The Report

The Fifth Advisory Council Meeting of the RIKEN BioResource Center

June 8 – 10, 2014

Foundation for Discoveries
And
Access to the Future

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Dr. Ogura, Dr. Wakana, Dr. Abe, Dr. Gondo, Dr. Noda, Dr. Masuya,
Dr. Fukami, Mr. Imaizumi
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[Black: AC members / Gray: BRC members]

June 8 – 10, 2014
RIKEN BioResource Center
and
Okura Frontier Hotel Tsukuba

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The List of the Advisory Council Members

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Terms of Reference for the Center Advisory Councils from the President of RIKEN

1. The key concept of the Third Five-Year Term is "mobilizing RIKEN's overall strength" for problem-solving research, and a new framework has been put into place to encourage cross-disciplinary research throughout RIKEN. In order to evaluate how well this new framework is functioning to promote cross-disciplinary research within RIKEN, each center advisory council is asked to cover the topics in item (1).

   The centers for Emergent Matter Science, Advanced Photonics, Sustainable Resource Science, Quantitative Biology, Integrative Medical Science, and Life Science Technologies are asked to also include the topics in item (2).

   (1) Is the center's research output and personnel up to international standards? Is the center a world-leader in its field? Please make concrete proposals that could lead to quantum leaps.

   (2) Evaluation of the center's management policy
   - Appropriateness of the research roadmap
   - Measures for attracting top international human resources
   - Budget allocation system (balance between research and human resource costs)
   - System for personnel turnover
   - Collaboration with groups both inside and outside RIKEN, progress of collaboration including global efforts

2. RIKEN will be operating under a new system for Independent Administrative Institutions, starting in April 2015. As such, RIKEN's primary objective will be to maximize its research and development capabilities and define goals for creative, outstanding world-class results in selected areas of problem-solving research. Each center advisory council is asked to recommend specific research topics by which the center can apply its special attributes to contribute to those areas of specialty (not only issues confronting society, but also those specific to science and technology) in which RIKEN should be dedicating its comprehensive resources.

Terms of Reference for the 9th RAC from the President of RIKEN

1. The 9th RAC is asked to evaluate RIKEN's response to the proposals made by the 8th RAC.

2. The key concept of the Third Five-Year Term is "mobilizing RIKEN's overall strengths" for problem-solving research, and a new framework has been put into place to encourage cross-disciplinary research throughout RIKEN. The 9th RAC is ked to evaluate how well this new framework is functioning to promote cross-disciplinary research among RIKEN's centers.

3. RIKEN will be operating under a new system for Independent Administrative Institutions, starting in April 2015. As such, RIKEN's primary objective will be to maximize its research and development capabilities for creative, outstanding world-class results. The 9th RAC is asked to give advice on the goals RIKEN should pursue as a world-class research institution, as well as recommendations on strategies for developing a system dedicated to problem-solving research and maximizing research outcomes.

   - In particular, the RAC is asked to make recommendations as to how RIKEN can further enhance its comprehensive strength in the life sciences.
   - The RAC is also asked to address the directions RIKEN should take in fields in which its centers have been operating for 10 years or more (Brain Science Institute, Center for Developmental Biology, BioResource Center, Nishina Center for Accelerator-Based Science).

4. The 9th RAC is asked to make proposals for attracting international human resources and give advice regarding any other areas that need to be further strengthened.

5. The 9th RAC is asked to propose measures for increasing the number of female scientists and female administrative employees, especially in management positions, at RIKEN.

June 8, 2014

The Fifth Advisory Council Meeting of the RIKEN BioResource Center
Terms of Reference from the Director of the RIKEN BRC

Yuichi Obata
BioResource Center Director

The BioResource Center (BRC) is scheduled for a major revision of its activities at the end of March 2018, as per an April 1, 2013 directive from the RIKEN Executive Board (Document 1). In this directive, the term "review" was used. But the real meaning is "revision", since the decision will be made long before the end of March 2018, as early as the upcoming RIKEN Advisory Council (RAC) which will take place November 10–13, this year. If the BRC activities, and the activities of its Divisions, Teams and Unit, are judged to have achieved exceptional results that warrant their being continued, the BRC will continue to exist under a new research plan. In carrying out this review, it is also required that BRC take into full consideration national policies and the needs of its users.

This revision will be discussed at the RAC, as indicated in the RIKEN President's Terms of Reference for RAC and for BRAC (Reference 2). The findings of the BRC Advisory Council (BRAC), and that of the individual resource and review committees which were convened this past April, will play an important role in these discussions.

The plans outlined are premised on RIKEN's change of status to a new system for Independent Administrative Institutions, starting April 2015.

My Terms of Reference for the 5th BRAC are as follows:

I. BRC overall activities

We ask that you give us your evaluation, advice, and suggestions on the following terms by referring to the evaluations and opinions of the resource and review committees for each BRC Division, Team and Unit.

1. Achievements

(1) Has BRC become an indispensable infrastructure for researchers inside and outside Japan?

(i) Is BRC responding to the expectations of research communities inside and outside Japan, providing resources, technologies and information in an organized and timely

fashion, and offering sufficient opportunities to users?

(ii) Does BRC offer advanced resources required for cutting edge researches?

(iii) Is BRC helping to meet the needs of industry? Around 20% of BRC resources are currently being provided to industry.

(iv) Is BRC securing and offering resources that will contribute to efforts to sustain mankind and enhance the lives of the Japanese people, and are users achieving such results?

(2) Has the research and technology development carried out by each Division, Team and Unit helped to increase the value of BRC?

(i) Have the R&D activities of the resource Divisions (the Infrastructure Divisions) contributed to increase of trust on BRC's resources activities and to improvement of efficiency?

(ii) Are the R&D activities of the Bioresource Engineering Division and the individual Teams and Unit, front-running and innovative?

(3) Have BRC's efforts for training and education been adequate? Have BRC's collaborations, within BRC and RIKEN, and with other organizations in Japan and overseas, as well as our public relations activities been sufficient?

2. Evaluation, advice and suggestions regarding BRC's plans

(1) Given its plans and strategies for the next 5 to 7 years, can BRC be expected to make dramatic advances?

(2) Given BRC's research and technology development plans for the next 5 to 7 years, can it be expected to make dramatic advances?

