguished Japanese researchers have still remained.
- Easy generation of versatile bioresources by the genome editing technology.

- Recent progress of the precision medicine and agricultural science based on genome information.

[Threats (external/negative)]

- Declining trend of the relative scientific power of Japan, associated with decreased number of researchers in the Life Science, and as consequence resulting in decreased number of resource depositions and requests.
- Unforeseeable and rapid change of research trends that impact the focus for bioresources.

TOR 3

[Collaborations/S&T Hub/Internationalization]

BRC is an active participant in Asian (Asian Network of Research Resource Centers: ANRRC, Asian Mouse Mutagenesis Resource Association: AMMRA) and World networks of bioresource centers (Mouse: IMSR, IMPC; Cell: ISCBI, ICLAC; Plant: MASC; Microbes: WFCC). The BRAC encourages the BRC to continue its special focus on Asian bioresource centers through membership in the ANRRC and other resource-specific organizations including the AMMRA.

TOR 4

[PIs' contribution to the center mission]

Fully aligned and consistent with the overarching RIKEN mission, all PIs of the BRC improve quality of the relevant operations, Bioresource Infrastructure, Key Technology Development and Bioresource Frontier Program, and maximizes their R&D achievements.

[PIs' Performance]

【Research output and impact】

The establishment of the four new research teams has enabled BRC to maintain its leadership position in new and challenging scientific areas. In these ways, the BRC's achievements are significant, long-lasting, and positive contributions to society and to the research community within Japan and overseas.

【Bibliometric analysis】

The scientific value and reputation of BRC resources is evidenced by the high number of requests received over the past 15 years. For example, between 2003 and 2018, the BRC distributed over 255,000 items to nearly 7,200 domestic institutions and approximately 5,400 institutions in 71 countries around the world. In addition, the

BRC has contributed to the publication of over 10,460 papers and the awarding of nearly 1,640 patents.

【Extramural activities/Accomplishments other than R&Ds】

BRC is fostering world-class leaders through a variety of training courses for external scientists, students and technicians, and participation to Tsukuba University Ph.D. Program in Life Science Innovation.

【Other notable findings (optional)】

All PIs of the BRC have demonstrated extreme attention to the highest standards of quality control practices to ensure the rigor, reproducibility, recoverability, and reliability of its resource holdings.

[Laboratory management]

All PIs of the BRC are working appropriately on their own Division/Team management and operation.

[Support for early-career researchers]

All PIs of the BRC are excellent mentors for the early-career researchers, and are committed to helping young talent develop under their care.

IV. The Report

Executive Summary of BioResource Research Center Advisory Council

- Fully aligned and consistent with the overarching RIKEN mission, the BRC improves the quality of operations and maximizes R&D achievements.
- The BRAC applauds the success of Dr. Yuichi Obata in directing and building up the BRC over the last 14 years and in the recruitment of a high-profile excellent research scientist Dr. Toshihiko Shiroishi to serve as the next director.
- All BRC Bioresource Infrastructure Divisions (animal, plant, microbe, cells, gene engineering, IT) provide the highest quality bioresources with guaranteed reproducibility and play a significant role in domestic and international research programs and projects.
- The Key Technology Development Program provides support and services that enhance the scientific value of all BRC activities.
- The BioResource Frontier Program conducts R&D and technology development at the highest level possible and substantially adds value and usability to the bioresources.
- The BRAC applauds the recent reorganization of the BRC which optimizes administration and management of resource infrastructure and enables participation and proactive engagement with new avenues of research.
- Reorganization and integration of the Bioresource Information Division has been wisely implemented and opens opportunities for further growth.

TOR 1. Achievements and the 4th Mid-to Long-term Plan of BRC

(1) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

The BioResource Research Center (BRC) is now in the second year of its 4th Mid-to Long-term Plan (2018-2024) to serve the needs of Japanese society and the domestic and international research community. In that context, the likelihood of the BRC's future success is built upon a solid foundation of past accomplishments. To that end, the number and extent of achievements of the BRC over the past several years were assessed within each of its 3 major missions: 1) the Bioresource Infrastructure Program established to collect, preserve, and distribute high quality, reliable, and cutting-edge bioresources, including experimental mice and plants, human and animal cell lines including induced pluripotent stem (iPS) cells, microorganisms, genetic materials, and information associated with the bioresources, to fulfill societal and research needs promptly, 2) the Key Technology Development Program tasked to develop and improve technologies for preservation of frozen embryos, transportation, rederivation of living animals from frozen germplasm, quality and homogeneity of stems cells, and dissemination of technologies, 3) the Bioresource Frontier Program established to conduct research and development studies to promote the use and application of bioresources to solve scientifically important questions in aging and symbiosis, conquer intractable and age-related diseases, facilitate drug discovery, and increase food production.

Overall, the BRC has made significant and noteworthy achievements within each of these 3 major missions, thereby significantly contributing to society and the research community both domestically and internationally. These achievements, including its extensive collection of scientifically valuable resources, strict attention to the highest QC standards, distribution of world-class research resources, and conducting R&D and technological development to promote active use of bioresources, are particularly noteworthy because they are difficult for individual universities to accomplish. By providing valuable scientific bioresources, the BRC has contributed significantly to raising the efficiency of Japanese and global research activities. For example, the 5 Core operations within the Bioresource Infrastructure Program have met and, in many cases, exceeded expectations in regard to expanding, maintaining, and disseminating its resources, earning the highest evaluation from the 3rd Term of the Ministry of

Education, Culture, Sports, Science and Technology (MEXT)-Japan Agency for Medical Research and Development (AMED) National BioResource Project (NBRP). The bioresources have grown steadily in numbers, quality, and scientific value, including large depositions of human, animal, and microbial cDNAs, over 3,000 microbe strains from the University of Tokyo, and cancer cell lines from the Institute of Development, Aging and Cancer at Tohoku University, and very high-profile depositions of mouse strains, cell lines, and microbes from 4 Japanese Nobel laureates. The international reputation of the BRC is evidenced by the fact that approximately 70% of microbes and related material are deposited from 41 countries. Once deposited, the BRC has demonstrated extreme attention to the highest standards of quality control practices to ensure the rigor, reproducibility, recoverability, and reliability of its resource holdings. The scientific value and reputation of BRC resources is evidenced by the high number of requests received over the past 15 years. For example, between 2003 and 2018, the BRC distributed over 255,000 items to nearly 7,200 domestic institutions and approximately 5,400 institutions in 71 countries around the world. In addition, the BRC has contributed to the publication of over 10,460 papers and the awarding of nearly 1,640 patents. The BRC has concluded multiple comprehensive license agreements for contemporary research tools (e.g., CRISPR/Cas9) and fluorescent proteins (e.g., GFP) to enable its academic users' freedom to operate without fear of infringement of third-party IP rights. In addition, the establishment of the four new research teams have enabled BRC to maintain its leadership position in new and challenging scientific areas. In these ways, the BRC's achievements are significant, long-lasting, and positive contributions to society and to the research community within Japan and overseas.

(2) Have the current achievements reached the standards of other major international bioresource centers?

On many levels, the BRC has implemented operations based on best practices that meet or exceed the standards of other major world-class bioresource centers. For example, when benchmarked against other similar biorepositories, the BRC has the largest collections for human and animal-derived cell lines, second for mouse, plant, and genetic resources, and third in number of depositions for microbes. In addition, the BRC's attention to quality control sets it apart as one of the world's finest bioresources. Like other top bioresources around the world, the BRC's emphasis on quality control

practices have significantly reduced the proportion of defects in its resources from 10% to less than 0.01% of its resources. It has also made great strides in protecting its resources from natural disasters by splitting its cell, mouse, microbe, and plant archives between the main laboratory at Tsukuba and a distant backup facility on the Harima campus. Further, the level of excellence is recognized by its membership and participation in several international organizations, including the International Mouse Phenotyping Consortium (IMPC), the International Stem Cell Bank Initiative (ISCBI), the International Cell Line Authentication Committee (ICLAC), and the Multinational Arabidopsis Steering Committee (MASC). In particular, the BRC has been a major leader in the Western Pacific/East Asia region, serving as a founding member of the Asian Network of Research Resource Centers (ANRRC); former BRC director Yuichi Obata served as ANRRC president from 2011-2016. Finally, the BRC fosters world-class technical and scientific leaders, both through in-house training opportunities and hosting courses and workshops for international trainees from around the world. In summary, the current achievements of the BRC has reached and exceeded the standards of other major international bioresource centers.

(3) Is the action plan for the whole BRC in line with the RIKEN's 4th Mid-to Long-term Plan (7 years from 2018 to 2024)?

Maximization of R&D achievements and improvement in the quality of other operations serves as an overarching theme in RIKEN's 4th Mid-to-Long-term Plan. In this light, the BRC fulfills all requirements as Japan's core center in the area of bioresources. The BRC has taken measures to foresee and react to research trends as well as social needs. The three-tier architecture of BRC's operation has been, and will be, essential for contributing to the aims of the 4th Mid- to Long-term Plan: (1) Development and Operation of Bioresource Infrastructure has ensured the world of first-class operation with respect to usability, associated information, and quality by grasping scientific and social needs. The repositories have and will continue to offer the highest quality material and information to the Japanese research community as well as those outside Japan, which are difficult for individual laboratories or even universities to manage. (2) Development of Key Technologies will advance the preservation, transfer, and usage of bioresources. (3) BRC's active research portfolio within the Bioresource Frontier Program promotes and enriches the bioresource with additional knowledge and value. For this reason, BRC has started four new research

teams to lead the development and incorporation of bioresources. This new development is a direct response to the changing landscape in research and societal needs. Along this line the creation and implementation of the new “Integrated Bioresource Information Division” is highly appraisable and will serve all units of the BRC. In addition, it will ensure to fulfill the mission of the 4th Mid- to Long-term Plan of RIKEN. With all these measures the BRC will contribute to the effective and efficient promotion of cutting-edge research and innovation and to solution of societal needs. Taken together the BRAC is very confident that the action plan of the BRC is fully in line with the 4th Mid- to Long-term Plan of RIKEN.

(4) Does the plan contribute to enhancing the BRC's function in Life Science including Health, Agricultural and Environmental Sciences, and ultimately to returning the benefits of research to society in Japan and the world?

The forward strategy of the BRC lies in several complementary areas, each of which has been convincingly demonstrated in the action plan. The primary function of a resource center is the acquisition of materials and associated data, under appropriate conditions, and the onward distribution of those materials enriched by additional metadata. Careful preservation, curation and a quantifiable quality control of those materials is critical to this process. Underpinning this approach requires internal technical development outputs to ensure relevance of the resources. To promote usage there must be an ongoing integration of existing materials and data, proactively adding value to downstream users. Additionally, it is critical to a perception of the Center and its continued longevity to promote outreach at the research level through publication and patents and more diffusely to the general society.

BRC is clearly a world-leading bioresource center with a strong reputation for providing rapid distribution of high-quality low-cost resources at a very high fidelity. The forward plan expands on these elements without sacrificing those core goals. Several clear strategies are presented in the plan towards significant progression in the Center's mission for health, food, and environmental solutions, as well as complementary development of some novel model systems. The BRC bioresources are not limited to excellent basic science and fundamental research opportunities, but also extend to the development of practical application and translational opportunities. The present plan openly contributes to the advancement of BRC through multiple instances

of new technical development, both internally and through collaboration with other institutions that possess similar technology. Given the critical mass of the Center, this provides a high probability for development of novel and unexpected application of technologies. New research teams have recently been established and substantial infrastructure has been generated and modified to convincingly support this effort moving forwards.

User accessibility to resources alongside enriched accession information is absolutely critical to future development. Data must be connected in a user friendly and supportive manner, both internally with existing databases and with external information sources. To this end, a solid plan for future integration has been strongly presented including a benchmarking and the consultation of other leading resource centers abroad on this matter. The plan also shows suitable attention to user feedback, particularly from clinicians and commercial users. Priorities and strategies for proactive transfer of established technologies to domestic research institutions, together with appropriate training, guidance, and transferable experience in standardization are evident and commendable. The BRC also has a convincing and appropriately broad strategy towards acquiring external funds and participating in international projects.

Finally, the plan includes several areas where educational resources for the Japanese society are explicitly described for future development. This kind of outreach is essential to maintain interest and support for the BRC both from the general public and supporting stakeholders.

TOR 2. SWOT Analysis of BRC by the Director

(1) Is the result of the SWOT analysis valid?

The BRAC finds the BRC Director's SWOT analysis to be appropriate, comprehensive, and valid. The BRAC took the initiative to make additional comments, which are available in the Recommendations from BRAC to President Matsumoto.

(2) Are the countermeasures for the result of the SWOT analysis appropriate?

The BRAC finds that the countermeasures recommended by the Director are appropriate and fully address all items within the SWOT analysis. Further, the countermeasures are fully aligned with the additional comments by the BRAC. The additions to the SWOT analysis that the BRAC has offered might suggest measures for consideration.

TOR 3. International Collaboration

(1) Is BRC conducting the international collaboration actively, and functioning as an international hub?

The BRC is and continues to be fully engaged in international collaborations in many areas, including with regards the sharing of bioresources, the recruitment and training of technicians and scientists, membership and leadership of international societies and organizations, contributions to international standards and best practices, and the international sharing and dissemination of protocols and technologies. For example, over the last several years, the international distribution of physical resources from BRC has ranged from 10% to 30% of total distribution for the different resources. As a result, the rate of foreign use is either stable or increasing over time as a proportion of distribution. In each case where the distribution proportion has increased, the domestic distribution has also increased. In particular, the BRC is actively conducting international collaborations with bioresource centers in Asia, Australia, Europe and America. The BRAC encourages the BRC to continue its special focus on Asian bioresource centers through membership in the Asian Network of Research Resource Centers (ANRRC) and other resource-specific organizations including the Asian Mouse Mutagenesis Resource Association (AMMRA).

The BRC's engagement with the International Mouse Phenotyping Consortium (IMPC) is particularly noteworthy, contributing mice and phenotyping data on more than 70 genes to the global effort to functionally annotate the mammalian genome. The BRC is also actively engaged internationally with its other resources too, cells, plants, and microbes, including the International Stem Cell Banking Initiative (ISCBi),

International Cell Line Authentication Committee (ICLAC), the Multinational Arabidopsis Steering Committee (MASC), and the World Federation for Culture Collections (WFCC). Further, the BRC participates internationally in the training and development of young scientists and technicians, such as through the Summer Mouse Workshop involving RIKEN BRC, Nanjing University Model Animal Research Center and Seoul National University. Throughout it all, the BRAC takes notice that BRC is fully compliant to the Convention on Biological Diversity (CBD) and the Nagoya Protocol. Further, promotion of robust and substantial collaboration with Asian countries that have high ratio of young generation and strong economic growth, such as Indonesia, will yield great benefits in the 4th Mid- to Long-term Plan.

In summary, largely due to the extraordinary efforts of the former director, Obata, the BRC is leading several efforts to promote international collaboration more rigorously. The BRAC has no doubt that the new director, Shiroishi will continue to actively engage in international relationships and build on the foundation established before him to ensure the RIKEN BRC solidifies its position as a hub of global interaction and collaboration in the Western Pacific/East Asia.

TOR 4. PI assessment

1: Experimental Animal Division

Division Head: Atsushi Yoshiki

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. Dr. Yoshiki leads a Division that has been collecting, performing microbial and genetic QC, and distributing large numbers of high-quality mutant mouse lines for decades. The group also has introduced CRISPR/Cas9 genome-editing tools to accelerate their work and adhere to the demands of the research community. Thus, the PI is fulfilling his role in line with BRC's mission.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. Over the last 6 years, the PI's group successfully collected over 250 mouse lines

and distributed about 2,500 items each year. The BRC is recognized as having the 2nd largest collection of mutant mouse lines in the world. The constant contributions to both national and international research communities are well recognized and appreciated.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. By collaborating with companies, the PI's group developed a "Marker Gene Detection Kit" for genetic QC. Originally for internal use, the kit is now commercially available to the research community. Although background purity needs to be examined by SNP analysis, the kit will help decrease the risk of genetic contamination by human error.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

The PI and his group continue to build on fundamental technologies and their results feed back into their infrastructure. Through domestic collaborations, the PI has developed fluorescent reporter-mouse lines as well as Cre-driver lines. As CRISPR/Cas9 edited mouse strains increase, the group needs to implement a preselection process for new mouse lines because of limited budget and space. Importantly, BRC will benefit from better advertising of their achievements, such as an improved website.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

The PI does an excellent job managing 9 operational groups with about 70 members. The PI and BRC organized an international laboratory-animal network and spent a reasonable amount of effort into training and educating young researchers and technical staff.

2: Experimental Plant Division

Division Head: Masatomo Kobayashi

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. The Experimental Plant Division is functioning as an important international center for the established distribution of seeds for *Arabidopsis* and has recently expanded to

Brachypodium as an alternative experimental plant model for grain species. They distribute various cultured cell lines for both model plants and commercially important species, and hold a large collection of unique molecular genetic resources and vectors. The significance of this center's presence is at a high level of clear international standard. Dr. Kobayashi has been a powerful force in pushing the Plant Division to its current level.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

The preservation and distribution of various Japanese derived germplasm and clonal resources is a significant and unique contribution to Japanese and international research communities. Strict quality control of resources and careful management of data-related resources by the PI's team meets the world's highest standards of plant resource management. The provision of resources from the Division has led to research results publications in leading journals such as *Nature* and *Science*.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

The Division is also active in resource development and research promotion through close collaboration with other research institutions. As a member of the Multinational *Arabidopsis* Steering Committee, they are strengthening collaborations with foreign resource institutions. The Division is becoming the strongest international hub for the Japanese plant science.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. The following future plans are appropriate: 1) The construction and maintenance of a web catalogue integrating germplasm data and clonal resources. This will facilitate external user access to resource metadata and allow efficient searching for available materials. 2) The consolidation of resource information and associated metadata for an expanding collection of plant cultured cells. 3) The maintenance and development of new *Brachypodium distachyon* resources.

In addition, the PI is performing proof of concept research into the translational use of

Arabidopsis research to support crop protection, and they are actively investigating the feasibility of collecting resources for alternative model plant species such as *Marchantia* (bryophyte), and are contributing to internal projects on plant symbiosis. They are also active in public and educational outreach.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The PI has been making sufficient efforts, and the Division operating smoothly with some staff attaining notable institutional recognition for achievement. Training of young staff with skills necessary for resource preservation is well-promoted and existing staff have been appropriately developed to improved positions.