(3) Three Teams and one Unit will have been in operation for 10 years by the end of March 2018, and will undergo major reviews at that time that will decide whether they are to continue or close down. If there are any teams or unit that should be closed down or undergo major overhaul, what fields of research and development should BRC pursue?

3. Advice and suggestions regarding BRC's plans for external funding, such as funds from private sectors, competitive research funds and distribution fee

RIKEN President Noyori strongly feels that BRC should work to attract funding from private sectors. Which areas of BRC–resources and R&D and what topics should be funded in this way, and to what extent?

II. BioResource Infrastructure Divisions

Every year, the Experimental Animal Division, Experimental Plant Division, Cell Engineering Division, Gene Engineering Division, and the Microbe Division undergo review and evaluation by their respective resource committee. This April, the resource committees

were asked their evaluation, advice and suggestions on the following terms of reference and their respective reports are attached. We ask that you verify their evaluations and comments and suggest changes or additions as necessary.

1. Achievements

(1) Are there any activities or achievements worthy of special mention?
   (i) Is the Division functioning adequately as an infrastructure for science? What are its plans and achievements? What of the quantity and quality of its users' output (number of papers)?
   (ii) Is the Division functioning adequately as an infrastructure for society? What are its industry and international contributions? Is it returning the fruits of its achievements to the Japanese people, and has it stimulated people's imaginations?

(2) R&D, technology development, resource development, characterizations and quality control
   · Have these activities been effectively applied in advancing BRC's bioresource infrastructure program?
   · Have advanced and innovative results been produced?

(3) Other matters
   · Education and training
   · Collaborations within BRC and within RIKEN
   · Collaborations inside and outside Japan
   · Public relations activities

(4) Response to previous evaluation and advice

2. Plans as RIKEN's proposed change of status to a new system for Independent Administrative Institutions

(1) Are plans of the Division appropriate to the proposed change in RIKEN's status? Please evaluate and give us advice and suggestions from the following view point:
   (i) Can dramatic advances be expected from their strategies and plans for the next 5 to 7 years?
      · Will they be able to function as an essential infrastructure for science, innovation, and society?
      · Are there any new resources that they should place priority on collection?
      · What kinds of results and effects can be expected?
   (ii) Can dramatic advances be expected from their research and technology development plans for the next 5 to 7 years?
      · Are these plans effective and essential to promoting BRC's resource infrastructure?
      · Can advanced and innovative results be expected?

(2) Are suggestions made previously reflected in their current plans and strategies?
Have they endeavored to re-inspect their activities to date and made appropriate decision about what should be continued or discontinued?

III. Key Technology Division and BioResource Frontier Programs

The following undergo review once every 2 to 3 years: Bioresource Engineering Division, Mammalian Cellular Dynamics Team, Technology and Development Team for Mouse Phenotype Analysis: Japan Mouse Clinic,Team for Advanced Development and Evaluation of Human Disease Models, Mutagenesis and Genomics Team, and the Technology and Development Unit for Knowledge Base of Mouse Phenotype. This April, the review committee was asked their evaluation, advice and suggestions on the following terms of reference and their respective reports are attached. We ask that you verify their evaluations and comments and suggest changes or additions as necessary.

1. Achievements

(1) Has the Division, Team or unit achieved sufficient results? Please evaluate and give us advice and suggestions from the following view point:
- Has contribution been made to reinforcing BRC's raison d'etre?
- Have advanced, innovative results been achieved?
- Have scientific results been produced?
- Has there been social impact?
- Has contribution been made to advancing BRC's resource infrastructure?

(2) Other matters
- Collaborations within BRC and within RIKEN
- Collaborations inside and outside Japan
- Public relations activities

(3) Response to previous evaluation and advice

2. Plans as RIKEN's proposed change of status to a new system for Independent Administrative Institutions

(1) Are their plans appropriate to the proposed change in RIKEN's status? Please evaluate and give us advice and suggestions from the following view point:
Can dramatic advances be expected from their strategies and plans for the next 5 to 7 years?
- Should proposed plans be undertaking in BRC?
- What topics are effective and essential to implementing BRC's resource infrastructure?
- Can advanced and innovative results be expected?
- Can achievements that will lead to innovation be expected?

- Can a major impact on society be expected?
- Are the proposed plans novel, do they have high priority, and are they sufficiently specific?

(2) Are suggestions made previously reflected in their current plans and strategies?
Have they endeavored to re-inspect their activities to date and made appropriate decision about what should be continued or discontinued?

Document 1

Timing of reviews of RIKEN's research programs adopted by Board of Executive Directors

Adopted by Board of Executive Directors
April 1, 2013

Articles 29 and 30 of the law on general rules governing independent administrative institutions stipulate that all IAIs must have a mid-term plan covering a maximum of 5 years (we call it the 5-year term at RIKEN), and in accordance with Article 35 of the law, at the end of each term, we must conduct an examination of what programs need to be carried over into the new term and how the organization will be structured, and must put into place measures to carry out those changes.

However, in order to ensure that research programs reach their goals, our research needs to be carried out based on a span of about ten years, considering the need to secure personnel and fulfill the program missions, so we need to lay out our basic thinking on that issue.

Specifically, in the review process, the Board of Executive Directors makes decisions on the continuations of programs and possible need for revisions, including the possible strengthening and expansion of programs that are seen to have strong future potential, after listening to the opinions of internationally recognized experts acting as advisors, based on how the missions of the programs are progressing and changes in social needs. In cases when a decision is made to keep a program going, there is a need to redefine the research plan for the period until the end of the new five-year term.

1. RIKEN's research programs undergo a review five years into the launch, focusing on the research plan, and then undergo a restructuring in the tenth year, which includes a fundamental review of the organization of the program.

2. During the fifth year of the program, the research plan is reviewed with a focus on achieving results more effectively in the following five years.

3. During the tenth year of the program, each program undergoes a review with a possibility of fundamental restructuring to achieve the goal of ensuring that the human resources nurtured during that period are effectively used, and that the functions developed at the center are put to use effectively and efficiently within RIKEN to promote further research outcomes. This review may lead to the strengthening or expansion of the program or to a restructuring of its organization. In cases where significant achievements have been made at the program under review and where it is desirable for the program's research to be further pursued within RIKEN, the renewed

program can be carried out with this research.

4. The review described in paragraph 3 shall not be applied to research programs such as SPring-8 and the K computer that operate large-scale facilities for shared use as stipulated in Article 16 Section 2 of the RIKEN Law, but the review at the end of each five-year term described in paragraph 2 will be carried out. Further, for research programs carrying out duties stipulated in Section 1, Paragraph 3 of the same article (sharing facilities and equipment), reviews will be conducted in consideration of government policy and the situation of users.

5. As has been the case in the past, employment contracts cannot carry over into a new five-year term. In order to continue employment after the termination of a research program, the researcher must have a guaranteed place in a new research program.

Document 1

Name of program	Timing of review detailed in paragraph 2 above	Timing of review detailed in paragraph 3 above
Brain science	—	End March 2018
Developmental biology	—	End March 2018
Bioresources	—	End March 2018
Synchrotron radiation research	End March 2018	—
Accelerator science	—	End March 2018
Promotion of interdisciplinary collaborations	End March 2015	End March 2020
Drug discovery and medicine Drug discovery and medical technology Preventive medicine and diagnosis innovation	End March 2015 End March 2018	End March 2020 End March 2023
Biomass engineering	End March 2015	End March 2020
Computational science	End March 2018	—
Quantitative biology	End March 2015	End March 2021
Emergent matter science	End March 2018	End March 2023
Sustainable resource science	End March 2018	End March 2023
Advanced photonics	End March 2018	End March 2023
Integrative medical sciences	End March 2018	End March 2023
Life science technologies	End March 2018	End March 2023

The Report

Response to Terms of Reference from the President of RIKEN

Following the legacy established by the late Founding Director Dr. Kazuo Moriwaki, Director Yuichi Obata has led the BRC to significant new heights in research accomplishment and resource development since the last BRAC review in 2011. The collections of mice, plants, cell lines, genetic material and microbes rank all within the top three worldwide. The advisory board congratulates Prof. Obata and his team for this outstanding achievement. Through its several key Divisions and Frontier Programs, the BRC has made significant scientific and technological contributions in a number of areas, including mouse genetics, stem cells, reproductive biology, cloning, next-generation genome sequencing, high-resolution intra-vital imaging, experimental plant (Arabidopsis and Brachypodium) biology and genetics, microbial biology and genetics, and comparative biological database platforms. Some of these achievements deserve special mention, such as the development of 3-dimensional internal structural microscopy, cloning of mice from microinsemation of karyoplasts from minute blood volumes, derivation, standardization, and validation of disease-specific iPS cells from human disease patients, the Project for Development of Innovative Research on Cancer Therapeutics (P-DIRECT) strategy research and discovery pipelines for developing novel cancer therapies and diagnostics, and patient derived xenograft (PDX) technology. The publication record has also been exceptional, with several hundred papers in just the last 3 years, many in high-impact scientific journals (e.g. *Nature, Science,* etc).

These accomplishments are noteworthy not only because of their world-class nature, but they also have contributed to the recognition of RIKEN BRC and its scientists on the world stage through invited participation and membership in several prominent global organizations, such as the International Mouse Phenotyping Consortium and the International Cell Line Authentication Committee. This level of performance has also contributed to RIKEN's essential role as the only specialized and comprehensive biological resource and distribution center of highly important scientific reagents including mice, plants, cell lines, genetic material, and microbes. Researchers in Japan and around the world request and receive materials essential for their research from the RIKEN BRC. In addition, BRC staff's strict attention to quality control serves an indispensable role in ensuring the reproducibility of research conducted by scientists using RIKEN-distributed materials.

The Council members strongly encouraged the funder to ensure sufficient, stable, and sustainable funding for the BRC and access to its resources for all researchers at an affordable

price. This will leverage the investment in BRC dramatically and facilitiate BRC securing additional funding opportunities.

The successful outcome of past accomplishments bodes well for the likelihood of success of the research activities proposed for the next several years. In particular, RIKEN BRC scientists should continue to emphasize research on the development, refinement, and application of genome editing technologies (e.g., CRISPR/Cas9) in various species, the derivation, characterization, and validation of disease-specific iPS cells, the use of PDX and other appropriate genetic animal models for translating basic science discoveries into better diagnostics and therapies for human disease, and on research that promotes the development, understanding, improvement, and sustainable use of its rich repository of irreplaceable bioresources, including mice, plants, and microbial collections. Research in these and related areas will ensure that RIKEN BRC retains its position on the world stage as a global leader in science and discovery. RIKEN BRC should continue to give highest priority to conducting all of its work with the very highest of quality control and assurance standards that it has demonstrated over the last several years.

Finally, RIKEN should also continue to strive to expand and enhance its outreach activities, not only to the general public but also to professional scientists and students through advanced education and training courses and programs. These measures will contribute to the building of cross-disciplinary research within RIKEN and to the development of new and promising academic-industry partnerships. To that end, RIKEN BRC should continue its association and participation in the National BioResource Project. To ensure success in its bioresource, technology and frontiers program, it is strongly recommended that RIKEN BRC participate without delay as a full and active member in a new system for Independent Administrative Institution.

Response to Terms of Reference from the Director of RIKEN BRC

1. Evaluation of BRC overall activities

(1) Has the BRC become an indispensable infrastructure for researchers inside and outside Japan ?

Since the last review in 2011, BRC has been developing as a world leading bioresource center. The collections of mice, plants, cell lines, genetic material and microbes all rank within the top three worldwide. The advisory board congratulates Prof. Obata and his team for this outstanding achievement. The BRC not only is the essential repository in Japan but also indispensible to ensure the highest standards of quality and reproducibility. Deposited material from universities and institutions have a certain degree of misidentifications and contaminations. BRC has been solving these issues and has been distributing only material of highest quality. This role of BRC should not be underestimated since it is essential for reproducibility of experimental results.

As a global player BRC distributes research material around the globe. US and Europe are amongst the top international customers, which reflects the quality and importance of the BRC resource. As a result, the "BRC brand" has achieved the highest reputation around the world.

(2) Has the research and technology development carried out by each Division, Team and Unit helped to increase the value of BRC?