3: Cell Engineering Division

Division Head: Yukio Nakamura

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. In response to demand from society, the PI has been operating a cell line collection system and rapidly incorporating disease-specific iPS cell lines into BRC's collection. As an ICLAC member, he is continuously aware that preventing cell misidentification through international cooperation is a very important issue. Thus, the PI excels in his efforts towards achieving BRC's mission.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The number of publications by researchers using the PI's resources is greater than 1,000/year and the number of patents has exceeded 100/year. This demonstrates the Division's constant contributions to all fields of study from basic science to applied research.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

The PI is hosting regular training courses on human ES/iPS cells to support domestic research. The PI serves as a member of the Expert Committee of Specified Embryonic

Research, a subcommittee of Bioethics and Biosafety organized by the MEXT.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

As an expert in the management and operation of bioresources, the PI is committed to making national guideline policies and deciding future directions.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

The PI is appropriately committed to management and operation of the Division as well as the training and development of young talent. The PI is striving to advance the careers of senior staff and to secure human resources.

4: Microbe Division

Division Head: Moriya Ohkuma

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. Based on the numbers of microbes collected and preserved, maintenance of type strains, numbers of distribution and users, the Committee concludes that the PI is fulfilling his role in line with BRC's mission. One of the PI's remarkable contributions is the stimulation of Asian microbiological studies through a positive spiral of microbe deposition, publication, and microbe distribution.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The PI's work contributed to the publication of 3,424 scientific papers and 478 patents by the users between 2013 and 2018.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. The PI is a subleader and governing board member of the All-RIKEN cross-center project "Integrated Symbiology (iSYM)", a subleader of the competitive RIKEN Pioneering Project, and the chair of the committee for RIKEN safety and regulation for

microorganisms.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

The PI is very active in scientific publication (179, from 2013-2018) and makes himself available for reviewing papers. The PI contributes to the activity of academic societies as the President of the Japan Society of Microbial Resource and Systematics and a board member of the Japan Society of Microbial Ecology.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The PI is shifting to a group system consisting of multiple individuals, aiming for information sharing and the standardization of roles. The management and operation of the Division is being addressed appropriately. The PI is training and instructing many postdoctoral researchers and graduate students. The promotion of laboratory staff is also emphasized, and the results of training a diverse range of young talent are highly valuable.

5: Gene Engineering Division

Division Head: Yuichi OBATA, Presenter: Takehide MURATA

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, the PI's work is in line with BRC's mission. High praise should be given regarding the consistently high number of distributed bioresources, >1,200 items every year over the past 6 years. Moreover, the PI is prioritizing metadata enrichment, which will promote active use of the bioresources. Further, the PI is promoting collaboration with other databases such as the Kyoto Encyclopedia of Genes and Genomes (KEGG) and PubMed to enhance usability.

Identification of resources and confirmation of their authenticity are extremely important for ensuring the resource reliability that forms the basis of the Center's operation. Such QC can only be possible with careful work by devoted staff members, and we would like to express our respect to the PI that he is sincerely and decidedly committed to the QC.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. Consolidation of meta-information and sequence information is steadily advancing in the Gene Engineering Division, under the slogan “No information, no bioresources.” However, it would be good to see more frequent updates to the analytical results.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. The PI is contributing to the goals of his specific mission. Looking forward, there is significant opportunity to expand support for outside researchers and develop new pioneering fields of research. The Committee hopes that the PI will restructure his Division so that research-supporting staff members are fully committed to collecting and maintaining bioresources and that researchers can focus on pioneering new fields which are in line with the mission of the Division.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. Information dissemination and public relations activity for the general public, such as the “Tsukuba PhD kids program: science experiment classes” and “lectures for high school students” seem simple, but are actually highly significant activities that not only facilitate understanding and the education of local residents, but also support the foundation of Japan as a nation that values and produces top-level science and technology. We look forward to the BRC’s continuous activities in the realm of social education.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes, the PI is constructing and operating a system that complies with laws pertaining to exports. In terms of training young staff, the PI is actively encouraging the Division’s members to conduct the following activities:

- Participate in lectures for qualification as ISO9001 Quality Management internal auditors
- Survey users’ papers

- Draft brief PR flyers for distribution at academic conferences. Post online articles that introduce specific bioresources
- Participate in major academic conferences

To further develop and pioneer new fields of research in the future, we would like the PI to recruit diverse young staff and actively promote interactions with other Divisions within the BRC.

6: Integrated Bioresource Information Division

Division Head: Hiroshi Masuya

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, the PI is fulfilling his role very well. His Division contributes to the development of original applications, especially the novel mathematical analysis using machine learning and basic technology related to data integration for bioresources. The PI is satisfactorily fulfilling the mission from the perspective of data resources, and he has great potential for the future.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The number of accesses to the BRC website is almost equal to that of the Protein Data Bank Japan (PDBj) and the National Bioinformation Center (NBDC) portal, which are international websites. This indicates that the PI's Division has reached international standards for information dissemination. By participating in IMPC and distributing mouse resources and information, BRC is reaching the standards shared by the major bioresource centers around the world.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes, the following 4 plans are on-going:

- Data integration of bioresource-related data by ontology
So far, annotations for 91% of the records in the Mouse database and 86% of the records in the microbe database have been completed. For the field of genomic clinical research of rare diseases, the Division has integrated disease information

and mouse-phenotypic data using Human Phenotype Ontology and Monarch Disease Ontology. As a result, users are able to search for bioresources by disease name on the BRC website.

- Improvement of the bioresource online catalog database

The Division has developed and maintained a general-purpose data-convention pipeline. Metadata integration, international standardization, and development of a search system across the BRC resources represent major efforts toward the development of the new web catalogue.

- Wider dissemination of bioresource data

By using Resource Description Framework (RDF), the PI is developing an integrated gateway with the iPS portal database in Kyoto Univ, NBDC, and Database Center for Life Science (DBCLS).

- Website renewal

Renewal of the website is underway, which will improve usability via a new graphic user interface. The BRAC recommend domestic and international beta-testers to guide development and implement a feedback loop before launch. Considering customer feedback should be an ongoing process.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. The Division has made efforts to conduct Big Data analysis and to develop new visualization technology for bioresource data. The result was comprehensive phenotype-phenotype associations from IMPC data. This is a unique and meaningful way of adding more value to RIKEN BRC resources.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The management and operation of the Division is appropriate, and training of young talent is also being put into practice. The PI is working appropriately to recruit researchers for Big Data analysis. Personnel for metadata integration and data consolidation, as well as annotators and curators, should be employed stably in this Division.

7: Bioresource Engineering Division

Division Head: Atsuo Ogura

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. Dr. Ogura has shown strong leadership and under his guidance, the Division has produced highly original and outstanding research in line with the BRC's mission. The newly developed technologies should be advertised and utilized inside and outside BRC.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The Division has developed and improved reproductive bioengineering technologies, including anti-inhibin serum-mediated superovulation, embryo cryopreservation, estrous cycle synchronization via progesterone, and micro-insemination. Further, the group has published 79 papers (2013 to the present) in high-impact journals.

Although scientific impact can be easily recognized by scientists, novel technologies need to be advertised so that they can be used worldwide. Movie clips that explain and demonstrate skilled technologies may help these new and exciting techniques gain recognition.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. As a core part of the BRC, the Division greatly contributed to the development of novel reproductive technologies. Anti-inhibin antibody-mediated super ovulation is just one example.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. Their recent genome editing research on hamsters has produced remarkable results that could not have been anticipated from mouse studies. This technology has led to interdisciplinary collaboration with researchers studying hibernation, further joint research with other researchers can be expected. Additionally, high praise should be

given for receiving the 5-year Grant-in-Aid for Scientific Research on Innovative Areas for his group to research totipotency.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The PI appropriately manages the Division and is committed to helping young talent develop under his care. Young researchers in his division have published numerous original papers. Further, they have won competitive funding and awards, advanced their careers with new positions, and are playing active roles in scientific research. We foresee that lab members whom the PI has trained will themselves become PIs in the near future.

8: Technology and Development Team for Mammalian Genome Dynamics

Team Leader: Kuniya Abe

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, the PI continues to successfully fulfil his role in line with the BRC mission by producing novel EpiSCs and developing technology for analyzing how stem cells transition from naïve to primed. In addition, the PI has established CRISPRi and CRISPRa expressing iPS cells, which are a useful resource for researchers in Japan and around the world.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes, the PI's achievements in research and development have met high international standards. This is evidenced by the publishing of a number of original papers regarding new resources and established methods.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes, the Team has disseminated their research, collaborated within RIKEN, and acquired several intellectual property rights. In particular, the Dox inducible CRISPRi/a

system will add additional value to the existing cell lines and the BRC.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes, the Team is developing a new non-invasive method for epigenome dynamics sensing, which has allowed them to find a 3rd type of pluripotent stem cell, non-naïve but not primed. These research projects have the potential for achieving international prominence.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes, The PI is appropriately handling the management and operation of his Team. The PI is an excellent mentor for his Team, in addition to the promotions received by his research trainees, he has taken on the training and education of graduate students, including those from outside Japan.

**9: Technology and Development Team for Mouse Phenotype Analysis
Team Leader: Masaru Tamura**

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, considering the PI's participation in the IMPC, his activity is in line with the BRC's mission. Additionally, he is contributing to the BRC's mission by directing the development of novel research methods, including X-ray micro-CT technology and contrast agents.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. The Team has conducted high quality joint international research that has led to publications in high-impact international journals. The Team's output and impact are satisfying international standards.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes, the Team is focusing on phenotyping and has effectively collaborated with other laboratories. In addition, they have provided their platform to the Japan Mouse Clinic services and participated in collaborations with researchers inside and outside of RIKEN.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Micro-CT analysis method that provides a new level of embryo phenotyping analysis. In addition, the Team is striving to establish a new telemetry-analyzing technique that will greatly help in the efficient and automated analysis of phenotyping. Implementing this new telemetry system using AI-based analysis will lead the next generation animal phenotyping analysis.

To this end, close linkage with the Integrated BioResource Information Division will be very important, because formidable AI technologies are now developed. It may be synergistic to develop joint appointments between the Team and the Integrated BioResource Information Division.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. Initially, this Team lacked a sufficient number of researchers who were able to conduct phenotyping of large numbers of mice. However, after great effort, the PI was able to recruit young talent for the Team. The PI is appropriately managing the Team. The Team will be strengthened even more if they were able to recruit informaticians.

10: iPSC-based Drug Discovery and Development Team
Team Leader: Haruhisa Inoue

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. The PI is formulating and carrying out research and development strategies leading to the use of disease-specific iPS cells held by BRC in the drug discovery field. Thus, the PI is playing an important role in accordance with the mission.

(2) Do the PI's achievements in R&D reach the international standard in light of the

following three aspects?

(i) Output and impact

Yes. Publication of original articles in high-impact factor (IF) journals is proceeding steadily for each individual topic. The PI is promoting research at a high international standard.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. At the BRC satellite Keihanna laboratory, the PI is fulfilling his own mission to promote the utilization of disease-specific iPS cells. In addition, by hosting international symposia, the PI has actively promoted collaboration and social contributions both in Japan and overseas.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. The PI promotes collaboration with industry in order to utilize the disease-specific iPS cells, providing not only cells, but also methods for evaluation. Additionally, these efforts promote collaboration and social contributions both in Japan and overseas.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

The PI is working to manage and operate the Teams appropriately. Development of young talent will be an issue in the future.

**11: iPS Cell Advanced Characterization and Development Team
Team Leader: Yohei Hayashi**

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. The PI is conducting challenging research aimed at technological developments that will yield unique outcomes. At the same time, it is important to balance this activity with his commitment to developing bioresource infrastructure.

(2) Do the PI's achievements in R&D reach the international standard in light of the

following three aspects?

(i) Output and impact

As a young researcher, the PI's previous achievements are noteworthy and some of them have already had great impact.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

The proposed research direction closely follows BRC's mission, and the Team is expected to make significant contributions in the near future.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. Introducing laser technology as a new methodology for characterizing iPS cells is a unique project. Production of reporter-iPS cell lines should be performed with focus on good communication with research community.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

The PI has newly established his laboratory and is appropriately tackling the management and operations of his Team. The PI is also committed to training and development of young talent.

12: Next Generation Human Disease Model Team

Team Leader: Takanori Amano

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes. The PI has only just begun his current position. However, he understands the BRC's mission well and is setting forth appropriately aligned research plans.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

It is too early to say, but his plans will likely be fruitful. At his former post, the PI built a

solid track record of research into the control of gene expression. The PI's notion that studying the function of non-coding variants is necessary for a comprehensive understanding of the causes of human disease is important for the disease research community.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. Based on social needs, the PI selected Alzheimer's disease, frontotemporal lobar degeneration, Hirschsprung's disease, and branchio-oto-renal syndrome as target diseases for study. The Team has begun generating human-disease models by introducing point mutations using CRISPR/Cas9 genome-editing technology. With the aim to achieve optimized precision medicine, the Team has already begun joint research projects with researchers and clinicians who specialize in disease-genome analysis.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

Yes. The PI is working on understanding genetic context of difference in penetrance of mutant phenotype by comparison of the phenotype on the two genetic backgrounds of B6 and JF1 and on clarifying relevant *cis*-regulatory variations and gene-regulatory networks using RNA-seq of F1-hybrid mice. This is thought to be a challenging but important project for developing a better understanding of human diseases, but it will need careful assessment when set against the priorities of generating and analyzing key models of disease variants.

Generation of real disease models and subsequent research need to be based on the demand from the clinical research community.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

As the PI has just been appointed, selection of staff for the generation of mouse models and phenotype analysis are now in process. The Council trusts that appropriate personnel will be brought on board and trained.

13: Plant-Microbe Symbiosis Research and Development Team

Team Leader: Yasunori Ichihashi

(1) Is the PI fulfilling the role in line with the BRC's mission?

Yes, the PI is playing a role in accordance with BRC's mission. The PI is developing novel technology to use arbuscular mycorrhizal fungi (AMF) resources, as well as establishing a model system for the study of plant-microbe symbiosis. Such efforts are viewed as fulfilling his role well. The Team is already advancing the *in vitro* propagation of AMF. In the future, we anticipate the development, storage, provision, and characterization of novel resources.

(2) Do the PI's achievements in R&D reach the international standard in light of the following three aspects?

(i) Output and impact

Yes. Adopting the national research project “Cross-ministerial Strategic Innovation Promotion Program (SIP)”, supported by the Japanese Cabinet Office, as a primary research project is commendable. Additionally, the PI published a co-authored review of plant-microbe symbiosis in *Nature Plants*, with high international impact.

(ii) Contribution to specific missions of each laboratory regarding resource infrastructure, R&D, and collaboration with other laboratories

Yes. The PI is participating in RIKEN's internal cross-sectional program, iSYM. Further increase of research results is expected in the future.

(iii) Pioneering new resource infrastructure, R&D, creation of new scientific fields, and social contribution

The PI is actively addressing integration of different research fields, including plant science, agricultural science, microbiology, and informatics. The PI established a foundation for conducting strategic research, e.g., field omics analysis and the screening of uncultured microbes using microdroplet technology. The PI is now progressing with the acquisition of an external budget to form the foundation for implementing their plan. The PI is also planning to apply IP to contribute to the novel use of breath-capture technology and pursue patenting. Additionally, the PI contributes appropriately to outreach activities, such as the Tsukuba City Future Creation Conference.

(3) Is the PI appropriately managing and operating the Division/Team?

In addition, does the PI make efforts for training and development of young talent?

Yes. The PI is working appropriately on team management and operation. He is also making efforts to develop young talent. Despite a broad range of planned research projects, the PI is utilizing the latest information systems to create smooth communication within the Team, and has consistently conducted excellent management and operations. The PI has also received large external funds, such as the SIP (FY2018-FY2023). Although the Team is still in its inaugural year, the Team members, including young researchers and research assistants, seem to be working well. Young members should be mentored to ensure that they produce results relevant to the research Team. In addition to developing a laboratory comprising mainly young members, the PI is also making efforts to train a visiting researcher from a private company and a visiting student from a university.

TOR 5. Advice for further improvement of the activity of BRC

(1) What are R&Ds and technical innovation that should be commenced immediately (within 2-3 years).

- Reinforcing R&D for functional genomics (e.g., single cell genomics), phenotyping (e.g., pathophysiology), data analysis, enhancing the collection, integration, dissemination of genomic, phenotypic data and information on existing bioresources.
- Consider best practices that enable precise identification of genomic information.
- Capitalize on model plants resources for genome editing, gene modification, and other manipulation.
- Adopt the Findable Accessible Interoperable and Reusable (FAIR) Data Principles.
- Adopt internationally-recognized systems (e.g., Research Resource Identifier, RRID) for all appropriate bioresources, protocols, and reagents.
- Establish a process for regular and remote offsite data backup (e.g., tape drives, cloud storage, etc.).

- Develop the infrastructure necessary for integrating all bioresource-related data and to make it minable, searchable, and browsable to enhance its utilization and dissemination.
- Establish multiple routes for regular feedback from the user community (e.g., formally established user groups, user surveys, webinars, etc.).
- Undergo a strategic planning process to understand global research trends that could inform new ways to utilize the resource and increase distribution both domestically and internationally.

In addition:

- Discuss with the appropriate RIKEN leadership how to increase recruitment of more female scientists as principal investigators, group leaders and junior faculty. In particular, improvement of gender imbalance should be urgent task.
- Consider recruiting, hiring, or collaborating with a qualified mouse pathologist.
- Consider establishing limited, customized sequencing services available on-campus.

(2) What are novel resources and new research fields to be developed from a long-term perspective toward the 5th Mid-to-Long-term Plan?

- A new program on Big Data analysis is an important development, in particular the integration of machine learning (ML) as a tool for the analysis of rich, complex data. One area that will be important for the future is to ensure that Big Data developments at BRC are enriched by cross-talk to large high dimensional datasets from Biobanks and Rare Disease datasets, in Japan and potentially further afield. A relevant option is to accelerate development of phenotyping platforms based on the ML technology, and strive to recruit, hire, and/or establish formal collaboration with a critical mass of bioinformaticians with expertise in the AI and ML technologies and Statistical Mathematics that can be applicable to Life Science.
- The BRAC recognizes the indisputable value of *in vivo* models, especially mice, to inform functional knowledge of the genome. For example, *in vivo* functional analysis of human orthologs in the mouse genome is crucial to the success of translational research that can be relevant to society.

- Investigate utility of pursuing accreditation by the Association for Assessment and Accreditation of Laboratory Animal Care.
- Develop QC control for genetic drift caused by accumulation of spontaneous mutations in live stocks. It is particularly important for many inbred strains derived from wild mice, which are unique to RIKEN BRC.
- Perform a self-review and audit to determine if barrier to access to BRC bioresources exist, either through slow response times, high costs, limited awareness, ineffective communication or outreach, poor technical or customer service, restrictive MTA's or IP issues, etc.

Other options to be considered:

- Comparative genomics of bioresources with natural diversity
- Investigation of complex traits and quantitative traits and development of new mouse resources for these fields
- 4-D phenotyping that produces time-series data of morphology, physiology, and behavior
- Upgrade and expansion of existing physiological screening technologies with next generation non-invasive screening devices
- Development of currently unavailable tools for high throughput customized phenotype screening
- Investigation of non-coding regulatory elements and relevant mutations
- Projects to more thoroughly investigate modulators of gene expression

References

Reference 1

Program for the Seventh Advisory Council Meeting of RIKEN BioResource Research Center

Date: July 3- July 5, 2019

Venue: RIKEN BioResource Research Center and Okura Frontier Hotel Tsukuba

Day0: July 2 (Tue)

Time	Subject	Presenter	Venue
15:00-17:45	Laboratory Tour		RIKEN BioResource Research Center
17:45-19:00	Move to Hotel from RIKEN		
19:00-19:05	Welcome Remarks	Dr. Toshihiko Shiroishi, Director, RIKEN BioResource Research Center	Okura Frontier Hotel Annex 1F Subaru
19:05-19:40	Introduction to RIKEN, and Terms of Reference to RIKEN Advisory Council from the RIKEN president	Dr. Shigeo Koyasu Executive Director, RIKEN	
19:40-19:50	Q&A		
19:50-20:00	Introduction of BRC Members and Supporting Staff		
20:00-21:30	Informal Reception		

Day1: July 3 (Wed)

Time	Subject	Presenter/Chair	Venue
9:00-9:05	Opening Remarks	Dr. Toshihiko Shiroishi, Director	RIKEN BioResource Research Center
9:05-9:10	Remarks from Chairperson	Dr. Martin Hrabě de Angelis	
9:10-9:30	Terms of Reference to the BRC Advisory Council (BRAC) from the Director of RIKEN BRC	Dr. Toshihiko Shiroishi, Director	
9:30-10:30	Missions and Current Achievements of RIKEN BRC, and Plans of RIKEN BRC in the 4th Mid- to Long-Term Phase	Dr. Toshihiko Shiroishi, Director	
10:30-10:50	Break		
10:50-11:25	Experimental Animal Division	Dr. Atsushi Yoshiki, Head Dr. Masahito Ikawa, Chair	
11:25-12:00	Bioresource Engineering Division	Dr. Atsuo Ogura, Head Dr. Masahito Ikawa, Chair	
12:00-13:00	Lunch		
13:00-13:35	Technology and Development Team for Mammalian Genome Dynamics	Dr. Kuniya Abe, Team Leader Dr. Satoru Takahashi, Chair	
13:35-14:10	Technology and Development Team for Mouse Phenotype Analysis	Dr. Masaru Tamura, Team Leader Dr. Satoru Takahashi, Chair	
14:10-14:45	Next Generation Human Disease Model Team	Dr. Takanori Amano, Team Leader Dr. Satoru Takahashi, Chair	

Time	Subject	Presenter/Chair	Venue
14:45-15:00	Break		
15:00-15:35	Cell Engineering Division	Dr. Yukio Nakamura, Head Dr. Junya Toguchida, Chair	
15:35-16:10	iPSC-based Drug Discovery and Development Team	Dr. Haruhisa Inoue, Team Leader Dr. Junya Toguchida, Chair	
16:10-16:45	iPS Cell Advanced Characterization and Development Team	Dr. Yohei Hayashi, Team Leader Dr. Junya Toguchida, Chair	
16:45-17:00	iPS Cell Research Unit for Drug Discovery (RIKEN Program for Drug Discovery and Medical Technology Platforms: DMP)	Dr. Yukio Nakamura, Head Dr. Junya Toguchida, Chair	
17:00-17:15	Break		
17:15-17:50	Gene Engineering Division	Dr. Takehide Murata, Senior Research Scientist Dr. Sumio Sugano, Chair	
17:50-18:25	Integrated Bioresource Information Division	Dr. Hiroshi Masuya, Head Dr. Satoru Miyazaki, Chair	
18:40-19:00	Move to Hotel from RIKEN		
19:00-20:30	Official Reception Hosted by the Director of RIKEN BioResource Research Center	All BRAC and the BRC Members	Okura Frontier Hotel Annex 1F Subaru
20:30-23:00	Discussion among the BRAC members	Closed meeting	Hotel Annex 2F Yubae

Day2: July 4 (Thu)

Time	Subject	Presenter/Chair	Venue
9:00-9:35	Experimental Plant Division	Dr. Masatomo Kobayashi, Head Dr. Tetsuro Mimura, Chair	RIKEN BioResource Research Center
9:35-10:10	Microbe Division	Dr. Moriya Ohkuma, Head Dr. Hiroyuki Ohta, Chair	
10:10-10:45	Plant-Microbe Symbiosis Research and Development Team	Dr. Yasunori Ichihashi, Team Leader Dr. Hiroyuki Ohta, Chair	
10:45-11:00	Break		
11:00-11:30	Summary of reports from the domestic committees to BRC, and result of the SWOT analysis of RIKEN BRC	Dr. Toshihiko Shiroishi, Director	
11:30-12:00	Q&A, Discussion	Dr. Martin Hrabě de Angelis	
12:00-13:00	Lunch		
13:00-15:30	Discussion among the BRAC members	Closed meeting	
15:30-15:45	Break		
15:45-18:30	Discussion among the BRAC members	Closed meeting	
18:30-19:00	Move to Restaurant		
19:00-20:45	Working Dinner	All BRAC members and the BRC Researchers	Restaurant Kisoji
20:45-21:00	Move to Hotel		
21:00-23:00	Drafting the Report (the BRAC members)	Closed meeting (*)	Okura Frontier Hotel Annex 2F Yubae

Day3: July 5 (Fri)

Time	Subject	Presenter	Venue
9:00-10:20	Drafting the Report (the BRAC members)	Closed meeting (*)	Okura Frontier Hotel Main Build. 4F Tachibana
10:20-10:30	Break		
10:30-12:00	Drafting the Report (the BRAC members)	Closed meeting (*)	
11:30-12:30	Lunch		Okura Frontier Hotel Restaurant Camellia
12:30-13:00	Chairperson and available BRAC members move to RIKEN from Hotel		
13:00-14:30	Completing the Report (the BRAC members)	Closed meeting	RIKEN BioResource Research Center
14:30-15:30	Reporting from the Chairperson to the Director of RIKEN BRC	Dr. Martin Hrabě de Angelis	
15:30-15:40	Comments from the Executive Directors	Drs. Shigeo Koyasu and Motoko Kotani Executive Directors, RIKEN	
15:40-15:50	Closing Remarks	Dr. Toshihiko Shiroishi, Director, RIKEN BRC	

Note: Each PI has 15 minutes for presentation including summary of report from the domestic committee, followed by 5 minutes of comments from Chair of the domestic committee, then followed by 15 minutes for Q&A and discussion.

(*) The Director of BRC and Senior Advisor wait in the room next to the meeting room to respond to inquiries from the advisory committee.

Reference 2

List of the RIKEN Participants

Dr. Shigeo Koyasu	Executive Director, RIKEN
Dr. Motoko Kotani	Executive Director, RIKEN
Dr. Toshihiko Shiroishi	Director, BRC
Dr. Yuichi Obata	Senior Advisor Division Head, Gene Engineering Division, BRC
Dr. Kuniya Abe	Deputy Director Team Leader, Technology and Development Team for Mammalian Genome Dynamics, BRC
Dr. Masatomo Kobayashi	Deputy Director Coordinator Division Head, Experimental Plant Division, BRC
Dr. Atsushi Yoshiki	Coordinator Division Head, Experimental Animal Division, BRC
Dr. Yukio Nakamura	Coordinator Division Head, Cell Engineering Division, BRC
Dr. Moriya Ohkuma	Division Head, Microbe Division (Japan Collection of Microorganisms) , BRC
Dr. Atsuo Ogura	Division Head, Bioresource Engineering Division, BRC
Dr. Hiroshi Masuya	Division Head, Integrated Bioresource Information Division, BRC

Dr. Masaru Tamura	Team Leader, Technology and Development Team for Mouse Phenotype Analysis, BRC
Dr. Haruhisa Inoue	Team Leader, iPSC-based Drug Discovery and Development Team, BRC
Dr. Yohei Hayashi	Team Leader, iPS Cell Advanced Characterization and Development Team, BRC
Dr. Takanori Amano	Team Leader, Next Generation Human Disease Model Team, BRC
Dr. Yasunori Ichihashi	Team Leader, Plant-Microbe Symbiosis Research and Development Team, BRC
Dr. Takehide Murata	Senior Research Scientist, Gene Engineering Division, BRC
Mr. Hiroshi Shishido	Director, RIKEN Tsukuba Branch
Mr. Kazumi Kawashima	Director, BioResource Center Planning Office

Reference 3

Members List of Domestic Resource Committees and Review Committees

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- Plant-Microbe Symbiosis Research and Development Team

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Reference 4

Meeting Dates of Domestic Resource Committees and Review Committees

January 16, 2019

Resource Committee of Gene Engineering Division

January 22, 2019

Resource Committee of Experimental Animal Division

Review Committee of Experimental Animal (A):

Technology and Development Team for Mammalian Genome Dynamics

The Technology and Development Team for Mouse Phenotype Analysis

The Next Generation Human Disease Model Team

Review Committee of Experimental Animal (B):

Bioresource Engineering Division

February 14, 2019

Resource Committee of Cell Engineering Division

Review Committee of iPS Cell:

iPSC-based Drug Discovery and Development Team

iPS Cell Advanced Characterization and Development Team

February 25, 2019

Resource Committee of Integrated Bioresource Information Division

March 5, 2019

Resource Committee of Experimental Plant Division

Resource Committee of Microbe Division

Review Committee of Plant-microbe Symbiosis:

Plant-Microbe Symbiosis Research and Development Team

Reference 5

Evaluations and Suggestions for the BRC Director by Domestic Resource Committees and Review Committees

1. 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 of Experimental Animal Division and Review Committees of Experimental Animal]

- 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 Animal 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 Plant and Microbe Divisions 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 of 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 Committee of iPS Cell]

- 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 Keihanna 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 Gene Engineering Division]

- 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.

2. 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 Animal]

- The former Director lead 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 Plant and Microbe Divisions 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]

- 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 Gene Engineering Division]

- 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.

3. 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 of Experimental Animal Division and Review Committees of Experimental Animal]

- 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
- 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 Plant and Microbe Divisions 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]

- 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 Gene Engineering Division]

- 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.
- 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/International Nucleotide Sequence Database Collaboration

(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 of Experimental Animal Division and Review Committees of Experimental Animal]

- 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 Plant and Microbe Divisions 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 Committee of iPS Cell]

- 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.

Reference 6

Evaluations and Comments for the Divisions by Domestic Resource Committees

Division Name: Experimental Animal Division

Division Head: Atsushi YOSHIKI

1. Achievements and plans for the Division

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- Collection, Preservation, and Distribution

Experimental Animal Division reached the highest global standard in all aspects as mouse repository such as the numbers of preserved and distributed mouse strains and the variety of collections. Approximately 250 mouse strains are collected annually. As of FY2018 nearly 8,500 strains have been collected and after the 18-year operation since its foundation. The Division is evaluated that it has become one of the top 3 major mouse repositories in the world together with the Jackson laboratory holding 9,000 strains in the US and the European Mouse Mutant Archive (EMMA) with 6,000-7,000 strains in Europe. The Division has made a particularly large contribution to the collection of the unique mouse strains developed in Japan. Since the start of its operation, BRC as a whole has provided a total of 5,099 overseas institutions in 71 countries with its bioresources, including mice to 800 institutions in 39 countries.

- Quality control (QC)

The Division also reached the highest standard in QC. They have advanced the QC of mouse strains by implementing original genetic and microorganism tests. Furthermore, a high level of microbial tests is being developed by the support from FY2018 National BioResource Project (NBRP) “Fundamental technology upgrading program”.

- User's outcome

Mouse users have published 870 papers and 37 patents using the mouse lines since the start of operation. Over 80% of papers were published in high-impact journals with an impact factor of 3 and above (IF 3+).

(2) *Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?*

- The Division provides 300-500 mouse strains in Japan and to overseas constantly each year.
- The number of publications made by users of these mouse strains, and the number of mouse strains provided to industry and patents established by R&D with the resources, all demonstrated that the Division has made a very significant contribution to the research community in Japan and overseas, as well as to the industry. Apparently, those facts reflect their high level of QC.
- The Division has been correcting information required for genetical QC and cleaning-up microbial contaminations. This improvement contributes to high accuracy in animal research and improves the animal welfare.
- It is highly evaluated that the Division developed with a company a PCR Test Kit for genetical QC based on the Division's original method and made the kit commercially available to research community through the company.
- The Division is contributing to improvement, expansion of applications, and safety assessments of genome editing technologies, by improvements in fundamental technologies and generation of disease models in the NBRP project and the international consortium.
- The Division is contributing to the society through a variety of outreach activities in regard to the recognition of the importance of bioresources.
- Active involvement and contribution to international collaboration such as those from the International Mouse Phenotyping Consortium (IMPC) are encouraged. From now on, it is necessary to provide Japanese and international research communities with information from previous large-scale mouse mutagenesis programs as their novel properties could be useful and relevant for current researches.
- It is difficult to evaluate the production and provision of mouse models which reflect genomic information for patients with rare and intractable diseases because of the limited number of such mouse strains at present. However, we hope such mouse models should contribute to society and the patient community in the future.
- It is recommended that the Division will make full use of the results of the QC tests as in feedback for depositors and users as well as disclosure of information associated with resources. In the future, it is recommended to further strengthen

the collaboration between researchers and related institutions, in order to improve community relationship.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- The Division is contributing to the development of BRC by fulfilling their important mission of collection and distribution of genetically-modified mice as bioresources. It is obvious that the Division is internationally appreciated as the Division is not just collecting mouse resources but conducting high level genetical and microbial QC.
- The current activities and plans with the major objectives of “Understanding sophisticated life phenomena, improving human health, and conquering diseases” consist of the core of the 4th Mid to Long-Term Plan and will serve as the driving force for the development of BRC.
- Based on the results of the 3rd Mid- to Long-Term Plan, the Division plans to generate and supply more sophisticated disease models by incorporating state-of-the-art imaging technology, gene expression analysis technology, and physiological and morphological analyses. This plan is consistent with the center's mission.
- As was in the 3rd Mid- to Long-term Plan, collaboration with teams within BRC is recommended in the current 4th Mid- to Long-Term Plan. The present plan will contribute to the advancement of BRC by accelerating new technical development through increase of collaboration with other institutions that possess similar technology.
- Because the Division's collaborations with research communities are currently limited, more effort is required to expand. To accelerate the progress of the development plan and thereby contribute to the center's advancement, the Division must strengthen the cooperation with other institutions that possess genome editing and other technologies, and must listen to the opinions of clinicians on what kinds of mouse models should be generated.
- Genome editing allows simple knock-out and knock-in mice to be generated by any researcher, so the Division should try to distinguish BRC's resources from others.
- While it is understandable that resource operation will take time, the Division head

is encouraged to make future improvements in the quality and number of paper publications, in which the Division head is the corresponding author.

- A clear explanation of the position or role of this Division in the IMPC is required.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-term Plan?

- It is difficult to determine what kind of mouse strains should be collected as it depends on user's need. However, the dissemination of information on previously collected and archived resources is required.
- It is recommended to generate and supply new highly versatile mouse strains in response to the growing needs.
- Since further human resources and financial support are necessary to advance the planned technological and research developments, the Division should draw a road map and ensure its proper implementation.
- The Division should search the needs of the institutions which are studying aging mice and supply necessary aged mice.
- Mouse resource database should be developed in BRC, incorporating information on human diseases. Items to be considered are:
 - Improvements in the dissemination of information on previously collected and archived mouse strains
 - Integration of resource information for similar mouse strains, and
 - Link mouse strains with relevant cell lines such as human iPS/ES cell lines and genetic materials.

2. SWOT Analysis

(1) Are the results of the presented SWOT analysis valid?

- The results of the SWOT analysis are generally reasonable.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- It is important to disseminate the information associated with mouse resources, as mentioned in the Weaknesses in supplying the resources, and it is recommended to incorporate the linkage to Mouse Genome Informatics (MGI) at the Jackson Laboratory in the US as well as to the information accumulated in our nation.

- Based on the foundation that the Division has built, comprehensive plans and policies are appropriate countermeasures to the results of the SWOT analysis.
- In regard to grasping users' needs and improving service as mentioned in the enhancement of the Strength, it is recommended that future analysis of users' data is necessary for marketing. This would include mouse models that are frequently requested and research fields that can be widely utilized.
- Publishing papers should be the countermeasure for the Weakness.
- To ensure the BRC's continuation, the Division should diversify the sources of income to secure financial resources and limit the threats, and they should develop Human Resource, and employment systems to ensure successors. More specific policies must be made and presented.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Division functioning as a hub of international science and technology?

- International collaboration has been carried out through information dissemination, such as through the International Mouse Strain Resource (IMSR) portal.
- The Division is recognized as one of the three major mouse repositories, together with The Jackson Laboratory in US and EMMA in Europe. Furthermore, the Division has functioned as an international hub of science and technology, as the Editorial Policies in "Nature" introduced the Division as a representative supplier of research materials for reproducible research.
- Besides the international collaboration as in the IMPC, the Division is functioning as an international hub and a leader in Asia, pioneering unique collection of mouse resources containing genetic variations that correspond to variants in human populations.
- It is recommended that the Division should increase their international presence by focusing on Japan's strengths, high-level collaboration within RIKEN, and active dissemination of information in Japan and overseas.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- As clearly demonstrated by the numbers of collected mouse strains and those distributed in Japan and overseas, Dr. Yoshiki is fulfilling the PI's role in line with the BRC mission and he has had an excellent achievement.
- The PI leads the Division that has acted from both the global and local aspects, by addressing global issues, as an international hub organization, and local issues, such as the development of models for rare and incurable diseases which specifically affect Japanese. The PI is fulfilling its role in line with the BRC's mission.
- The BRC has been renamed as the Bioresource Research Center while spread of genome editing technologies are boosting interests and needs of general researchers toward bioengineering. We recommend that the PI should promote advanced technological developments as a world-class national research and development institute. We hope BRC will accomplish its missions during the 4th Mid- to Long-Term Plan.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

Regarding (i)

- Their highly reliable genetical and microbial QCs have been appreciated by more than 1,300 institutions from Japan and overseas. There have been nearly 1,000 publications from researchers who have used their resources, of which almost 80% have been published in IF 3+ journals and are considered to be high-impact results.
- Their achievements in collection, preservation, and distribution of mouse strains are highly evaluated.
- Publication of papers by the PI as a corresponding author will be addressed for future evaluation.