From our perspective the active research and technology development program is essential for the success of the BRC. The quality and quantity of BRC publications is very high and reflects not only the importance of the repositories but at the same time the active involvement of the team in research and development. The Advisory Council unanimously congratulates the BRC for this achievement. Often, resource centers fall behind standards if no research and technology development is carried out. This of course is not the case with the RIKEN BRC, which recognizes the essential linkage between scientific research and outstanding resources.

Some of these achievements of the BRC deserve special mention, such as the development of 3-dimensional internal structural microscopy, cloning of mice from microinsemation of karyoplasts from minute blood volumes, derivation, standardization, and validation of disease-specific iPS cells from human disease patients, the Project for Development of Innovative Research on Cancer Therapeutics (P-DIRECT) strategy research and discovery pipelines for developing novel cancer therapies and diagnostics, and patient derived xenograft technology.

(3) Have BRC's efforts for training and education been adequate? Have BRC's collaborations, within BRC and RIKEN, and with other organizations in Japan and overseas, as well as our public relations activities been sufficient?

Training and education is very important to spread knowledge and to build standards for the best use of the bioresources. At the same time, training courses are important to attract people and to promote a center. BRC is very active and productive in this respect and offers training courses for scientists, students and technicians. To mention a few, there are frequent courses on cryopreservation of embryos and sperm, culturing method for plant and cell lines, recombinant viral vectors, culturing and preservation method for anaerobic microbes and culturing human ES and iPS cells. We recommend considering an additional course to teach the outstanding results from the team for mammalian genome dynamics. This would add value to the existing portfolio of courses.

To bring things to the next level a "Graduate Program in Resource Science" should be considered by the director of the BRC. Such a program would be of pioneering character. The "Graduate Program in Resource Science" would educate graduate students in the field of research infrastructures, repositories, research and development for the enhancement of resource centers and management plus legal issues, and effective use of the various media for information exchange. An additional positive aspect would be to build the next generation of leaders in the field.

With respect to public relation the Council thinks that public outreach is more important than ever. Rcently, there has been some negative press on a RIKEN researcher at a laboratory not associated with the BRC. In this situation it is very important to inform the public about the solid and important work conducted at the BRC. BRC is at the forefront of quality control which ensures highest standards and reproducibility.

2. Evaluation, advice and suggestions regarding BRC's plans

(1) Given its plans and strategies for the next 5 to 7 years, can BRC be expected to make dramatic advances?

The council feels, that the ground plan shown in this advisory council meeting is adequate, and we expect that BRC will make dramatic advances if the plan is implemented. From this perspective we fully support the plan.

(2) Given BRC's research and technology development plans for the next 5 to 7 years, can it be expected to make dramatic advances?

Since speed of progression of life science is so fast, it is not easy to imagine what will happen

in science 5 to 7 year later. However, It is most likely that genome-editing technology will continue to advance further such that we can introduce any kind of change to any gene of interest with minimum cost and time. This may heavily influence activities of bioresource center. Plans should well correspond to this change of the technology.

(3) Three Teams and one Unit will have been in operation for 10 years by the end of March 2018, and will undergo major reviews at that time that will decide whether they are to continue or close down. If there are any teams or unit that should be closed down or undergo major overhaul, what fields of research and development should BRC pursue?
Advance of the genome-editing technology, represented by CRISPR/Cas9 system, paves a new way to generate mutant resources irrespective of animal and plant. The day will come that researchers can easily make knockout and knockdown mutants of target genes using their own hands. This may in turn decrease the demand for mutant resources stocked from BRC. On the other hand, quality controlled animal resources derived from CRISPR/Cas9 might be in high demand. In addition, resources derived from wild populations in nature cannot be produced by our technologies, because they have accumulated vast amount of genome variations. Therefore, wild-derived resources and neighboring species (subspecies) of the currently used model organisms (e.g., plants, microbes) are likely to continue to be important resources in future. In this light, the divisions and teams are indispensible, but adaptations to future needs will be required and have been planned.

Director Obata should keep track of the scientific contributions to the BRC of the Team for Advanced Development and Evaluation of Human Disease Models. The BRAC values the potential for facilitating the interaction of physician-scientists within the BRC and in the clinical scientific community.

The Division of Bioresource Information is essential for proper function and outreach of the BRC. There appeared to be an issue on the leadership of this division. The Council recommends seeking a solution to this challenge without delay. We believe the Director of the BRC should have the necessary resources and support to implement an effective solution appropriate to the needs and aspirations of the BRC as a valuable research and resource center in RIKEN.

3. Advice and suggestions regarding BRC's plans for external funding, such as funds from private sectors, competitive research funds and distribution fee
RIKEN President Noyori strongly feels that BRC should work to attract funding from the private sector. Which areas of BRC–resources and R&D and what topics should be funded in this way, and to what extent?

BRC's primary mission is to support science of academic sectors (societies) rather than that in the private sector. Of course the private sector has full access to the resources and is using the BRC frequently, on different levels. If BRC shifts its major activities towards needs from industry its reputation and the needs of academia might fall a bit short, a balancing problem.
But, there are opportunities which might be explored: Human iPS cell lines prepared from varieties of disease patients, the patient's derived Xenograft (PDX) cancer models and new plant model of Poaceae, Brachypodium distachyon, could be good examples that could potentially be funded from the private sector, because use of these resources directly leads to commercial activities of pharmaceutical and food companies. A distribution fee is now charged for resource users. The Council members strongly encourage the funders to ensure a sustainable funding level for BRCs resources and access for all researchers at an affordable price. This will leverage the investment in BRC dramatically and from a business perspective makes perfect sense.

Evaluations and Recommendations to Divisions and Teams

Experimental Animal Division

Division Head: Doctor Atsushi Yoshiki

Achievements

We applaud the Division for having built up one of the world's largest mouse repositories. All measures of quality control have been implemented properly and in the category of collection, preservation and distribution of mouse strains, RIKEN BRC now occupies the second position in the world, next to the Jackson Laboratory.

The resource was built up from nationally and internationally derived mutant mouse lines and is heavily used by the national and international scientific community. The high demand for the mouse lines reflects the relevance of the repository. However, orders for mice have plateaued over the last two years. Several reasons for this can be considered: 1) most researchers who needed RIKEN BRC mice have already obtained and bred them in their own animal facility, and they thought that replacement or exchange of the mice would currently be unnecessary. In addition to this, many users have requested very narrow ranges of mouse strains such as those for bio imaging of autophagy, i.e. a specific purpose. These users need a small number, just two to three mating pairs.

Cre-loxP, TET and optogenetics strains are becoming increasingly important and will be collected with highest priority to ensure the attractiveness of the repository. In addition mouse production for the IMPC project is one of the Division's tasks. This is greatly appreciated and should be continued to ensure a proper supply of mice to the JMC.

As regards quality control, the Experimental Animal Division (EAD) staff has developed effective systems for genetic and pathogenic microbial monitoring and as a result both genetic and microbial quality has been maintained at a high level. Indeed, RIKEN BRC mice have been ranked as the highest quality in the world.

Technology Development: A clever, new, effective technique has been developed for cryopreservation of wild-derived mice.

The EAD made correct and proper responses to the seven comments from the previous BRAC. The most important one was to trace back the publications and patents in which BRC mice were used. The EAD staff managed to identify 500 papers (mean inpact factor = 9.4) and 10 patents and the methods they used are now in place for future monitoring. Also, as a response

to one BRAC comment, the division made a strong collaboration with the R&D team for Mammalian Genome Dynamics, and together they achieved a great advance in their research, publishing several papers of high originality and quality.

Recommendations

Efforts to advertise BRC's achievements to the research community and the public are strongly recommended. To do so, decisions must be reached on a unique BRC policy for collecting mice. What kind of mice other than Cre driver mice and human disease mice should be collected and should the collection be restricted and specified?

It is important to mention that the EAD joined the NBRP (National BioResource Project), which supports research infrastructure. NBRP has been maintained by a national policy for bioresources and has firmly been developed. The activities of EAD are evaluated as excellent in the NBRP committee. Therefore, the BRC's future plan is to cooperate with NBRP and to specify activities based on the NBRP plan. It is also important to make a harmonization between the NBRP and RIKEN BRC collection policies.

Dramatic benefits can be expected in the following two areas. The first is establishing a large collection of tissue-specific Cre and other reporter mice, such as lacZ mice. As regards verification of tissue-specific Cre mice, EAD has to decide its policy before proceeding to the decision of whether to prioritize or not. The second is to establish a large collection of human disease model mice to coordinate with by the use of related iPS cells, and to also coordinate it with mutants made in both species using the CRISPR/Cas9 system. The newly developed method, CRISPR/Cas9 system is drastically changing the field of generating KO and KI mouse. It is important to make an effort for applying this effective technique to generate a large collection of model mice for human outstanding and noticeable diseases.

It is also important to develop model mice for tissue-specific bio-imaging to make it easier to conduct phenotype analyses mainly done by Japan Mouse Clinic (JMC). The technological development for cryo-recovery should be requested, together with a new cryopreservation technology done by the Bioresource Engineering Division.

Again, BRC's achievement in EAD should be strongly and effectively advertised to the research community and to the public through the Web. To do so, it is important to cooperate with information scientists.

Experimental Plant Division

Division Head: Doctor Masatomo Kobayashi

Achievements

The Experimental Plant Division has been recognized as an international foundation for plant research and is making an international contribution to the research area. Their goal is to become the international center of plant research in Asia. It is highly appreciated for maintaining a foundation of basic research and is making good progress, based on its plans, in respect to contributions to the development of advanced technology that will aid academic research on plants, and to developing an experimental plant for research on breeding grains. The head of this division has led the international society of basic plant researchers as the leader incubating BRC as one of the main three Arabidopsis Resource Centers, and participated for a long time in the multinational Arabidopsis thaliana International Steering Committee.

It will be most important to maintain the quality of resources for high standard research. Careful quality control systems provided in the division ensure that BRC is evaluated as ahead of the other resource centers. Also as a new tool of studying genetic, ecological and evolutional variations, following to the recommendation made by the previous Advisory Council, this division puts effort on collecting natural accessions of Arabidopsis and providing the community as a handy seed package of 100 representative natural accessions.

A bold shift of the central activity of the Experimental Plant Division is required from "strengthening functions of Arabidopsis thaliana as a standard resource" to "creating a novel plant model and standardizing it internationally". We agree with its plan to develop *Brachypodium distachyon* as a novel model plant of Poaceae, the monocot rice family, which includes almost all of the major crops, rice, wheat, barley and maize. This model should be developed in coordination with international efforts on the organization of *Brachypodium* resources. Development of the transformation technology and mapping cDNA clones of *Brachypodium* made in the Division was a major breakthrough and it is appreciated as a significant result. A collaborative study with a rice researcher at Nagoya University to elucidate gene function is a useful start to develop excellent research results. The future plans for the development of genome editing technology are also reasonable.

The Division also puts efforts in research directed toward improving crops against abiotic and biotic stress, including drought, and we encourage it to pursue the objectives by providing information related to the usability of the model plants and tight collaboration with strong research groups.

As described above, the Division is actively involved in agricultural research, and is expected to develop cooperation with the research institutes of Independent Administrative Institutions under the jurisdiction of the Ministry of Agriculture, Forestry and Fisheries. They are applying for funding to the cross-ministerial Strategic Innovation Promotion Program, which is very important for BRCs goals.

The Experimental Plant Division fulfills a highly useful task nationally and internationally by distributing to 1,123 labs and research groups in 45 overseas countries and to 641 labs and groups in Japan since 2002. The plant resources, particularly those originally developed in Japan are unique and important resources worldwide. The Division has also distributed cultured plant cells in addition to seeds and clones. They have enhanced quality control and compliance making them highly appreciated both domestically and internationally. Especially single-cell analysis of the homogeneity and diversity of cultured cells will be important for basic science and stable applied research.

The number of research papers from users (609 since 2002) based on results obtained from these resources is high, supportive of the fact that the scientific community trusts the Experimental Plant Division as a foundation for their research. These papers are also found in very highly rated scientific journals.