Regarding (ii)

- The Division is steadily supporting researchers within BRC and collaborating with those in other RIKEN research centers.
- Considering the overall scale, there is still room for further development in RIKEN's internal cross-collaboration programs, as well as the collaborations with labs in Wako, Kobe, and Yokohama campuses.

Regarding (iii)

- Recognition by general public is not so high, as compared to their contribution to the scientific community. But this is reasonable, considering the difficulties with disseminating the information due to the presence of activists opposing animal experiments.
- It is recommended that the PI should make a plan of marketing research in the medical and pharmaceutical industries.
- Their active efforts towards enlightening the general society on animal experiments are encouraged as their social contribution.
- Considering recent decline of interest in sciences in primary education, it is recommended that the Division should make contributions to giving knowledge to elementary, middle and high school students and enlightening them.
- It is difficult to evaluate their achievements in light of “interdisciplinary collaborations.”

(3) Is the PI appropriately tackling the management and operation of the Division? In addition, does the PI make efforts for training and development of young talent?

- The PI smoothly operates the Division with a total of nearly 70 staff members.
- In training the next generation of talent, it is important to consider aspects of international gender diversity.
- Although there are issues in the entire field of animal research, it would be ideal to train personnel for both management operations and research activity.
- The training and development of young researchers have not yet produced sufficient results. More efforts are needed in the development of human resources, in further cooperation with universities and research institutions both in Japan and overseas.

Division Name: Experimental Plant Division

Division Head: Masatoshi KOBAYASHI

1. Achievements and plans for the Division

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- The Division is functioning as an important international center for the distribution of the seeds of *Arabidopsis* and some other experimental plants, various culture cell lines, genetic resources and vectors. In particular, following the Nagoya protocols, it can be expected that obtaining resources from foreign countries will become more difficult. Accordingly, the significance of this center's presence may well continue to increase.
- Regarding *Arabidopsis* resources, RIKEN BRC Experimental Plant Division developed rapidly during the 3rd Mid- to Long-Term Period. Consequently, a position of the Division was established ranking alongside with the Arabidopsis Biological Research Center (ABRC) and Nottingham Arabidopsis Stock Centre (NASC).
- Without doubt, strict quality control of resources by the Division meets the world's highest standards. The thoroughness of quality control of seed resources is worth mentioning. Moreover, the Division is managing data-related resources through a public database. It is particularly valuable that the Division is providing beneficial advice to users, such as proposals for alternative clones.
- Development and distribution of cultured cell lines and vectors necessary for genome editing are effective measures for future resource use. They are being managed appropriately.
- Although it appears that jasmonic acid reduces thrips by improving defenses, the other result also suggests that there may be a small number of thrips resistant to jasmonic acid. Therefore, in the future, it will be necessary to come up with measures for resistant thrips.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The preservation and distribution of various resources is the most significant contribution to Japanese and international research communities. The Division plays an important role in preventing the loss of important experimental materials

which can happen by transfer or retirement of researchers, or termination of projects.

- The Division has made a particularly large contribution to the research community by the preservation and distribution of unique and excellent resources. These include domestically developed *Arabidopsis*-related resources and, moreover, BY-2 and *Arabidopsis* T87 cultured cells. These contributions are now linked to the worldwide presence of Japanese research standards. Arguably, the Division also contributes to society by increasing Japan's standing as a nation of science and technology.
- Experimental plants have become attractive resources for researchers in agriculture.
- The provision of resources from the Division has led to research results published in leading journals such as *Nature* and *Science*. This indicates the achievements of the resource center's main role.
- Information of Ds insertion site and partial sequence of introduced gene insert in FOX lines are extremely useful for users.
- As biology becomes increasingly significant to secondary education, the distribution of educational resources plays a vital role. In fact, the importance of this outreach may exceed that of distributing materials to universities.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- The Division's plans are also appropriate from the perspective of the center's development. Of particular note is the thoroughness of their genetic resource quality control. This is a superb bioresource project of which Japan can be proud.
- The future plan is appropriate, given the status of various efforts including: 1) the consolidation of resource information for plant culture cells, 2) the maintenance of a web catalogue integrating the data of resources, and 3) the maintenance of *Brachypodium distachyon* resources, which contributes to research on plant-microorganism symbiosis. Collaboration with the center's new team is also planned.
- It is desirable that the Division should show how basic plant science research will be linked to the output of applied research. However, this may be a difficult task for the study of plant-microbe symbiosis alone. A plan of actively leading

researchers in the agricultural and bioengineering fields to handle *Brachypodium distachyon* is desirable.

- Although the use of *Brachypodium distachyon* is intended to be a bridge to applied research, it is nevertheless important to appeal to user groups which are quite different from the *Arabidopsis* users. At the present time, it remains unclear how this outreach should proceed.

(4) *What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?*

- Sufficient plans are in place. Implementation of these plans is of primary importance.
- It may be necessary to expand to other plant resources, especially to crop resources. As the age of model organism-focused research appears to end, strategic planning of increasing resource capacity seems worthwhile. Research demand for Japan-specific crop resources may increase in the future.
- Liverwort may be taken up as a resource. Japan has led technology and strain development of liverwort as a model plant. At present, liverwort-related researches are increasing among the Botanical Society of Japan and the Japanese Society of Plant Physiologists. Many mutants, CRISPR and genetically modified strains have been developed in Japan. Active use of liverwort is also expanding in Europe.
- Strengthening of dissemination of useful, and detailed resource-related information is desirable. It would also be beneficial to conduct joint research more closely.
- At present, the Division should focus on improving the quality of resources that they currently have and not on developing novel resources. Quality improvements include the preparation and dissemination of information. Moreover, the Division should be sensitive to the needs of the research community. There may lie the seeds of new resource development.

2. SWOT analysis

(1) *Are the results of the presented SWOT analysis valid?*

- It is adequate.
- Contributions to education should also be examined.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- The strengths of the analysis results are fully utilized.
- Information dissemination program of this Division is considered to be a weakness. The Division has made much effort. The plan to make things advance, for example, reviewing website contents, will be a big future issue.
- Technical training may also become an important contribution.
- It is necessary to investigate tactics for future budget reductions.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Division functioning as a hub of international scientific technology?

- As an international hub for the supply of experimental materials, the Division is actively distributing to overseas. Information is also being disseminated in English, and is considered to play an important role in international collaboration.
- While the use of TAIR is becoming more restricted, this center's role regarding *Arabidopsis* remains significant to Japanese researchers.
- In the future, development of *Brachypodium distachyon* as an international material will be important.
- As a member of the Multinational *Arabidopsis* Steering Committee, the Division is strengthening collaboration with foreign resource institutions. Moreover, the Division is becoming the strongest international hub in the Japanese plant science.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- Dr. Kobayashi has been a powerful force in pushing the Plant Division of the BRC to its current level. It is no overstatement to say that, more than simply playing the role set out in the mission, His actions themselves have functioned as the mission.
- As Dr. Kobayashi is performing an indispensable role, the question of finding an eventual successor is a major issue.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output

and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- The maintenance and distribution of resources is proceeding beyond satisfactory. The results based on this are linked to extremely important results in Japan. A satisfactory contribution is being made in accordance with the center's mission and by the development of technologies to raise the scientific level of resource distribution, and maintenance.
- Not just an institution which provides resources, the Division is also active in resource development and research promotion through close collaboration with other research institutions. The Division is making efforts to reach international standards, and the Division is generally successful.

(3) Is the PI appropriately tackling the management and operation of the Division? In addition, does the PI make efforts for training and development of young talent?

- The PI has been making sufficient efforts.
- The Experimental Plant Division is currently operating smoothly.
- Training of young staff who possess the skills necessary for resource preservation is well-promoted.
- It is desirable that talent who can diligently absorb the resource center's techniques should be developed. This is especially important due to one of the Experimental Plant Division's special characteristics; namely, high levels of quality control. Rather than accepting temporary trainees from overseas, it is desirable that the PI should train and secure young talent that can reliably carry out the Division's roles.
- In order to attract young talent, it is necessary to create a system that accounts for the career paths of young staff. Future employment should be planned for young talent.

Division Name: Cell Engineering Division

Division Head: Yukio NAKAMURA

1. Achievements and plans for the Division

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- The achievements by the Division are evaluated as high as those by related other international biorepositories.
- The Division has collected the world's largest number of cell lines, which makes it a global leader in bioresources.
- The Division has several unique advantages compared to other centers as described below, and hence should be highly evaluated.
 - The Division has collected and is ready to distribute a large number of Epstein-Barr virus (EBV)-transformed B cell lines developed from healthy Japanese. It is extremely important that human leukocyte antigen (HLA) information is attached to the cell lines. Even if similar collections or even larger collections were established in other countries, it would still be a significant collection as a diverse repertoire of Japanese HLA.
 - Sonoda-Tajima collection, EBV transformed B cell lines collected in various countries from the Pacific Rim, Eurasia, and Africa are expected to have great significance in the future, as the development of evolutionary biology has been remarkable in recent years.
 - The Division has also collected B cell lines derived from patients with cancer and those with rare diseases such as Werner syndrome.
 - The Division is distributing several different preparations of human umbilical cord blood-derived cells, i.e., nuclear cells, mononuclear cells and CD34+ cells.
 - As for pluripotent stem cells, the Division has provided a large number of mouse embryonic stem (ES) cells, which contributes to infrastructure for basic research. Moreover, the Division's contribution by distributing human ES cells and disease-specific induced pluripotent stem (iPS) cells as national bioresources is not limited to basic science, but extends to the development of practical application.
- As a member of the International Cell Line Authentication Committee (ICLAC), the PI is actively warning not to use misidentified cell lines and emphasizing the

importance of quality control (QC). The Division is not only world-leading in the numbers of cell collections and varieties, but has also reached the global standards for QC as it has acquired ISO9001 certification. In addition, the Division is contributing to improving the quality of global cell banks and research.

- The research activities unique to the Division have been carried out and improved global recognition of the Division.
- The Division's projects collaborating with other BRC divisions that deal with mice and genes will lead to efficient operation of the center and improved its strength by novel resource development. This is considered unique advantage of BRC. The Division should keep on actively promoting such collaborating projects.
- To demonstrate its presence globally, it might be necessary to promote domestic and international distribution more actively.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The Division is distributing high-quality bioresources to large number of academic institutions and companies within Japan and overseas. Their contribution to domestic community can be evaluated as significant. However, the achievements in the international position are slightly insufficient.
- There are a considerable number of published research papers and patents by using the cell lines supplied by the Division, which indicates that the Division making a sufficient contribution to society, as well as to research community.
- The Division's initiative against misidentified cells can be evaluated as significant in QC.
- Besides handling their deposited cell lines with strict QC, the Division is consistently raising awareness of researchers for microbial and contamination with other cell lines. This makes an extremely large contribution to the improvement of the quality of research in our country. A striking example by the continued supply of properly-quality-controlled cell lines is its contribution to a Nobel prize-winning results.
- The Division's efforts to regularly host technical training courses which are expected to boost the number of users. It is a laborsome activity, but it is hoped that the Division to continue the course by all means. Nevertheless, for accurately evaluating the Division's contribution by the technical courses, specific information including the number of participants and their occupation need to be presented.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRCs 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- Their activities and plans are based on the achievements of the 3rd Mid- to Long-Term Plan and are in line with the 4th Mid- to Long-Term Plan. They are appropriate and expected to contribute to the further development of the center.
- Though flexible responses may be required in the activities in some occasions within this 7-year period, the Division has the capability to actively respond to the new knowledge and development.
- The infrastructure has been established for a stable supply of cell resources such as modified ES cells and disease-specific iPS cells that are expected to be requested more.
- New research teams have been established to investigate the characteristics of iPS cells and to promote their application. The foundation has been established for developing new cell lines through application of genome-editing technology. These are expected to contribute to the further development of the center in response to the increasing diversity and acceleration of stem cell research in the future.
- There is a lack of awareness on the importance of clinical information. The expanded application of genome editing was planned, but it is not necessarily regarded as established technology, and therefore the Division needs to assess to what extent BRC should proceed and whether this is feasible with the current number of staff.

(4) What are resources to be developed and research/technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?

- The Division has established significant infrastructure with regards to cancer cell lines. It is recommendable that the Division should make more efforts toward clinically useful materials such as patient-derived xenograft models (PDX).
- Establishment of a system to share clinical information for a wide variety of diseases is extremely difficult. For sharing clinical information, the Division should consider cooperation with existing disease registration systems.
- The enrichment of resource information is very important. In order to add more information, it is essential to handle various data in an integrated manner,

including cooperation with existing databases, although it may be difficult to do all by themselves. Information on the relationship between diseases and resources is particularly important. Such information is sensitive personal information, but it is most significant for the research indispensable for promoting public health and medical care, and therefore it is recommendable that the Division to actively address this issue.

- The integration of clinical information of donors of cell lines with omics data, such as the genome and transcriptome data, should be further promoted. The former information is steadily integrated, and the Division should focus on the latter. For example:
 - Exome sequencing costs less than 100,000 yen even if outsourced. It is recommended to introduce such sequencing, giving priority to the cell lines that are heavily used. This may lead to enhanced QC.
 - Data of single nucleotide polymorphism (SNP) typing should be attached to disease-specific iPS cells. Research using disease-specific iPS cells has been designed with a comparison of a cell line derived from patients with a disease, with that from healthy individuals. While this is useful for pathogenesis is directly associated with genetic factors, this is not necessarily useful for diseases with multiple environmental factors or multifactorial diseases. Therefore, recent approach of research incorporates grouping and comparison of patients based on the presence or absence of disease-susceptible SNP, rather than comparison of patients with healthy persons. Therefore, it would be significantly beneficial to be able to respond to user's order like "I would like to have 3 cell lines with rsXXXXX C allele homo, T allele homo, and CT hetero." This will also lead to utilization of the results of the many GWAS performed in Japan.
 - Such an approach will promote research and drug discovery for multifactorial diseases. Large population of target patients with multifactorial diseases provides possible large market opportunities that highly motivate companies. A large number of patients will be benefited, and thus, it is expected that the contribution attributed to bioresources will be dramatically enhanced.
 - With regard to transcriptomes, Japan has a world-class cap analysis gene expression (CAGE) technology. By collaborating with the Functional Annotation of the Mouse (FANTOM) team, they will definitely obtain data to be internationally accredited. This will also lead to the creation of a more stringent catalogue of cell phenotypes.

- Since importance of immunotherapy for cancer patients and transplantation is increasingly emphasized today, enrichment of HLA information has a great significance.
- The Encyclopedia of DNA Elements (ENCODE) is an international integrated platform for omics data. If these data were linked with bioresources, then a truly unique global platform would be created.

Financial resources for implementing the aforementioned items may include increase of the in-house budget or establishment of projects funded by the Japan Agency for Medical Research and Development (AMED). However, specific proposals should be drafted by BRC.

- It is important to prepare modified ES cells and disease-specific iPS cells with high efficiency for the banking without sacrificing quality. The Division needs to examine the whole process to make it more efficient or to automate the cell preparation. Kawasaki Heavy Industry's equipment might be effective; but if their stable support cannot be obtained, another automation system should be searched.
- It is recommended that the Division should examine the efficient promotion of bioresources utilization by collaborating with companies or corporate groups.

2. SWOT analysis

(1) Are the results of the presented SWOT analysis valid?

- It is considered to be adequate.
- However, it could be analyzed with a larger perspective. The suggestions mentioned above in (4) could also be incorporated into the Opportunities. More items can be listed as Strengths.
- This may be too specific, but for example, the Sonoda-Tajima collection is a great Strength and they could aim at global coverage in the future if they could incorporate cell lines from Europe. If the HLA information and other accompanying information are gradually expanded, this can be included as greater Opportunity.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- The countermeasures are appropriate.
- The countermeasures could be analyzed with a larger perspective.
- To maintain a system for preserving and distributing iPS cells is a national project

for the development of science and technology in Japan, and hence we would like the Division to ensure constant funding.

- The AMED disease-specific iPS cell bank project is scheduled to be terminated in 2019. Continued support is required. The Division should keenly ask for understanding the necessity.
- Regarding the project that follows the ongoing one, partner should not only be limited to AMED but various opportunities need to be sought urgently, for example, with other agencies or as other projects and joint research with companies.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Division functioning as a hub of international scientific technology?

- The Division is actively working on and acting as an international hub for science and technology.
- As an ICLAC member, the PI is globally contributing to the improvement of research resources by enlightening the importance of improving the quality of cell lines as well as importance of the QC within each biorepository.
- Information concerning international collaboration is slightly scarce. We would like the Division to broaden the scope of international collaboration by actively sharing technology and information. With the presence of many similar international organizations, the Division should consider how to demonstrate the uniqueness of RIKEN BRC.
- As some international frameworks are needed for enhancing collaboration on resource information in the future, it is recommended that the Cell Engineering Division should ensure that it can lead global research community as it holds a world-class large number of disease-specific iPS cells.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- It is evaluated that Dr. Nakamura is fulfilling the PI's role in line with the BRC mission.

- The PI is not only committed to the operation with the cell line collection, but he has also rapidly incorporated disease-specific iPS cell lines into their collection, based on the trend that indicates increasing necessity and potential demand in the future. The number of publications by the users exceeds 1000/year and that of patents exceeds 100/year, which demonstrates the Division's constant contributions to all study fields from basic science to applied research. The PI is continuously raising the awareness of the importance of preventing microbial contamination and cell misidentification in appropriate handling of cells. As an ICLAC member, the PI is also contributing to the spread of proper research environments through international cooperation. Thus, Dr. Nakamura is fulfilling the PI's role at high level in accordance with the BRC mission, and these activities are serving the national interests.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- In each item, the PI's achievement has sufficiently met international standard.
- The PI's noteworthy achievements and the items to be conducted for future improvement are as follows.
 - (i) It is necessary to take some measures to increase the number of distribution in the future and to improve the efficiency of operation by promoting active use of preserved bioresources.
 - (ii) The PI is hosting regular training courses on human ES/iPS cells to support domestic research foundation.
 - (iii) The PI's contribution to society is regarded as significant as he serves as a member of the Expert Committee of Specified Embryonic Research, a subcommittee of Bioethics and Biosafety organized by the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) and he is committed to making national guideline policies and deciding future directions as an expert in the management and operation of bioresources.
 - (iv) It is necessary to improve the efficiency of operation by actively obtaining and commercializing intellectual property right and promoting fusion of different

fields.

***(3) Is the PI appropriately tackling the management and operation of the Division?
In addition, does the PI make efforts for training and development of young talent?***

- The PI is appropriately committed to management and operation of the Division as well as the training and development of young talent.
- The training and development of young talent is considered to be a particularly difficult issue; however, it is recognized that considerable efforts have been made and rewarded by achievements.
- We consider that human resource can be developed by making the best of special characteristics of the operation performed by the Division. We expect young talents not to stay in BRC but to take an active role in the world.
- It is desirable to examine how to develop the potential of mid- to senior-level staff, more specifically, how to develop human resources who can succeed current PI or act as his substitute in certain situations and how long it takes.
- The PI is striving to improve the careers of senior staff and to secure human resources.

The International Air Transport Association (IATA) courses and training on ISO9001 are also regularly performed, which serves as a basis for maintaining the integrated world-class biobank. We expect the PI to actively promote further improvement and reform of the project operations with an awareness of the Plan-Do-Check-Adjust (PDCA) cycle and to give us a report about his highly-motivated staff members actively participating in the project.

Division Name: Microbe Division
Division Head: Moriya OHKUMA

1. Achievements and plans for the Division

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- Based on the numbers of microbes collected and preserved, maintenance of type strains, numbers of distribution and users, the Division is reaching the international standards. Quality control, the wide range of various strains, and their contribution to Asian microbiology research are all of a high standard. Moreover, the Division is highly evaluated for undertaking major efforts rescuing for resource collections whose continuation is threatened. In particular, the Division's contribution to Asian microbiology studies should be noted. There are no problems in terms of improving added value of resources and compiling information.
- The Division is the world's second-largest in total number of type strains, and third in the annual number of deposition. Of the deposits, 75% comes from overseas, while 33% of distributing resources goes overseas. It is evident that the Division has reached standards of major bioresource centers of the world.
- The Division has been certified and maintained the ISO9001:2015 international standard quality management system and have reached global standards in terms of quality control.
- Between 2013 and 2017, resources distributed from the Division have contributed to the publication of 2,855 scientific papers as well as to 480 patents by the users.
- Every year the members of the Division have published over 30 scientific papers of their own.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The Division has made achievements contributing to the research community, which is clearly shown by the numbers of publications and patents, and commercialization outcomes, by the users. In addition, the publications of research results by the JCM members are commendable.
- Research papers using JCM strains and articles describing deposited strains with the JCM numbers have been published in leading scientific journals such as *Nature*. By responding to research needs, and by leading cutting-edge research, the

Division is making a large contribution to scientific research.

- As JCM strains have been used in many public patents and some of them have led to commercialized products, JCM has greatly improved not only technical development and innovation, but also people's lives and welfare.
- The following activities have created a positive spiral which contributes greatly to microbiology research in Asia: 1) deposits made by researchers from various Asian countries, 2) publication of deposited strains, 3) supplying resources to researchers in various Asian countries, and 4) the publication of research results using supplied strains.
- The Division is becoming an increasingly important microbial resource center for researchers, both within Japan and overseas. JCM has rescued valuable endangered microbial resources from other institutions both in Japan and worldwide.
- The Division is working on characterizations of holding strains, development of genome information, enrichment of the catalogue database, and raising value added in order to respond to the needs of users.
- Annual technical training course have been carried out on the handling of microbial resources. Also noteworthy are the public relations activities in academic societies.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- The major objectives to be achieved are based on performance during the last plan and are both appropriate and in line with the BRC's 4th Mid- to Long-Term Plan. In particular, the focus on the microbial collection of symbionts of plants and animals, and that relating to bioenergy and metal corrosion, is appropriate. It is expected that research in environmental and health sciences will accelerate.
- The Division plans to supply resources and services which are both sought after by multiple research fields, and in high demand from both basic and applied fields such as taxonomy based on genome sequence and health-related research. The Division's contribution in these areas help the center's development.
- The 4th Mid- to Long-Term Plan includes challenging R&D in addition to appropriate research plans. Besides the cross-centers all-RIKEN program, the Division is also acquiring external funds and participating in international projects.

These efforts will steadily advance the plan and will have substantial impacts on the center's development.

- Regarding its international hub function, international collaboration has been performed to analyze genome information for “type strains” of prokaryotes. This collaboration is commendable.
- They are also making leading efforts, such as introducing mass spectrometry to improve quality control.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?

- Expansion of their resource lineup to meet the various needs of society and research is an important initiative. Additionally, to improve convenience for users, it would be helpful to examine means enabling simple access to target resources in the catalogue database.
- Regarding the analysis of genome information for type strains, their participation in international projects has been appropriate, and this is expected to make a significant contribution.
- Classification of microorganisms is transitioning to genome sequence-based taxonomy faster than expected. It is necessary to support relevant researchers within Japan and overseas, and to develop infrastructure for the support.
- The Division has participated in the international project for analyzing genome information of prokaryotic “type strains” at the World Data Center of Microorganisms (WDCM). However, under the Convention on Biological Diversity, arguments have arisen insisting that not only genetic resources, but also sequence information, should be targets for access and benefit sharing. The Division ought to pay attention to the argument.
- Research plans focusing on difficult-to-culture or yet-uncultured microorganisms will lead to innovation through the application of microorganisms.
- Collection of difficult-to-culture microorganisms associated with animals such as humans and livestock, and those within plants and rhizospheres, should be prioritized from the perspectives of food, health, and environmental sciences.
- It is necessary to develop single-cell analysis platform that does not require culturing microorganisms. Of course, single-cell analysis technology entails the examination of single-cell genome. In addition, it is also important to develop technology for cellular evaluation, i.e., identification at genus and species levels as

well as function using single-cell imaging.

2. SWOT analysis

(1) Are the results of the presented SWOT analysis valid?

- These are reasonable.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- These are appropriate.
- The Division has already planned for collection of resources to meet needs. Positive results are expected.
- Collaboration with experts in genome analysis and informatics experts will be essential.
- In the next few years, staff who have been active in JCM for many years will retire. To construct a system for the next phase smoothly, efforts should be made to recruit and train young staff, to transmit techniques and knowledge to the next generation, and to resolve vertical splits of the JCM structure.
- The declining number of Japanese microbiologists may require responses and countermeasures. There seems to be a need not only to increase numbers of overseas users, but also for measures to prevent a decline in the number of Japanese researchers. For this, the Division should consider adopting measures by collaboration with relevant academic societies, while strengthening education and enlightenment activities.
- A countermeasure for the delays in the quality checks by gene sequencing of some microbial groups has been taken by the checks immediately prior to supply. However, it would seem beneficial to proceed with a certain number of checks each year for strains which are not asked for supplying.
- It would be good to self-assess the extent of their attainment, with specific examples of implementation and measures.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Division functioning as a hub of international scientific technology?

- International collaboration has shown results without problems.
- The Division is participating in a number of international projects, such as establishing a WDCM global catalogue, determining genome sequence of type strains, and analyzing genome information of budding yeast. Researchers in JCM have become many of committee members of international organizations (including the World Federation for Culture Collections (WFCC)); clearly, they are functioning well as an international hub for science and technology.
- The acceptance of overseas researchers and publication of collaborative papers with these researches are the evidence for JCM as an international hub.
- The Division has been actively taking on international exchange and collaboration, focusing on Asia in the Asian Network of Research Resource Centers (ANRRC), the Asian Consortium for the Conservation and Sustainable Use of Microbial Resources (ACM) etc. and has been demonstrating strong leadership.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- The PI is playing his role satisfactorily, in accordance with the BRC's mission, and continues to provide results in line with the BRC's 4th Mid- to Long-Term Plan. Aspects of this undertaking include the followings: 1) maintaining the world's top-level resources, 2) functioning as an international research hub, 3) contributing to broad research and development, spanning from basic to applied science, 4) implementing world-leading quality control and information dissemination, and 5) returning results to the research community and society.
- The catalogue database functions to provide a method enabling users to efficiently select the particular resources they require from a huge number of varying resources. However, its development may well be a topic for the future.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- The PI's research and development achievements meet international standards:

Regarding (i)

- Besides output, the PI is also having world-leading impact in numerous areas, including: 1) the number of microbial strains deposited and preserved, 2) quality control, 3) a large number of users' and of his own papers including cutting-edge research, 4) a large number of published patents by users, and 5) examples of commercialization.

Regarding (ii)

- The PI is carrying out collaborative studies in many fields. For example, as sub-leader of the all-RIKEN cross-centers program symbiosis, the PI leads the program and is producing many excellent results. The PI serves various committee members and chiefs, while making efforts to support research.

Regarding (iii)

- Through metagenomes, integrated omics, single-cell analysis, and isolation and cultivation of microbes, efforts are being made to open up new fields of research. These attempts include the construction of research platforms for symbiosis through combination and upgrades of cutting-edge technologies held by RIKEN. Results and achievements are commendable, and include the followings: 1) patent applications spanning topics relating to environment and food, 2) authoring explanatory articles in books, 3) being elected as the next president of the Japan Society for Microbial Resources, 4) acquisition of intellectual property right, as well as 5) social enlightenment and contributions.

(3) Is the PI appropriately tackling the management and operation of the Division? In addition, does the PI make efforts for training and development of young talent?

- The PI is working appropriately on team management and operations, and is making efforts to develop young talent.
- Using the ISO9001 system, the PI is redeveloping the conventional laboratory system, wherein only one individual is in charge of a group of microbial strains. Instead, he is shifting to a group system consisting of multiple individuals, aiming for information sharing and the standardization of roles etc. The management and operation of the lab is being addressed appropriately.
- The PI is training and instructing many postdoctoral researchers and graduate students. The promotion of laboratory staff is also emphasized, and the results of training a diverse range of young talent are highly valuable. Hiring postdoctoral

researchers using competitive funds, thereby increasing the flow of trained successors, is an effective approach in securing superb talent.

- From a long-term view point of increasing the number of microbiology researchers, it may be worth examining the possibility of the education of university graduate and undergraduate students by providing lectures and offering internships.

Gene Engineering Division

Division Head: Yuichi Obata/ Presentation by Takehide Murata

1. Achievements and plans for the Division

(1) Have the current achievements reached the standards of the projects (research) from the major international bioresource centers?

- The Division has the second largest number of bioresources in the world, and they are of the similar to or even higher level in diversity and quantity when compared with the world's major bioresource centers. The Division holds unique, versatile, high-quality, and comprehensive lineup of resources such as those developed in Japan, bacterial artificial chromosome (BAC) libraries of mouse strain C57BL/6N, and cDNA libraries comprising 80% and more than 50% of human and mouse genomes, respectively. By dealing with many intellectual property rights and licenses, the Division is enabling the distribution of various resources such as those with the Gateway system and fluorescent reporters. Recently, the Division has also collected the resources related to new technologies like CRISPR/Cas9-related vectors. It is also important that the Division is committed to maintenance, preservation, and provision of bioresources in compliance with the law, as a public institution. The number of distributed bioresources is increasing year by year.
- The Division maintains exceptionally high-quality resources and satisfies global standards. The Division has become internationally accredited for the quality control (QC) with a recall rate of 0%. Sequence confirmation is performed for the collected vectors, and the preservation and distribution procedures are thoroughly managed. Barcodes will be introduced for shipping management.
- It is important as an infrastructure for the research community that the Division acquires various information that accompanies bioresources, arrange and consolidate it, and make it available for users. This is also important for maximizing the active use of bioresources.
- It is of great significance as the world-leading bioresource center that the Division is actively committed to the development of novel bioresources and technologies necessary for the maintenance and preservation of bioresources within the BioResource Research Center (BRC), as it leads to improving ability and motivation of the staff as well as the quality of overall operation.
- The amount of distributed resources is one tenth of that of Addgene. This may be

partly due to the large differences in types of resources that are possessed and the scale of laboratories. However, it is necessary to analyze the main causes and make improvements.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The Division provides approximately 1,300 resources each year to universities, research institutions, and companies in a wide range of fields internationally, particularly focusing on medical and dental universities within Japan. The Division has made sufficient achievement. There are over 300 new users every year. The number of distribution to new users is also growing. In particular, the fact that the Division distributes resources to for-profit companies can be referred to as the Division's contribution to society and strength that is not found in Addgene. As the accomplishment of the resource distribution, approximately 100 papers are published every year, and thus, the Division is contributing to the development of academic research in Japan.
- It is appraisable that the Division is focusing on further expanding Japan's original bioresources and promoting their active use by approaching researchers within Japan and overseas and asking for the deposition of the unique bioresources they established.
- The Division has made a constant contribution to research community, but it is expected that the Division will give more impact by further increasing the number of collections and raising the quality of bioresources to be distributed. It is also necessary to secure budget achieve this.
- The Division is hosting technical training courses for research community as well as lectures and events for the public.
- It should be noted that there are only few repeat users.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- Current activities and plans are in line with the mission of the 4th Mid to Long-Term Plan and generally appropriate. They are being operated appropriately and will contribute to the development of the center.
- There are some situations to be noticed, such as the emergence of Addgene,

- It would be desirable to more actively promote joint research with domestic and international research institutions. Moreover, in order to further promote utilization of bioresources, it is necessary to make efforts to increase the number of repeat customers. To achieve this, it is important to create next opportunities for the users to request resources by encouraging them through the value of the BRC, which will be raised by increase of resource lineup, rapid distribution of high-quality resources at low cost, periodic delivery of information on the applications and newly added resources, and improvement of search function.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?

- Novel genetic materials that never existed before have emerged with newly-developed technologies such as barcode technology. Whether or not these materials should be collected and distributed is a matter to be discussed in the future, and it is necessary to exchange information with researchers who are developing such technologies.
- The Division needs to be engaged in cost-effective challenges using cutting-edge technology, making a clear distinction from private entities.
- In recent years, endeavor is being made toward realization of personalized medicine. In this context, researchers in medical research on diseases and drug discovery for the treatment are elucidating pathological mechanisms based on more detailed disease segmentation and conducting more detailed research for individuals with different genetic backgrounds and complex environmental factors. Therefore, the clinical samples and bioresources derived thereof that are characterized with individual variants and the differences with genetic backgrounds are becoming increasingly important. It is desirable that the BRC is equipped with not only the bioresources as "references" for classifying "wild-type," "normal," and "healthy," but also those with more complexity and genetic diversity that can be characterized as "disease," "variants," and "polymorphism".
- It is also important to add and consolidate various information associated with bioresources for increase of their value. Information on the relationships between diseases and genetic variants/polymorphisms as well as genetic characteristics and omics information of cell lines and model mice greatly stimulate researchers in selecting research materials. Accompanying information should not necessarily be

prepared by the BRC itself. In recent years, databases of various research results have been compiled, and there exist widely-used databases for each research field, such as the NCBI's Gene, OMIM, ClinVar, and dbSNPs databases in the US as well as the Sanger Institute COSMIC database in the UK. By strengthening the linkages with such external databases, researchers would be directed to the information on BRC bioresources when they consult articles and databases, and naturally they will be actively using the bioresources.

2. SWOT analysis

(1) Are the results of the presented SWOT analysis valid?

- They are reasonable.
- Comparison of the Division with Addgene in the SWOT analysis was very informative. There are many common features in that they both operate a biorepository, but as a public institution, the BRC is clearly different from Addgene. It should be more emphasized that BRC is actively engaged in the development of novel bioresources and new technologies for preservation and active use of bioresources and in technical support and human resources development for related organizations in Asian countries, which makes the BRC distinguished from Addgene, merely a bioresource supplier.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- The countermeasures are appropriate.
- "Selection and concentration" of resources is necessary.
- It is necessary to increase the numbers of distributed and utilized bioresources by further enhancing dissemination of information to users and promotion of active use.
- The Division should not hesitate to vigorously adopt the merits for which Addgene is highly evaluated, such as the simplicity and speediness of procedures, free from their conventional operation while maintaining their QC and reliability that only the BRC can provide.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Division functioning as a hub of international scientific technology?

- The Division is actively committed to international collaboration.
- The Division is playing a pivotal role in Asia, exchanging information with the staff of relevant divisions in other repositories at the international meeting of the Asian Network of Research Resource Centers (ANRRC).
- RIKEN BRC functions as an international hub for bioresources, together with the biorepositories in Europe and the US, and its activity is regarded as a model project in developing countries. However, in recent years, efforts to retain bioresources within their own countries are fueled up, and the promotion of international cooperation, particularly with other Asian countries, is an important issue.
- Regarding cooperation and sharing with resource centers in other nations, the BRC should ask them to conclude an agreement that resources developed in Japan should not be deposited to Addgene but to the BRC. It would also be beneficial for research centers to cross-link their home page's URLs, to ensure that both parties' resources can be searched at the same time.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- The PI is fulfilling the role.
- It is appraisable that the number of distributed bioresources has consistently exceeded 1,200 items every year over the past 6 years. Moreover, the Division is endeavoring to enrich necessary information for promoting active use of bioresources as well as to collaborate with other databases such as Kyoto Encyclopedia of Genes and Genomes (KEGG) and PubMed for enhancing usability.
- Identification of resources and confirmation of their authenticity are extremely important for securing the reliability that forms the basis of the bioresource center's operation. Such QC can only be possible with careful work by the devoted staff members, and we would like to express our respect to the PI that he is sincerely and decidedly committed to the QC, without neglecting its significance.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- The Division is collecting and distribution resources that have high utility value. The research outcomes and achievements of the Division, support for research activities, and social contribution are sufficient. Moreover, the Division is fulfilling the mission through close collaboration within RIKEN,
- (i) Consolidation of meta-information and sequence information is steadily advancing in the Gene Engineering Division, under the slogan "No information, no bioresources." However, it is disappointing that the analytical results of the data do not appear to be updated frequently. Moreover, examples of the cases where BRC resource is used and the achievements by the users are being posted in the BRC website as articles both in Japanese and English, and it is necessary to further increase such opportunities for promotion.
- (ii) The Division has a potential to further develop in the aspects of providing research support and pioneering new fields of research. It is hoped that the Division will restructure the organization so that research-supporting staff members are fully committed to collecting and maintaining bioresources and that researchers can focus entirely on pioneering new fields. It would be desirable that the Division should release a unique research outcome generated with RIKEN's full capacities; for example, such as novel research using differentiation reporter markers.
- (iii) Recent decline of interest in science among young people is a serious problem. Information dissemination and public relations (PR) activities for the general public, such as the events "Tsukuba PhD kids program: science experiment classes," "lectures for high school students," "facility tour for middle and high school and university students," "Open campus day during Science & Technology Week," and "Science lectures for adult citizens," are simple but highly significant activities that will not only facilitate understanding and education of local residents but support the foundation of Japan as a nation with top science and technology. We look forward to the BRC's continuous activities for social education in the future.