The scientists in this division have developed firm collaborations with some of the other organizations in Japan, which maintain and distribute plant resources. The Division has been proceeding with cooperation related to know-how of the resource project by liaising with the rice genome resource of the National Institute of Agrobiological Sciences and the NIAS Genebank for seed collection. The Division has been actively proceeding with liaisons with the Arabidopsis Biological Resource Center (ABRC) in the US and is contributing to international communities mainly by providing resources that originated in Japan. This is applauded because the collaborations will prove necessary when the scientists in the Division want to expand to other species. Special mention is made of the liaison with the RIKEN Center for Sustainable Research Science in Yokohama and the NIAS Genebank for seed collection.

It is important for future development of technologies in Japan to provide opportunities for technical experts who are responsible for the resource project to improve their skills and careers. The Division holds training course for cryopreservation of plant cells and others who wish to acquire technologies and cultivation techniques. But because it is difficult to accomplish this change only within the RIKEN BRC, it has to be considered from the view of

the entire National BioResource Project (NBRP). In addition, it would be appropriate for the Division to cooperate with the system for University Research Administrators (URA), which was established by the Ministry of Education, Culture, Sports, Science and Technology last year.

To advertise to the general public more efficiently and to enhance PR cost performance the Experimental Plant Division should listen to the opinions of clients on the effects of the center in each small electoral district and perform PR activities aimed at members of the Diet, which might be helpful in allowing the Division to become more familiar and widely recognized. The Division also energetically performs PR activities at domestic and international scientific conferences. In high school biology textbooks, the genetic process of flower formation of *Arabidopsis thaliana* has been described. However, teachers seem to have trouble obtaining these materials. The Division might want to consider contributing to this aspect of high school education. The Division actively makes an effort to return its knowledge to society by holding public exhibitions at the BioResource Center and by organizing observation events of *Arabidopsis thaliana* outside of the Center.

The Division has indeed initiated an effort to develop novel resources related to the production of food, biomass, and other useful materials, in addition to research on basic physiological function, growth, and differentiation of plants using model plants.

The Division has been proceeding with resource infrastructure and public relations by liaising with the RIKEN Center for Sustainable Resource Science and with the Biomass Engineering Program, and with research institutes of the Ministry of Agriculture, Forestry and Fisheries, Tsukuba University.

Recommendations

As the first step toward becoming the center of plant research globally, we anticipate the Division will become the international center of plant research in Asia.

Arabidopsis will remain the standard experimental model of plant science in future, if continuous renovation of resource value and development of the techniques are made. Research value of natural accessions of Arabidopsis will be increased as ecological and evolutional studies will be expanded in coming years as well as food and biomass researches.

Activities focused on *Brachypodium distachyon*, are useful and essential as an international resource infrastructure project in the future. To establish this plant as a standard model worldwide, the Division must apply strategic efforts in different areas, preparation of a useful

set of standard lines, development of technologies, and advertisement to international societies, collaboration with powerful researchers and showing good publications. In addition, the Division should consider informatics resources and the development of new technologies for analysis of big data. If data obtained from these projects are open to the public and an allocation system is established, the RIKEN BRC will be more strongly recognized as the international center of experimental plant work.

Reliability of resources and accuracy of additional information are the results of the accumulation of steady effort, and this continuous progress is a leap forward. As presented in the plans of research development and technology development, developing and providing the resources and the kits that researchers require, for both *Arabidopsis* and *Brachypodium*, will result in leading expansion of the research.

Practical matters: There are plans to make a backup facility for the stored resources in Harima, in western Japan, choosing the most important resources. The fees for distribution were raised 2 years ago and a budget for future projects should be designed.

Cell Engineering Division
Division Head: Doctor Yukio Nakamura

Achievements

This Division, under the excellent leadership of Dr. Nakamura, is to be commended for their work collecting various types of cells and distributing these cells nationally and internationally. In addition to the high quality of general-purpose cell lines, the Division has collected 9 mouse and 86 normal and 358 disease-specific human induced pluripotent stem (iPS) cell lines. The Division has already begun developing genome-edited cells and disease-specific iPS cells. These iPS cells have the potential to make a major contribution to the development of new disease models and discovery of new drugs.

The number of research papers published in a year that is known to use cells distributed by the Division has reached 700. The Division established cell misidentification testing with STR polymorphism analysis. The Division has built cooperative relationships with the world's major cell banks to eliminate cell misidentification. This is highly commendable.

In terms of quality control, the Division has established a quality management system and earned ISO 9001 certification. This was found to be very important and useful for ensuring reliability and stability, which are essential aspects of resource projects. There is a gradually growing awareness that researchers cannot present their results at academic conferences and in research papers unless they use quality controlled, guaranteed cells distributed by the major cell banks in the world such as RIKEN BRC. The Division is to be commended for working to raise awareness of misidentified cells as a member of the International Cell Line Authentication Committee (ICLAC).

The Division accepts commissions to perform analysis for quality inspections, which helps to raise the level of bioscience in Japan. The Division periodically hosts technical training on human embryonic stem cells and iPS cells and provides technical instruction to many researchers. This project is highly relevant to the handling of these cells.

The Division's position of actively preparing disease-specific iPS cells inspires great hope for citizens in general and especially patients suffering from hard-to-cure diseases. The Division is also steadily distributing cells to the private sector, but it will be necessary to do a survey of trends to determine what kinds of cells industrial users want the Division to prepare.

Collaboration within Japan includes close partnerships with the Japanese Society for Regenerative Medicine, the Japanese Tissue Culture Association, and others. It has a particularly close relationship with the Center for iPS Cell Research and Application (CiRA),

Kyoto University. Based on this foundation, it has built a system to establish disease-specific iPS cells and at the same time accept deposits of them. This is especially deserving of mention.

Internationally, several North American and European countries are also beginning projects to prepare disease-specific iPS cells. The Division will need to consider international partnerships while firmly securing its own intellectual properties.

In light of future growth in basic research and the pharmaceutical industry in Japan, the iPS cell project should go forward as the core of RIKEN BRC's cell bank project. RIKEN BRC will need to step up its efforts to secure a budget for large-scale preparation in its disease-specific iPS cell project.

Recommendations

It is anticipated that cells distributed by RIKEN BRC will become the standard cells for research in Japan. The Division is expected to perform even more thorough quality control and grow into its role as a world-leading organization for maintaining, distributing and providing advice about cell lines.