***(3) Is the PI appropriately tackling the management and operation of the Division?
In addition, does the PI make efforts for training and development of young talent?***

- The PI is constructing and operating a system that complies with laws pertaining to exports.
- As a part of training for young staff, the PI is actively encouraging the Division's members to conduct the following activities:
 - To participate lectures for qualifying the ISO9001 Quality Management internal auditors,
 - To survey users' papers,
 - To draft brief flyers to be distributed for PR at academic conferences as well as online articles for introducing focused bioresources, and
 - To participate in major academic conferences.
- To further develop and pioneer new fields of research in the future, we would like the PI to recruit diverse young staff and actively promote personnel exchange.

Division Name: Integrated Bioresource Information Division

Division Head: Hiroshi MASUYA

1. Achievements and plans for the Division

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- The access count of the BRC website is almost equal to that of Protein Data Bank Japan (PDBj), indicating that the Integrated Bioresource Information Division reaches the international standards in this aspect.
- Multifaceted efforts by the Division in total are leading the world.
- RIKEN BRC is well recognized by researchers within Japan and overseas. Its website that functions as its gateway to the BRC contains sufficient content and function.
- By participating in the International Mouse Phenotyping Consortium (IMPC) and distributing mouse resources and information, BRC is reaching the standards of the major bioresource centers in the world. The Division has contributed greatly to this achievement.
- The Division is working to attain international standards of all the aspects of its operation.
- The Division is working to establish the information infrastructure for disease research and to integrate mouse phenotype data and disease information. These efforts should be highly evaluated.
- It is recommended that the Division should grasp and analyze users' situations.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- Satisfactory achievements have been made.
- The access counts of the BRC website are steadily increasing. This is a clear indication that the Division is contributing sufficiently to the community.
- To confirm the contribution of the Division, detailed analysis of database usage log and the outcome by outside users should be conducted, separately by such elements as users' country of origin and academic/commercial entities and research fields.
- For the field of genomic clinical research of rare diseases, the Division has integrated disease information and mouse phenotype data using Human Phenotype

Ontology and Monarch Disease Ontology. As the result, users are able to search for bioresources by disease name on the BRC website. This is a clear indication of contribution of BRC to the society and the research community, both within Japan and overseas. There are only few researchers who can make such contribution in Japan.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- The Integrated Bioresource Information Division aims to “promote use of bioresources by information technology.” The Division planned the following three programs: 1) improvement of homepage contents, 2) data integration and standardization, and 3) big data analysis and data visualization. These plans are appropriate and will greatly contribute to the center's development.
- It is particularly important to develop information technology and to strengthen the information infrastructure to extract information and value from resources. It may be difficult to implement homepage enrichment and metadata integration with a limited budget and human resources. To overcome this problem, it is necessary to have cooperation from all Divisions in BRC.
- Regarding enrichment of BRC homepage contents, there are plans to reduce the number of servers and labor while making enhancements. Although it will take a great effort, steady progress is anticipated including consolidation of homepage contents.
- Metadata integration, international standardization, and development of search system across the BRC resources are the major efforts toward the development of the new web catalogue of BRC. These are leading the development of data utilization infrastructure for bioresources.
- Big data analysis and visualization technology should be developed by the Division but not by private companies. This is a unique and meaningful way for RIKEN BRC, the public entity.
- The implementation of the metadata integration and cross-search is core project of the Division. Progress should be measured by some metrics that enable the comparison between achievements and the plan.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?

- Automation of updates of Web contents.
- Follow-up survey on how the distribution of bioresources and information has contributed to the society.
- Development of indicators for reassessing the quality of data provided.
- Strengthen the security.
- For design and development of a sustainable system, investigation of possible use of the cloud and SaaS (Software as a service) systems and a data analysis environment.
- Performance issues should be addressed at the early stage of the Mid- to Long-Term Plan because they may occur with increased traffic.
- To ensure long-term quality of Resource Description Framework (RDF), it is recommended that the Division should examine continuously setting metrics as follows: 1) sufficiency and appropriateness of annotations; 2) relevance of searches and commonality with other databases; and 4) constant monitoring.

2. SWOT analysis

(1) Are the results of the presented SWOT analysis valid?

- They are reasonable.
- It represents a step in the right direction towards data integration, although there are weaknesses in RDF technology. It is important to integrate data as data + ontology, as RDF technology is not essentially important.
- Similar issues have been pointed out as weakness and threat for many other data centers. As the strength of RDF-related technology is generally difficult to understand, easy explanation should be given for data integration research community.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- It is appropriate.
- It is necessary to make plans for the Division to grasp user needs.
- Because target fields are particularly broad from medicine to agriculture, it is difficult to grasp users' needs by the Division alone. This is an issue that must be

examined by whole RIKEN BRC.

- It is necessary to prioritize research plans in consideration of budget and human resource issues.

3. International exchange and cooperation

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

- The Division is actively undertaking eight international programs, including the Monarch Initiative, and seem to be functioning appropriately as a hub for science and technology internationally.
- Collaboration with external databases for sharing of metadata and implementing cross-searches can be developed in the future.
- Head of the Division is expected to demonstrate leadership, to promote Division's work more actively, and to increase international activities.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- The PI is fulfilling that role.
- The PI is pursuing research and development which contributes to the application and development of basic technology for preservation and utilization of bioresources. Moreover, considering societal and research needs, he has also prioritized the collection, preservation, and supply of bioresources of the world's highest standards. These initiatives are part of the BRC's 4th Mid- to Long-Term Plan. The PI is satisfactorily fulfilling the mission from the perspective of data resources, and he has great potential for the future.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different

fields, and social contribution.

- International standards are being attained in each of (i)-(iii).
- The PI is meeting all three aspects of the international standard, especially by focusing on (ii).
- Development of the system allows users to search bioresources by disease name is particularly useful. The PI reaches international standards in the aspects of impact, mission, and novelty.

(3) Is the PI appropriately tackling the management and operation of the Division? In addition, does the PI make efforts for training and development of young talent?

- The management and operation of the Division is appropriate, and training of young talent is also being put in practice.
- The PI is working appropriately to recruit researchers for big data analysis. Personnel for metadata integration and data consolidation, as well as annotators and curators, should be employed stably at RIKEN.
- Since difficulties may arise in transferring personnel from pre-existed laboratories, the Director of BRC must take care of operation of the Division.

Reference 7

Evaluations and Comments for the Division/Teams by Domestic Review Committees

Division Name: Bioresource Engineering Division

Division Head: Atsuo OGURA

1. Achievements and plans for the Division

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- The Division is developing various technologies that are necessary for improved efficiency and advancement of Bioresource Infrastructure Projects. Furthermore, the fact that they continue to be an internationally accredited division is highly valued.
- In all the following novel basic technological development projects: 1) improvement of cryopreservation technology, 2) novel development of micro-insemination (ICSI) technology, 3) development of nuclear transfer cloning techniques, 4) development of novel stem cells and model animals, and 5) developmental biology research, the Division has had an excellent accomplishments and the Division is releasing information on all developmental bioengineering technologies to all over the world.
- Induction of superovulation from rare female mice through anti-inhibin antibodies and estrous cycle synchronization as well as the improvement of micro-insemination (sperm injection) and nuclear transfer cloning techniques are considered to be internationally accredited and highly ranked.
- The originality of the newly developed resources is highly regarded, including novel mouse models of allergies generated by nuclear transfer cloning using antigen-specific T cells, genome editing using a wild-derived strain (MSM), and knockout hamster lines etc.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The Division is supporting the research community by providing internationally

accredited knowledge and techniques in reproductive engineering research and the Division is making a large contribution to the research community within Japan and overseas.

- The Division has contributed to various areas of the research community through press releases, the current technology on the homepage, lectures in symposia, books, journal editing (chief editor for two journals), research collaborations. More specifically, the Division has participated in projects that are developing new methods for the preservation of gametes and embryos.
- In technical training backed by their advanced techniques, including a fundamental course on the cryopreservation of mouse sperm and embryos as well as a practical course on micro-insemination, the Division is meeting the needs of society and the research community. This has been highly valued by participants.
- The Division has contributed to society by teaching many graduate students and researchers, accepting high school and university student visitors, as well as providing outreach activities such as lectures for graduate students in universities.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- In the BRC's 3rd Mid to Long-Term Plan, the Division made solid and satisfactory achievements which were highly evaluated. The Division's current and future plans are based on these achievements, in line with the BRC's 4th Mid- to Long-term Plan. Their plans target the continuation and development of the following six areas of technological developments/researches: 1) cryopreservation, 2) micro-insemination, 3) nuclear transfer cloning, 4) generation of novel stem cell lines, 5) generation of novel animal models, and 6) developmental biology. The Division's current and future subjects to be addressed have been clarified and incorporated into appropriate plans. It is anticipated that they will contribute to the development of the center in the future.
- We look forward to the success of the research objective, positioned by the PI as challenging. In particular, the identification of the factors regulating the genome plasticity of the 129 strain and the results from the TS cell research are expected to be highly influential.
- Through the emergence of the CRISPR/Cas9 system, it is necessary to provide gene modification techniques and to establish research resources in animal species

other than mice. The Division has succeeded in the generation of a genome-edited hamster and the Division is expanding studies to take advantage of the hamsters' characteristics, which will undoubtedly contribute to the center's Mid- to Long-term development.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?

- Whilst male germline stem cells are consistently established and supplied, female germline stem cells have not been established so far. Their plan to establish the female germline stem cells from female primordial germ cells (PGC) is challenging, but if this is achieved, it will bring a significant impact.
- The transfer of established technologies to domestic research institutions is an important objective for raising their level.
- The development of anti-inhibin monoclonal antibodies will make a large contribution to the BRC and outside researchers. It will also be important for animal welfare. Therefore, it is hoped the Division will complete it by all means.
- In the field of genome editing, it is recommended that the Division will promote the advancement in basic technologies, such as improvements of micromanipulation and electroporation technologies, which may lead to the development of novel and unexpected application of technologies in embryology research.
- It is recommended that technical support and guidance for production of genetically modified hamsters will be provided by the center, as this technique cannot be easily acquired by other researchers.

2. SWOT analysis

(1) Are the results of the presented SWOT analysis valid?

- They are adequate.
- The Division's analysis on the fact that each staff member is burdened with a little excessive number of themes, which was pointed out previously, and their measures against it are considered to be adequate.
- Although the research objectives have been organized, we think it is true that the PI is currently overworked.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- It is appropriate.
- Steady plans are being made based on the achievements that they have made.
- The PI keeps considering introducing the recent acceleration of advanced analyses such as next generation sequencers into the embryology field, as was recommended in the last committee meeting.
- Reducing the PI's duties of academic societies is an effective countermeasure. However, as members of academic societies, we would like to ask him for continued contribution to some extent.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Division functioning as a hub of international science and technology?

- The Division is actively carrying out international research collaborations, which leave nothing to be desired more.
- The PI of the Division was committed to the operation of the World Congress on Reproductive Biology 2017 as the program chairperson and was appointed to the chief editor of international journals as well. These activities are recognized as significant contribution.
- The Division is accepting and sending many researchers, and thus, functioning as an international hub for science and technology.
- The Division is playing a pivotal role and is an important laboratory in this country. The PI is important researcher for Japan's germ cell research.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- The PI is developing highly original reproductive bioengineering technologies and providing them within BRC as well as outside of BRC, and his achievements have exceeded our expectations.
- As the core of the BRC, the PI can be evaluated as fulfilling the role in line with the mission to a high standard in regard to the fundamental technology of bioresource engineering and bioresource-related research and development. We hope he will

publish his achievements of international level in this Mid- to Long-Term Plan.

- As the PI's global position shows, his nuclear transfer cloning technology has a reputation for being highly specialized. We would like to recommend that he should have a vision that focuses on the further technical development of nuclear transfer cloning, its potential development as a bioresource, and the utilization of these techniques for other subspecies-derived mouse strains other than B6. We look forward to the future applications of the memory T cell clone mouse.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

Regarding (i)

- The impact of the stable cloning technology is highly regarded internationally, and the technology is satisfactorily contributing to the strengthening of the collaboration within RIKEN.
- In recent high-impact paper, the Division used epigenetic techniques to clone neural cells that previously could not be cloned (Mizutani et al. Biol Reprod 2015;92:81). The Division is consistently improving cloning technology, including in the aforementioned paper, and is internationally outstanding research group for cloning technology.
- The impact brought by anti-inhibin antibody utilization meets the international standards.

Regarding (ii)

- This Division functions as a hub for domestic germ cell research, and the PI is irreplaceable with other researcher because of his unique contribution.
- On the PI's support to the research conducted in other facilities and his involvement in the All RIKEN Project, we would like to see definitive descriptions on the collaborations and the output.

Regarding (iii)

- They meet the international standards.
- Remarkable results have been produced by his recent genome editing research on hamsters. These results could not have been anticipated from the

mouse studies. As he reported that this technology has led to interdisciplinary collaboration with researchers in hibernation, further joint research with different researchers can be expected.

- The PI has planned proliferation of female germ cells, which demonstrates his strong motivation to pioneer new fields of research. It can be expected that the outcome may directly lead to the acquisition of intellectual property rights as well as social enlightenment and contribution.
- The commercialization of anti-inhibin antibodies can be expected.
- It is difficult to evaluate the PI's achievements in the fusion of different fields.

***(3) Is the PI appropriately tackling the management and operation of the Division?
In addition, does the PI make efforts for training and development of young talent?***

- The PI is committed to the management and operation (personnel allocation and role allotment) of his Division appropriately.
- The PI is committed to the development of young talent. Young researchers in his Division have published their results in original papers. They have won competitive funding and awards, attained positions and are playing active roles. Thus, favorable results of young talent development have been attained.
- As bioresource engineering techniques are important, we hope that they are succeeded to many young researchers. Also, we hope that the PI will further commit to the acceptance and guidance of graduate students.

Team Name: Technology and Development Team for Mammalian Genome

Dynamics

Team Leader: Kuniya ABE

1. Achievements and plans for the Team

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- The Team is reaching the global standards for research by obtaining excellent achievements in the following points: (i) output and impact of research, (ii) specific missions such as research support and the RIKEN internal cross-collaboration program, and (iii) pioneering research fields, acquisition of intellectual property rights and commercialization, social enlightenment, merging of different fields, and social contributions etc.
- The Team is developing valuable initiatives for the development of novel resources by using techniques such as epigenotype analysis and genome modification to further clarify the control mechanisms of development.
- Through Wnt signal inhibition, they have established a highly efficient method for creating EpiSC lines, and have succeeded in the maintenance and homogenization of induced pluripotent stem (iPS) cells in an undifferentiated state. These have been used as a bioresource in quality control systems.
- The development of epiblast stem cell (EpiSC) and the cell phenotyping technology utilizing AI based on cell morphology are important for resource developments.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The Team is conducting international collaborative research and producing research results of the global standards.
- Since the Team is collaborating with companies for technological development, the Team should consider strengthening further collaboration with industry.
- Not only creating an environment that can supply the naïve and the primed stem cells, but also the Team has made consistent achievements by publishing research article and reports.
- The Team has published some of their results by the joint research and development projects with companies and other institutions, by establishing cell

lines for visualization of DNA methylation and generating a high-brightness luciferase genetic resource.

- As academic activities, the PI has served as the Secretariat of the International Mouse Genome Society since 2017. Moreover, he has been appointed three professor positions tasked with educational activities and has had a good record. The PI serves as a professor of the Cooperative Graduate School and the Collaborative Graduate School of the University of Tsukuba, Japan, and a visiting professor of the Universiti Sains Malaysia.
- It is necessary to advertise their achievements and the possible applications by showing the numbers of resource distribution and of citation of their methodology papers.
- How far actual developments can be made regarding distribution of resources to researcher communities within Japan and overseas and the promotion of joint research are issues for the next phase. It is necessary to clarify the objectives by making a road map of research plans.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- A plan has been formulated in line with the issues pointed out for the achievements of the 3rd Mid- to Long-Term Plan. The Team plans to develop a cell image processing technology as a cross-sectional project within RIKEN. This plan is appropriate and takes advantage of each participating team.
- The research plan is in line with the mission of the Bioresource Infrastructure Divisions "Understanding sophisticated biological phenomena, improving human health, and overcoming disease", and it may contribute to the development of BRC.
- When the plans of the Team are accomplished, significant progress will be made to the current cutting-edge technologies including the analysis of higher-order functions at cell levels and whole body level of animals, and the analytical systems for disease-related gene networks. The results may, therefore, contribute to the development and production of mouse strains and human iPS cell lines in which a whole target pathway is collectively controlled.
- The plan to construct a system that noninvasively assesses the state of iPS cell differentiation using time lapse imaging and machine learning is valuable. There is

a high possibility that the construction of a gene expression control system, using CRISPRi and CRISPRa, will be widely used by the research community. If noninvasive detection of epigenomic changes can be achieved, it will greatly contribute to the research community.

- The Team is putting significant effort into the development of advanced novel technologies, such as single-cell analysis and allele-specific gene expression analysis. It is appreciated, but they seem to be too much with introducing new technology. They must consider focusing and balancing their efforts.
- The Team is focusing on the development of technologies that standardize and analyze iPS and Germline Stem (GS) cells developed in Japan, which contributes to the Center's advancement. However, sufficient materials are not presented to evaluate if it actually contributes to the supply of resources and technologies from BRC.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-term Plan?

- It would be appreciated if cell image processing technologies are actively promoted.
- A new plan aims to develop a technology for detecting epigenomic changes in individual cells noninvasively and for analyzing the time-series changes as well as to develop bioresources relevant to these technologies. They are of great use for research on environment-genome interaction and aging process. These are highly anticipated areas of research that would enable the screening of influential environmental and aging factors.
- The above project faces many issues in the supply of resources, including the research and development of core technologies and the development of EpiSC. The Team should focus on the proposed technological developments and consolidations.
- The main research plans of this Team are epigenomic imaging and gene regulation. The both are highly needed. The Team should conduct the original research in order to be an international leader in this field.

2. SWOT Analysis

(1) Are the results of the presented SWOT analysis valid?

- The results of the SWOT analysis are appropriate.
- The hiring and keeping superb talent is necessary for the development of cutting-edge technology. However, when the staff members find out a good career to pursue, they should be pushed forward from the perspective of the development of young talent. Although this analysis is theoretically valid, this may be a difficult issue to resolve in practice.
- It is better to clarify that which personnel is in charge of each objective and to define their role in each objective.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- The PI's term is limited, and it seems to be difficult to secure employees.
- The project plans appropriately reflect the results of the “Weaknesses” analysis that “targets are diverse, and cannot necessarily be completed by his own team” and “the number of his staff is currently too small.”
- From the various diverse project plans, it is important to select and focus on highly-original technological development. Moreover, it is also desirable that projects will include dissemination of the developed cutting-edge analysis technologies and resources to the research community.
- The response to the lack of human resources, by engaging in joint research within RIKEN is appropriate.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Team functioning as a hub of international science and technology?

- This is being actively addressed, such as hosting a summer school.
- Individual joint research collaboration has been successful and highly appreciated over a long period.
- It would be beneficial if there were more international exchanges such as technical guidance and seminars.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- The PI is fulfilling his role in line with the BRC mission by contributing to three areas: (i) the production of novel resources, (ii) the development of technology to analyze resource characteristics, and (iii) internal collaboration within the center.
- It is necessary to appeal to companies and the research community on the utilization and potential applications of the developed technology and to promote its use as a resource.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- The achievements of the PI's research and development have met the international standards based on these three perspectives:
- The dissemination of the information from their research, collaboration within RIKEN, and acquisitions of intellectual property rights have been sufficiently conducted.
- It is necessary to publicize these results.
- New technologies should be proactively introduced to companies.
- As for the contribution to society and social enlightenment, it should be proceeded by the whole center, not just by a single team.

(3) Is the PI appropriately tackling the management and operation of the Team? In addition, does the PI make efforts for training and development of young talent?

- The PI is appropriately handling the management and operation of the Team. In addition, in the training and development of young talent, the PI has demonstrated accomplishments including researcher promotions, education of graduate students, and acceptance of international graduate students.
- A more accurate evaluation will be possible if the information on the carrier path of alumni from the Team is available.
- The replenishment of manpower is necessary to achieve the goals set out in the

research plan in the 4th Mid- to Long-Term Plan.

Team Name: Technology and Development Team for Mouse Phenotype Analysis
Team Leader: Masaru TAMURA

1. Achievements and plans for the Team

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- The Team is playing an important role in line with BRC's mission. The Team has been participating in the International Mouse Phenotype Consortium (IMPC) and its research projects are reaching the standards of the major bioresource centers in the world.
- In the IMPC project promoted by collaboration of 20 research institutions and funding agencies in 14 countries and regions worldwide, RIKEN BRC has been sharing the work of phenotypic analysis of 250 lines of knockout mice.
- It is difficult to operate constantly a phenotyping pipeline of high standard, but the Team has been carrying out well. The followings are highly appreciated as achievements in the research and development of phenotype analysis of the mouse: 1) results of the IMPC Early Adult Pipeline, the IMPC Late Adult Pipeline, and the IMPC Embryonic Lethal Pipeline; 2) the development of a new imaging technology for micro X-ray CT imaging; and 3) the development of method for high-resolution imaging. Achievements of the above results and developments can be highly commended.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The IMPC's results were published in the well-known high impact journals, indicating that the Team is performing competently.
- It seems necessary to examine whether the IMPC's results are being well-utilized by Japanese researchers.
- By providing Japanese researchers with opportunity to analyze their mouse strains by the world-class phenotyping pipeline via the “Japan Mouse Clinic,” the Team has been contributing to the Japanese research community, and to the strengthening of the Japanese research.
- The Team is disseminating the phenotyping methods named “SHIRPA” as well as advanced imaging technology of X-ray micro-CT.

- Phenotypic analyses at the Japan Mouse Clinic have exceeded 150 mouse lines developed by researchers out of BRC, and the number of deposit lines is steadily increasing. However, the number of publications of the results of these lines is currently limited. This requires improvement.

(3) Are they appropriate current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- In the 4th Mid- to Long-Term Plan, this group is expected to play an important role in fulfilling the center's mission of international contribution and collaboration. Based on the results of the 3rd Mid- to Long-Term Plan, the Team's efforts will be centered on the IMPC. Regarding development of new disease model animals, it is anticipated that the Team will support the center's activities through joint research and the provision of technology to research groups within Japan and overseas.
- Current activities and plans include phenotyping gene knockout mice, from the embryonic stage to old age, using a world-class phenotyping platform. This concurs with the 4th Mid- to Long-Term Plan, and it will provide great contributions to the center's advancement.
- The continuous phenotyping with the comprehensive pipeline, development of telemetry analysis for behavior phenotype align with the 4th Mid- to Long-Term Plan. The plans are considered to be appropriate and contribute to the center's development. Moreover, based on their unique achievements, development of high-resolution soft tissue X-ray micro-CT analysis and new contrast agents for the X-ray micro-CT is promising plan with high originality. These proposed developments are expected to raise quality standards, and the resulting analytical methods will be used widely among the research community.
- The Team plans to produce physiological, behavioral and morphological phenotype data, which improves the quality of bioresources. These resources are expected to be widely utilized by the research community.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-term Plan?

- New plans include developing new technologies to detect longitudinal change of

phenotype and to comprehensively analyze mouse resource characteristics as follows: 1) analysis of physiological change with ageing (telemetry analysis); 2) analysis of behavioral change; 3) analysis of morphological change; and 4) the development of a new contrast agent for X-ray CT and method of gene expression imaging. Phenotypic information on disease model mice, which will be obtained by these new technologies, is expected to advance and improve quality of the mouse resources.

- The development of a behavioral phenotype pipeline is much-needed by the society. Yet, it is also necessary to fully consider cost-efficacy. It is thus recommended that telemetry analysis should progress concurrently. It is desirable to devise a system incorporating industry-academia collaboration. Moreover, such a system ought to advance joint research with engineering departments of domestic universities that are carrying out related technological development.
- Regarding high-resolution soft-tissue X-ray CT analysis, and the development of new contrast agents, it is necessary to consider ways of strengthening collaboration with the disease research community and promoting resource use.
- The timely updating of equipment is an important topic. The Team should make efforts for continuous equipment renewal using various methods (such as the free loan of equipment developed through joint research).
- Though it was a topic of debate in the 3rd Mid- to Long-Term Plan, it is important to establish beneficiary charge system for the on-demand phenotyping by Japan mouse clinic that is conducted to accommodate requests from outside scientists, for continuation of its operation. The charge system should be examined.

2. SWOT Analysis

(1) Are the results of the presented SWOT analysis valid?

- They are generally adequate. The issues to be resolved have become clear.
- The development of young talent is an important topic. Superb young talent will not come if they cannot envision a subsequent career path. Accordingly, the PI must help young researchers to develop a clear career path.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- The Ogura's laboratory in BRC is doing an excellent job carrying out talent development. In this regard, it should be referred to as a model case.

- It is also necessary to appeal to disease researchers, including the medical community, to further improve resource promotion.
- While some operations can be automated, e.g., imaging analysis. On the other hand, there is an urgent need to fulfil those duties (such as dissection) that cannot be replaced by machine. Therefore, intense deliberation has been directed towards allocations within the budget, and the improving plan is reasonable. It is recommended that some of running costs will be secured by the AMED project, academic-industry collaboration, beneficiary charge and others.
- The issues of securing and developing young talent are concerns shared by universities. Examining their salary and the content of duties are necessary steps in resolving these issues.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Team functioning as a hub of international science and technology?

- The Team is participating in the IMPC and AMMRA/AMPC, and is also committed to ensuring a presence in Asia. Thus, the Team is functioning well as an international science and technology hub.
- Data from the Japan mouse clinic could be more useful and utilized more often if the data are linked to those of the MGI and IMPC.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- Considering the PI's participation in the IMPC, his role is in line with the BRC's mission.
- The Team leader is contributing to the BRC's mission by directing development of novel methods such as X-ray micro-CT technology, and the development of contrast agents.
- The Team leader needs to respond to the self-evaluation regarding delayed publication of the results of Japan mouse clinic.

(2) Do the PI's achievements in research and development (R&D) satisfy

international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- The PI is performing satisfactorily in terms of the above all three perspectives.
- When a new technology is developed, it must actively be transferred to commercial entities.
- The results of international joint research have been published in high-impact international journals. Research support, RIKEN internal collaboration, and social education activities are also being carried out steadily. Such activities are satisfying international standards.
- IMPC is exceptionally important in establishing research infrastructures, although the result of each project of IMPC has little impact. On this point, it is excelling. If the method of phenotype analysis with telemetry were developed, the committee hope that it will be international standard protocol.
- Due to the lack of documentation, the achievements of the acquisition and commercialization of intellectual property is unclear.
- Regarding social outreach on science, it is necessary to strengthen activities which focus on a broad range of research fields.

(3) *Is the PI appropriately tackling the management and operation of the Team? In addition, does the PI make efforts for training and development of young talent?*

- The Team lacks a sufficient number of researchers who are able to conduct phenotyping of large number of mice. Securing new talent and developing young talent has not progressed in these early stages. It is necessary to improve on this. There are issues in the mechanism for recruiting new talent. Young talents will not come if they are not sure they can build a career path. It is necessary for the PI to create career paths for them.
- The PI has acquired competitive funding and he is giving technical classes and lectures.
- Phenotype data is likely to be used more widely by the research community in the future. Therefore, it seems necessary to further strengthen information dissemination not only to basic biology researchers, but also to clinical researchers.

Team Name: iPSC-based Drug Discovery and Development Team

Team Leader: Haruhisa INOUE

1. Achievements and plans for the Team

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- The Team has established differentiation induction techniques and various cell evaluation techniques necessary for an approach making use of disease-specific iPS cells. The Team has produced most excellent results in this field. The Team's status is assessed to be a top-level laboratory of the world.
- In addition to banking the world's largest number of disease-specific iPS cells, it is also commendable that the Team has been disseminating methods for the use of the iPS cells. Dissemination of the information on "development of the basic technology for drug discovery, using iPS cells" by publication of many papers is also highly regarded.
- As a member within the BRC, the Team may be able to execute research and offer contributions with comparatively few problems. Nonetheless, the Team needs a thorough examination of and focus on what should be done as a BRC-related projects.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- Research has already been advanced to the development of disease-specific iPS cells to delineate the causes and processes of diseases. The Team has started to develop fundamental technologies for drug discovery using disease-specific iPS cell. Research has been carried out with a good balance between diseases with many patients worldwide, such as Alzheimer's disease, and rare diseases. It is hoped that this Team will make great contribution to social benefits. Although specific results have yet to be delivered, openness toward seeking collaboration with pharmaceutical companies is commendable.
- The Team has a track record of registering valuable disease-specific iPS cell lines in the global stem cell bank network. This is recognized as an extremely valuable contribution to domestic and international research communities. Activities for promoting use of iPS cells by research communities, such as by giving shared ID numbers are laudable. Regarding iPS cell lines deposited in the bank of overseas,

It is hoped that the Team will continue the effort to establish mechanisms enabling Japanese researchers to use them in the same manner as those lines held by RIKEN BRC.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- The current plan and achievements are in line with the 4th Mid- to Long-Term Plan. In terms of use and application of the disease-specific iPS cells, its contribution to the BRC's overall plan is high.
- Based on the achievements, R&D have been conducted appropriately, i.e., in accordance with the plan and with the mission of the iPSC-based Drug Discovery and Development Team. High levels of contribution are expected to continue in the future.
- It is hoped that the Team will take the lead in the use and application of the disease-specific iPS cell resources held by the BRC. For this, validating usefulness of disease-specific iPS cells in drug discovery and pathophysiology research is essential. Presenting successful results to researchers in Japan and overseas will further contribute to the center.
- Guiding users who wish to carry out “bridge research using disease-specific iPS cells” is a commendable future goal. Since “URS analysis of companies” and “consideration for reduction of cost, time, and effort reduction targets in technology under development” are as yet insufficient, these efforts must be continued.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?

- Even if the Team focuses on disease-specific iPS cells specialized for the nervous system, it is practically impossible to study all of iPS cells. The strategy of the research and development is needed to be well planned. However, in the case of this Team, it may be important to show not only the utility of cell resources, but also to develop and present methods of analysis and evaluation of iPS cells.
- The Team should focus on producing clear results by developing fundamental technologies in order to build a platform that many researchers can utilize. As an

example, development of an assay system using multi-electrode arrays is consistent with this objective.

- Collaboration with researchers in the engineering field (particularly in the evaluation of cells) should be prioritized over the targeting of many diseases.
- It is desirable that the Team sort out many methods for cell differentiation of the various organs developed in Japan and overseas. Moreover, it is necessary to advance the consideration of how various organ cells are “organ-like.” This will allow researchers to begin examining target values for methods of differentiation induction.
- Given the progress in establishing a drug discovery platform using human disease-specific iPS cells, it is also important to develop banking of control iPS cells of healthy donors and of normal organ cells as references.
- While not a biological concern, rare diseases with few patients require special solutions incorporating socio-economic science perspectives. These solutions should be shared among researchers as methods for providing cure to patients.

2. SWOT analysis

(1) Are the results of the presented SWOT analysis valid?

- They are reasonable.
- Next time, it will be needed to analyze this Team from the perspective of whether the projects contribute to the BRC.
- In relation to O, the Team must describe more specifically the needs of the iPS model in the drug discovery field, for example, appropriate selection of target organs/disease/market size etc. Also in relation to O, the PI should analyze what S and W are for the Teams. In section T, it is necessary to record analysis of external factors that may reduce the Team’s originality. It is likewise important to record any social circumstances/behaviors that may hinder the Team's mission within RIKEN BRC.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- It is appropriate.
- Based on the analysis of results, the necessity of further reinforcing S should be recorded. If strengthening is necessary, then the policy should go along with it. Alternatively, continuation of the current state may be desirable.

- In relation to W, more specific targets to be improved should be recorded. Whether the above policies for S and W are also appropriate for the self-analysis of O and T should be considered and recorded.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Team functioning as a hub of international scientific technology?

- There are many international joint studies, and international exchange is being addressed actively. Thus, the Team is functioning as an international hub for science and technology.
- The Team already has a high international profile in the form of numerous paper citations, requests for cell lines, etc. The Team plays a major role as a hub for BRC's international collaboration.
- The PI has a track record of organizing international symposia. These events are expected to produce synergistic effects which facilitate the fulfillment of the Teams' missions.
- In the future, more strategic implementation of international collaboration will be desirable. Such plans coincide with the Team's goal of contributing as a BRC member, and increasing efforts to heighten international presence.
- From next year onwards, it is hoped that the Team will manifest more specific examples of hub functions.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- The PI is formulating and carrying out research and development strategies leading to the use of disease-specific iPS cells held by RIKEN BRC in the drug discovery field. Thus, the PI is playing an important role in accordance with the mission.
- It is desirable that the PI should contribute to the management and operation of the Team as a leading researcher. It is also recommended that the PI should analyze societal needs. These actions will lead to increasing development of the BRC.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- The PI is acting to satisfy international standards for all items.

Regarding (i):

- Publication of original articles in high-impact IF journals is proceeding steadily for each individual topic. The PI is promoting research at a high international standard.
- Since the potential for societal implementation is also high, these actions have a great impact.

Regarding (ii):

- The PI is fulfilling his own mission to promote the utilization of disease-specific iPS cells in Keihanna laboratory as a BRC satellite.
- The PI is carrying out his mission at a high level by providing methodologies such as methods of analysis for disease models and drug discovery screening, as well as development of iPS cell lines of rare chronic diseases.

Regarding (iii):

- In addition to leading the “drug discovery/incurable diseases pathophysiological study” which has garnered worldwide attention, publication of research results is producing informed awareness in society, and thus a return on results.
- By hosting symposia, the PI has aimed to promote collaboration and social contributions both in Japan and overseas.
- It is desirable that the PI should present a model of commercialization by providing treatment opportunities for rare diseases.

(3) Is the PI appropriately tackling the management and operation of the Team? In addition, does the PI make efforts for training and development of young talent?

- Being mission-driven, the PI has been progressing development and adoption of necessary technologies. The PI is working to manage and operate the Teams appropriately.

- If the experimental systems such as RNA seq/single cell analysis etc. that are planned to be incorporated within this Team are half-finished, it may also be desirable to consider other options. Possibilities include utilizing world-leading research technology through collaboration with the RIKEN FANTOM Team, or outsourcing to reduce routine costs.
- In order to enhance application of disease-specific iPS cell resources at the BRC, a new laboratory was established in the Keihanna area. It is hoped that operation of the laboratory will be soon on track with the support of researchers and technical staff.
- Development of young talent is a pending issue. In the future, plans should be made to take into consideration not only recruitment of young talent, but also their future career paths.

Team Name: iPS Cell Advanced Characterization and Development Team

Team Leader: Yohei HAYASHI

1. Achievements and plans for the Team

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- Before Dr. Hayashi was appointed to the Team Leader (TL), he published his achievements using induced pluripotent stem (iPS) cells in highly-accredited international journals. He was evaluated as having reached the standards as the BRC's TL.
- Since it has only been a while since the establishment of the Team, there are not many achievements for evaluation. It is hoped this Team will make a world-class achievement in the near future.
- It is wonderful that the TL is developing his research in various directions. The committee encourages the Team to keep going forward with a hope that the Team will contribute to the development and operations of the BRC.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- As the TL of the BRC, Dr. Hayashi's contribution is promising in the future.
- The TL is actively conducting outreach and educational activities.
- Contribution using the research outcome is an issue to be addressed in the future.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- The Team's plan and activities are based on his previous achievements, and in line with the Plan. An achievement made by the Team will surely contribute to the development of the center.
- It is recommended that new research and development should be generated and advanced in collaboration with the other laboratories within the center.
- It is necessary to make plans that clearly distinguish the activities as the duties within the RIKEN BRC from those for research by competitive funding, and the TL should be more aware of this distinction.

- As pointed out in the committee meeting, it is advisable that Dr. Hayashi should revise his understanding of “advanced characterization”. The “advanced characterization” does not correspond to the analyses he is currently conducting. He needs to clarify first what are the analyses defined as “advanced characterization” based on experts’ opinions, then specify the activity that is feasible for the Team, and proceed with it.
- The Team should begin offering reporter cell lines as soon as possible. (On this comment, Dr. Hayashi answered at the committee meeting that the Team will begin it within fiscal year 2019.)