The Division plans to perform STR polymorphism analysis of human cells and to establish such a database, as well as to perform high-level characterization, including differentiation-potential analysis of disease-specific iPS cells and genome-edited cells. This technology development will be indispensable for pursuing cell bank projects in the future and is thus commended. It is therefore important to prepare many varieties of disease-specific iPS cells, as well as control iPS cells from healthy people, covering different ages and both genders. Detailed characterizations, including their differentiation-potential and cell growth control analyses, are very important aspects of quality control of iPS cells.

The Division is constantly re-examining its projects, and is clearly aware of those that should be ended, those that should be temporarily suspended, those that should be steadily continued, and those that should be newly undertaken. For example reducing the scale of the human umbilical cord blood project, after taking demand into account, is to be commended. Embryonic stem (ES) cells may be used as controls for iPS cells, so it may be necessary to expand this collection in the future, both from animals and humans. However, this is to be carefully monitored with probably more emphasis placed on iPS cells. It is likely that genome-editing technology will enable researchers to make ES and iPS cells with a variety of disease-related genetic defects, so the Division should actively monitor whether to include and/or prepare such stem cell lines.

Gene Engineering Division

Division Head: Doctor Yuichi Obata

Achievements

The Gene Engineering Division has had several significant accomplishments and achieved major milestones. The preservation of almost four million genetic strains from a variety of eukaryotic, bacterial, and viral species developed both in-house and deposited by extramural scientists, including several large clonal sets of scientifically important species (e.g., Rat and Drosophila BAC libraries) represent an important asset for future life science research.

The Division has been distributing materials to and exchanging information with 703 domestic institutes since 2001, proving itself as an invaluable hub to promote domestic research. Domestic and international distribution of genetic material has steadily increased over the last 5 years, reaching a peak in 2013 of nearly 2500 items to approximately 550 users. The proportion of products distributed overseas has increased to approximately 25%, establishing the international reputation of the Division. The number of research publications have also steadily increased to a new high of 90 papers in 2013, and 32 patents have been filed since 2009. These numbers likely do not represent the full extent of use of the Division's resources, as many more have yet to be recognized as either publications or patents.

The Division has also embarked on strategic marketing and promotion to ensure broader visibility of its resources both in Japan and internationally. To that end links between libraries within the Division and with databases at other institutes appears on the BRC website. Based on suggestions from the resource committee, the Division's resources have recently been linked to the Kyoto Encyclopedia of Genes and Genomes (KEGG), which should contribute to greater awareness and use by the research community, including the commercial sector.

The Division also supports many important domestic and international research projects which contribute to improvements for the nation's citizenry and increases the public relevance of the BRC. In one project, the Division has been collecting, preserving, and developing genes of enzymes, derived from termites and filamentous fungi, for research on biomass engineering. This work is valuable with respect to coping with the risk of global warming. Resources related to cellulase genes have already been distributed to and used by researchers, which indicates the possibility of a profitable return from this project to the public. In another project, the Division has been engaged in the development of adenoviral vectors that can be made visible by the expression of multiple proteins with fluorescence proteins.

The Division has also established very high quality standards on products it distributes,

although best practices indicate that recipients should always be reminded to conduct their own quality control testing on materials they receive. The Division has demonstrated that it will take immediate and appropriate measures in cooperation with a depositor if problems are discovered. For these reasons, the Division is well-trusted and held in high-esteem.

The Division has offered a few training courses in advanced technology, although the breadth and depth of expertise, capacity, and resources present even greater opportunities for additional and improved training courses. The navigation, look, and feel of the Division's website have been greatly improved, making it easier to access information and useful links. The Division is actively engaged in exhibitions at various scientific conferences. The Division has also engaged in efforts to enhance local understanding of its activities, including holding public exhibitions in Tsukuba City to attract children's attention to science and organizing facility visits by junior high school and high school students. These types of activities can only enhance the Division's standing in the community and garner public favor for itself and the BRC.

There were several areas of advice from the last review to which the Division has responded appropriately:

a) *RIKEN BRC should take the lead in resolving the use of resources that are entangled with private company licenses*. The Division has been actively negotiating the licensing of materials, such as fluorescent proteins, from private companies that possess the rights, and taking appropriate measures. We heard that it is necessary to carefully handle the transfer of products to private companies because of intellectual property issues. On the other hand, because the transfer can put pressure on the private sector, this matter should be discussed between the BRC and private companies.

b) *The RIKEN BRC should request that the BRC gene catalog number appear on KEGG*. This has been accomplished. The link between the KEGG database at Kyoto University and the clone list of the web catalog of the Gene Engineering Division was completed and released to the public, facilitating the search for clones.

c) *Training should be provided for very special techniques that are available only at the RIKEN BRC*. The Division has done well responding to this advice by selecting appropriate subjects for daily duties, as well as by making an effort to provide training for handling adenoviral vectors and in protein expression and enzyme activity measurements for biomass-related enzymes. In addition, training for highly specialized techniques available only at the RIKEN BRC is desirable, including for advanced research technologies, such as induced pluripotent stem (iPS) cells and clustered regularly interspaced short palindromic repeats (CRISPR).

d) *RIKEN's organization has been drastically changed and the RIKEN BRC will be reviewed*

five years from now. The BRC should, however, demonstrate its direction as a center in approximately three years' time. The BRC has taken appropriate measures for matters pointed out by the previous assessment: 1) Prior to the RIKEN Advisory Council discussion in November 2014, each team within the BRC and the Bioresource committee discussed the direction and 2) As a precondition, comments from the research community about the importance of bioresources were solicited. The problem is how the latter action should be performed promptly.

e) *The RIKEN BRC provides prompt feedback to users with information from the depositors, a follow-up service that similar resource centers are not thought to offer*. The BRC provides careful follow-up of research materials that they distribute. To continue this service, it is important to maintain a close liaison with the depositors, which should be promoted by the BRC.

Recommendations

The Division plans to prepare resources that are closely related to future health policy and drug development, such as the preparation of disease-specific iPS cell libraries and sources of gene groups related to cancer, psychiatric, and neurological fields. In addition, the Division should develop new and enhance extant preservation methods for resources.