(4) What are resources to be developed and research/technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?

- The Team’s current basic research plan may be of a sufficient standard, but as the TL of BRC, it is desirable that the TL will develop a novel characterization method of iPS cell lines.
- Dr. Hayashi should further refine his idea for what is required for the research using iPS cells, and for what contribution to BRC’s operation can be made by such research from a global perspective.
- The Team should develop iPS cells derived from healthy individuals, in which basic plasmids of CRISPRi and CRISPRa are transferred, and made them available to users immediately. These cells should be designed so that they can be used simply by introducing gRNA. It would be desirable to develop cells that have drug-inducible characteristics.

2. SWOT analysis

(1) Are the results of the presented SWOT analysis valid?

- The results of the SWOT analysis are generally reasonable.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- The countermeasures are appropriate.
- It appears that the TL is focusing on obtaining external funds, but it is better to downscale the future projects and strengthen the ongoing projects, rather than raising funds.

- Technical terms should be used appropriately.

3. International collaboration

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

- The Team consists of multinational members, which is regarded as the TL's commitment toward internationalization.
- Whether the Team can function as an international hub is an issue to be addressed in mid to long-range.
- The TL has worked internationally so far, and we expect him to be further committed to international collaboration through his contribution and to show his presence as a BRC staff member.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- It is evaluated that the PI is making much effort to fulfil his role in line with the BRC mission. However, it has only been a while since the establishment of the Team, and it is too early to evaluate his achievements at the present time.
- The PI's challenging research for technological developments is hoped to yield unique outcome. At the same time, it is important to have a good balance with the outcome by his commitment to the projects for bioresource infrastructure.
- The PI is planning to contribute to the research community through development and distribution of reporter cells, and he can be expected to fulfil his role in line with the mission.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- The PI's achievements sufficiently meet international standards in all three aspects.

Regarding (i)

- The PI's achievements meet international standards.

Regarding (ii)

- More effort is required for the achievement of the mission within RIKEN.

Regarding (iii)

- The TL's activities for introduction of laser technology as well as for social enlightenment sufficiently meet the international standards for a young PI and are appraisable.

(3) Is the PI appropriately tackling the management and operation of the Team? In addition, does the PI make efforts for training and development of young talent?

- As a young independent PI, the TL's capacities in management and operation are unknown, and we expect for the PI's future efforts
- The PI has newly established his laboratory, and he is tackling management and operations of his Team appropriately.
- The PI is also committed to training and development of young talent.

Team Name: Next Generation Human Disease Model Team

Team Leader: Takanori AMANO

1. Achievements and plans for the Team

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- At the former post, the PI built a solid track record in the research on the control of gene expression. Achievements have reached the standards of research projects in international bioresource centers.
- As this Team has only just been launched, evaluation of performance as a BRC project will depend upon the achievements of its future activities.
- The PI is viewed as having enough capability to produce satisfactory research results tied to the Next Generation Human Disease Model Team. The PI is further assessed as having sufficient ability to advance the bioresource center's projects, judging from following achievements in the previous position: 1) developmental genetics, 2) the study of gene regulation by non-coding regions, 3) the functional analysis of regulatory variants at the *Shh* locus, 4) genomics analysis, and 5) proposal of the threshold model of inactivation of multiple enhancers for multifactorial diseases.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The PI's notion that study of function of non-coding variants is necessary for comprehensive understanding of the cause of human disease is important for the disease research community. Aiming to achieve the precision medicine and its optimization, the Team has already begun joint research with disease genome analysis researchers and clinicians. The Team has begun generating human disease models by introducing point mutations using the CRISPR/Cas9 genome editing.
- This is a newly established team. However, going forward, the committee hope that the Team will produce results.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- As the BRC's 4th Mid- to Long-Term Plan sets out a policy for the active development of human disease models based on the development of genome editing techniques, the action plan of the Team is in accordance with the plan of the center.
- The following endeavors are also commendable: 1) the Team's focus on explaining the function of non-coding variants observed in human disease, 2) the generation of knock-in alleles using genome editing, and 3) detailed planning for functional analyses of regulatory elements.
- The Team made the following detailed plans "toward the realization of personalized and precision medicine": 1) functional validation of Mendelian genetic diseases, 2) functional analysis of regulatory variants, and 3) the development of complex mouse models necessary to elucidate the mechanisms of multifactor disease onset. These are important to the center's projects, and require efforts in collaboration with the International Mouse Phenotype Consortium (IMPC) and public databases. These efforts allow phenotype analysis of mice from the fetal stage to old age, and are expected to contribute to the center's future development.
- A research group in Johns Hopkins University has also been working intensely on enhancer-variant analysis of human *RET* in Hirschsprung's disease. Thus, considering this competition, it is necessary to demonstrate the superiority and significance of the Team's endeavors.
- Introduction and development of experimental animal models which reflect the diversity of human populations is useful to elucidate pathogenesis. Nevertheless, more careful planning, taking into account their usability as wide-ranging resources, is necessary. For example, complete replication of multifactorial inheritance, similar to that in humans, may then require complex breeding to obtain mice with a phenotype. These disease model mice may be difficult to use in the development of treatment. Disease model mice should be developed not only to elucidate etiology, but also to develop treatments of the diseases.

(4) What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-term Plan?

- The Team is planning to generate model mice for intractable diseases designated by the Ministry of Health, Labor, and Welfare in Japan. This is viewed as a good plan, considering social needs, the number of predicted users of the mice, etc. On

the other hand, there is a plan adopting JF1 mice as a reference strain. Although the importance of this particular plan can be fully understood, the basis for estimating the extent of its use is not explained sufficiently. If not used, there is a high probability that evaluation will be low. Therefore, a preliminary study prior to conducting full-scale research using JF1 may be necessary. In addition, because making of multifactorial disease models are laborious, it is necessary to limit the number of diseases to be investigated.

- In order to achieve precision medicine for human disease, the Team is planning to use JF1, which is derived from *Mus musculus molossinus* subspecies originated in Japan and East Asia, as an experimental animal to reflect the diversity of human populations. This can be evaluated as an appropriate plan, as the center maintains dozens of *molossinus*-derived strains as well as the know-how of reproductive engineering for this strain.
- Attempts to identify modifier factors by analyzing gene expression networks using JF1 strain in addition to B6 are of great academic interest. However, it is very difficult to consider that two subspecies can mimic the diversity of human populations. Thus, this must be presented in a way that does not cause misunderstanding.
- Instead of making JF1 mutants, perhaps the Team should examine the phenotype in F1 hybrid mice between JF1 and B6 mutant mice. It seems a priority to show JF1's utility by introducing known disease mutations into JF1 background, and comparing of phenotype data of the JF1 mutants with those of B6 mice possessing the same mutation.
- For the development of next-generation human disease models, projects can be set up using a comprehensive perspective which spans various levels. The use of different technologies, such as chromosomal engineering, is also recommended.
- Even with the genome editing technique, the generation of knock-in mice with long insert fragments is complicated. To overcome this problem, development of technologies to lower this hurdle may be necessary.

2. SWOT analysis

(1) *Are the results of the presented SWOT analysis valid?*

- It is a reasonable analysis. A weakness is a lack of manpower at this point.
- Based on achievements in the former work, and considering the Team's mission as

set out in the 4th Mid- to Long-Term Plan, the results of the SWOT analysis are adequate.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- The Team is currently recruiting new members and hopes to hire good ones. Along with the hiring of new staff (which facilitates the progress of joint research), it is recommended that collaborative research should be actively pursued within RIKEN to reduce the Team's burden.
- Balance is needed between resource development vs. research on technology development.
- It is necessary to strengthen mathematical and statistical modelling power to utilize big data in order to develop new disease models. The center ought to provide sufficient support in this regard.

3. International collaboration

(1) Is the international exchange being actively addressed, and is the Team functioning as a hub of international science and technology?

- The PI has been actively participating in international collaboration such as the IMPC and the Asian Mouse Mutagenesis Resource Association (AMMRA).
- The Team has only just been founded, and the Team looks forward to future activities. Establishing linkages to international researchers in disease genome analysis is particularly important in empathizing this Team's presence.
- The Team can be commended for a number of initiatives, including: 1) participating in the IMPC for KO mouse generation, 2) cooperating in international phenotype analysis (as well as making efforts to share and internationally standardize methods of phenotype analysis), 3) making efforts to collect disease model information while engaging discussions among model animal researchers, 4) participating in AMMRA, and 5) making efforts to generate model animals with Japanese-specific variants.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- The PI has only just been assigned. However, he understands the BRC's mission well, and is setting forth plans. Considering detailed needs for the disease models, trajectory corrections of the plans may be required.
- Since the development of model mice reflects the needs of clinical researchers, it is commendable that the Team has made active efforts to communicate with clinical researchers and gather information. Moreover, the Team is striving to achieve personalized medicine and precision medicine by recapturing patients' genotypes into mouse models. Lastly, they are attempting to use mouse models to evaluate diseases for which a definitive diagnosis cannot be made.
- Based on social needs, the Team selected Alzheimer's disease, frontotemporal lobar degeneration, Hirschsprung's disease, and branchio-oto-renal syndrome as target diseases.
- The PI's strength in cis-regulatory elements is also important. However, in order to achieve maximum results with limited funds, they should first focus on development of novel resources.
- Considering the time needed for manpower development and team establishment, it is necessary to emphasize efficiency by clarifying the priority levels of their many plans.
- Collaboration with researchers in the field of disease genome analysis is essential. First, it is important to strengthen collaboration by producing results. To this end, it is initially necessary to focus on introducing powerful disease-inducing point mutations. Doing so will help establish a system to advance efforts toward challenging matters, such as multifactorial diseases, from a long-term perspective.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- The PI satisfies the three perspectives (i), (ii), and (iii) simultaneously. The plan will also satisfy international standards if it is implemented.
- Because the PI has only just been appointed, evaluation of these items should be done based on future activities and results.
- The Team is collaborating with clinical experts on issues, and actively promoting

such cooperation since it is essential for generation of human disease model animals. The Team is striving for collection and sharing of information regarding genomic medicine. Moreover, in order to open up new fields of research, the Team is working on the development and maintenance of new reference mouse strains.

- Why not begin a genome editing support service using JF1?

(3) Is the PI appropriately tackling the management and operation of the Team? In addition, does the PI make efforts for training and development of young talent?

- As the PI has just been appointed, selection of staff for the generation of mouse models and phenotype analysis are now in process. The committee hope for the appropriate personnel to be brought onboard.
- Establishment of a phenotyping platform to evaluate phenotype is important in disease model development. On this point, it can be appropriate that the Team is to strengthen collaborations with external clinical experts.

Team Name: Plant-Microbe Symbiosis Research and Development Team

Team Leader: Yasunori ICHIHASHI

1. Achievements and plans for the Team

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- Achievements made by the PI at his former post are highly appreciated to contribute to the development of the BRC's projects.
- This Team was inaugurated in the current fiscal year. In addition to the PI's achievements at his former post, this year's achievements are the results from preliminary experiments for several objectives that the Team plans to advance in the future. Presently, all are reaching satisfactory levels, and the Team can be expected to accomplish its plan in the future.
- Research facility and instruments are being installed with which the projects can be conducted in comparable environment with the world's bioresource centers. Their projects are taking the form of 1) the development of resources for arbuscular mycorrhizal fungi (AMF) and rhizosphere microbes, 2) the establishment of a model system for plant-microbe symbiosis study by utilizing *Brachypodium distachyon*, and 3) the development of "Agroecological engineering system" to achieve a sustainable recycling-based society. In particular, the PI brings highly advantageous omics technology to the Team.
- Based on the novel transcriptome techniques which developed by the PI, the Team is proceeding with multi-omics analysis which are adapted to the agricultural field. The research approach can be evaluated as satisfactory to develop a new theory on the relationships among the plant-microbe-soil environments.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The Team's projects have just been established; however, a co-authored review on plant-microbe symbiosis was published in the journal *Nature Plants*. It is evident that the Team is making social contributions.
- It is highly appreciated that the Team organized the inaugural meeting of the *Brachypodium distachyon* and AMF consortium in order to understand the needs of the research community.
- Transcriptome and microbiome analyses of over 2,300 samples have been

performed from 47 collaborative research projects. These contributions to the research community is large.

- The contributions to the research community are evident as the PI gave guest lectures at domestic conferences and graduate lectures, etc.
- It seems waste of time and effort for this Team with young researchers to spend their time on outreach activities as a means of social contribution. However, considering their high ability to permeate into similar age brackets, these initiatives should be kept in the future, while maintaining a balance with research needs to be concerned.
- In the future, we expect that their contributions to the research communities within Japan and overseas will be more than satisfactory.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRC's 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- The “development of rhizosphere microorganism resources” fits to the BRC's 4th Mid- to Long-Term Plan, and can be expected to contribute to the center's development. It seems reasonable that the development of resource will be materialized by establishing a model system for plant-microbe symbiosis study as well as by the consolidation of information which contributes to its applications in the agricultural field. At the same time, promotion of a wide range of research projects from the establishment of model experiment systems to field omics may face the need for effective collaboration with other research institutions and the flexible management of the Team.
- Although the development of AMF resources is their most important mission, the Team needs carefully to collaborate with The National Agriculture and Food Research Organization.
- They are promoting the construction of multiple omics and informatics as bio-digitalization technology to develop a new system “Agroecological engineering system” to evaluate the interactions of crops, microbes, and soils in agricultural field. This project contributes to the center’s mission of health, food, and environmental solutions.
- When the technological developments progress well, it will greatly contribute to the center’s development.

(4) *What are resources to be developed and research/ technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?*

- At this time, smooth progression of the initial plan is the top priority.
- The research group organized by Dr. Maria Harrison leads AMF symbiosis research. They have generated many symbiotic mutants of *Brachypodium distachyon*. It is desirable for this Team to collaborate with her group to contribute to the research field.
- It is necessary to isolate the AMF strains which can be cultured *in vitro*, easy to analyze at the molecular level, and highly effective for crop inoculation. Moreover, it is desirable that the Team should supply the community with symbiotic microbes isolated and screened by the microdroplet technology that the Team will develop.
- Since the research projects utilize various comprehensive omics analyses integrated by informatics, reinforcement of infrastructure of informatics is vital for this Team.
- The development of AMF and uncultured rhizosphere microbes must be prioritized at the perspectives of food, health, and the environment. To accomplish this goal, it is necessary to develop the single cell characterization technology without culturing, a single cell's genome analysis as well as single-cell imaging analysis.
- The research and development focusing on resources unique to Japan like medicinal plants that the Team proposed, is anticipated from a practical aspect.

2. SWOT analysis

(1) *Are the results of the presented SWOT analysis valid?*

- They are generally adequate.
- “Members with various research backgrounds” is not entirely a strength. Depending on the method of management, disjointedness can become a weakness as “diversification of the research project” is listed under “weaknesses”. This concern is expected to be overcome by the effective team management.
- Some of the SWOT analysis results might be inadequately as research and development projects. “Decrease in students entering doctoral programs” is an analysis of societal factors and does not reflect the research Team's current state. In addition, the development of novel resources should be included in the SWOT

analysis since this will contribute significantly to the development of the BRC.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- It is generally appropriate.
- One positive external factor, a “shift in scientific trends toward symbiotic biology,” indicates an opportunity but also the difficulty of entry into fields where competition is increasing. Therefore, it is desirable that the PI deals effectively with the project management based on the opinions by the review committee.
- “Diversification of the research project,” cited as a weakness within the organization, is a major source of concern. However, this seems unavoidable for a team in its first year. As plans progress, it will become necessary to clarify how they will converge into the specific research project along with the BRC's missions.
- There may be some difficult aspects to intellectual property (IP)-related collaboration. If the Team has a researcher from private company, however, it may make R&D more closely in tune with society's needs.

3. International collaboration

(1) Is the international collaboration being actively addressed, and is the Team functioning as a hub of international scientific technology?

- The state of international collaboration is good enough as its initial stages.
- Active efforts, such as a visit to the international AMF resource center, are evident.
- The Team is taking part in an international symposium on plant-microbe symbiosis. Similar types of participation are expected going forward.
- Worldwide collaboration with symbiosis researchers who study on *Brachypodium distachyon* should be started in the near future.
- This is a stage where the Team should focus on getting the project on track. Its function as a hub for international scientific technology is a topic for future discussion.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- The PI is playing a role in accordance with the BRC's mission.
- The PI is developing novel technology to develop AMF resources, as well as establishing a model system for plant-microbe symbiosis study. Such efforts are viewed as fulfilling their role well.
- The Team is already advancing the *in vitro* propagation of AMF. In the future, it can be anticipated the development, storage, provision, and characterization of novel resources.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution.

- Considering this is the beginning phase, results according to the three international standards are satisfactory.

Regarding (i)

- Adoption as the project's representative of a primary national research project "Cross-ministerial Strategic Innovation Promotion Program (SIP)" supported by the Japanese Cabinet Office is commendable.
- A co-authored review of plant-microbe symbiosis has been published in *Nature Plants*, with high international impact.

Regarding (ii)

- The PI is participating in RIKEN's internal cross-sectional program (iSYM). Further increase of research results is expected in the future.
- It can be judged to reach international standards.

Regarding (iii)

- The PI is actively addressing integration in different research fields, such as plant science, agricultural science, microbiology and informatics.
- The PI established a foundation for conducting strategic researches, e.g., field omics analysis and the screening of uncultured microbes using a microdroplet technology. The PI is now progressing with the acquisition of an external budget to form the foundation for implementation of their plan.
- The PI is planning applications of IP for contributing to the novel use of breath capture technology that the PI developed. This is being adopted by the RIKEN

grant for patent strengthening.

- Additionally, the PI's role is being fulfilled by contributing to the outreach activities, e.g., Tsukuba City Future Creation Conference.

(3) Is the PI appropriately tackling the management and operation of the Team? In addition, does the PI make efforts for training and development of young talent?

- The PI is working appropriately on team management and operation. He is also making efforts to develop young talents.
- Despite of a broad range of research projects the Team planed, the PI is utilizing the latest information systems to create a smooth communication within the lab and have consistently conducted excellent management and operations.
- The PI is also in receipt of large external funds, such as the SIP (FY2018-FY2023).
- Although the Team is still in its inaugural year, the Team members including young researchers and research assistants seem to be working well. Young members should be watched intently whether they produce his/her own results relevant to the research Team.
- In addition to the laboratory comprising mainly young members, the PI is also making efforts to train a visiting researcher from private company and a visiting student from university.