The BRC should proactively provide research support in fields in which it is particularly expert. This includes adoption of rapidly developing research technologies worldwide, and providing them to researchers. The BRC can manufacture and provide the highest quality research materials upon request from the most advanced domestic researchers. To do so, the BRC must establish and culture relationships with researchers who are familiar with advanced technologies, such as CRISPR/Cas9. The Division should prioritize the preparation of cDNA sets of various species as new resources for the future. Because the CRISPR/Cas9 technique is predicted to be widely used, the synthesis of a guide RNA vector resource might be of value.

The Division is poised to prepare genetic materials as resources to promote sustainable development and environmental conservation. For example, development of enzyme resources related to fixation of carbon dioxide and atmospheric nitrogen is worth considering.
The rapidity and economy of development of research and technologies and the validity of research materials will be more important in the future. The Japanese government should plan to establish the BRC as a basic infrastructure and develop it permanently under a policy of promoting science and technology.

This resource project is very important and essential both domestically and internationally, to

keep technology research and development advanced and innovative for academic, innovation, and social infrastructure.

Preparation of biomass-related enzymes is anticipated to be effective in bioethanol production. Establishing collaborations with companies will be helpful to this goal in the future. Further, although the Division's plans now look reasonable, it should periodically review them to ensure they are keep abreast of the rapid advances in technologies in genome and mutant mouse preparation, and multiple sample analyses.

The Division plans to encourage more depositions of clones and collections to the BRC, by offering one free clone for every clone deposited. This is intended to attract business away from AddGene, its current competitor.

Succession planning is a concern, and trained resource managers are a great asset. There are master courses for resource directors, which could help to develop the next generation of resource leaders.

Division leaders within BRC leadership are planning to continue operations even as budgets continue to decline. These declining budgets have reached a point where further reductions will have no scientific benefit and only result in a serious detriment to the nation's scientific competitiveness. For example, recent budget declines have caused the Division to turn down the deposition of large clone sets which would have been archived and distributed to requesting investigators for a fee.

Finally, plans to bring students from inside and outside Japan to the BRC will benefit Japanese science as it will contribute to the development of the next generation of scientists. Since many BRC researchers are professors at the University in Tsukuba, these plans could be enhanced by making arrangements to bring trainees to visit and spend time at the BRC.

The previous review is indeed reflected in the current plan, especially in the genome field. Advanced technologies, such as visualizing technologies, have already provided excellent results, and diversification of visualizing technologies is also included in the current plan. This reflects the attitude of the Division toward embarking on this plan while solving of licensing-related issues.

With respect to CRISPR/Cas9, an advanced technology, leading practical strategies through the creation of liaisons should be given considerable weight, as should the collection and distribution of Cas9 and guide RNAs for each species.

The Gene Engineering Division should preserve resources that are rarely requested for distribution to allow for the conduct of research and development so that new resources that will be requested often for distribution are modified into more usable forms and enhance the system of distributing the resources.

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Microbe Division (Japan Collection of Microorganisms: JCM)

Division Head: Doctor Moriya Ohkuma

Achievements

As one of its most excellent achievements is that the JCM created a positive spiral with a synergistic increase in deposits/provision/research papers in Asia. The number of microorganisms deposited from and distributed to Asian countries over the past 10 years has dramatically increased with more Asian research papers utilizing JCM strains. It is no doubt that this is a result of the JCM continuously making strong alliances with other Asian countries over the years as well as accepting Asian students and researchers and providing them with education and research guidance. This amazing positive spiral is a phenomenon never seen in the microbial resource centers in other countries. The JCM pulled ahead of other organizations to rank No.2 in the world in terms of quantity of accepted deposits of new type strains of bacteria/archaea. The number of new type strains markedly increased in 2013, closing the gap to become No.1. The JCM established a solid reputation in the world both in name and in reality as the leading microbial resource center in Asia. However, if it is true that the number of microorganisms that can be deposited with the JCM is nearing its capacity, an appropriate improvement must be made so that there are no negative effects on storage and provision quality.

The JCM is intimately connected to R&D in Asia. Three-quarter of the deposits of new type strains are from overseas, demonstrating the JCM's unparalleled international contributions in research infrastructure. It was also confirmed that the microbial resources collected at the JCM have been frequently utilized by industry as well as for industry-academia collaborative R&D. Each year, the resources have been used in at least 100 patents aimed at solving environmental problems and improving human health. Some of the patents have already been commercialized. JCM's efforts are actually returned to the lives of the general public through the industrial and academia uses.

The JCM performs quality control in compliance with ISO 9001. This ensures the reliability of the resources and speaks to the excellent infrastructures.

The Nagoya Protocol of CBD will affect the industrial and academic uses of bioresources collected from foreign countries. The JCM should be highly praised for completing an investigation into the countries of origin and acquisition history of strains recorded in 1993 and later and preparing for the enactment of the Nagoya Protocol.

Difficult-to-culture microorganisms are provided in bulk so that future technology and social innovations can be achieved using new microorganisms. The JCM has been conducting the

project of providing genomic DNA and active cultivation of difficult-to-culture microorganisms with good results.

The JCM actively conducts public relations activities including education and training, publication of reports and pamphlets and research collaborations including many research groups and organizations within BRC, within RIKEN, and inside and outside Japan. In particular, the advancement of Asia-centered international alliances will become more important for managing the many strains deposited from Asia once the Nagoya Protocol goes into effect.

Recommendations

The plans of the JCM are appropriate to the proposed change in RIKEN status. The plans include three important items so that the JCM can further develop as a leadership resource center of microorganisms in the world. The first is development of new genome resources of yet-uncultured microorganisms by R&D of high through-put single cell analysis system and single cell genome sequencing. The second is the functional development of new microbial resources using their genome information for future green and life innovations, such as microbes degrading and converting biomass, microbes influencing iron corrosion, probiotics interacting host immune systems, commensals suppressing pathogens and maintaining health/homeostasis, etc. The third is building a new system that is the equal to or better than the registered collections of EU.

The RIKEN BRC should create a microbial research and development team to build a system leading to advancements through a close relationship with the bioresource infrastructure project. The JCM can fulfill its role in providing academic and social infrastructures for future green and life innovations and create a positive interaction between research and the infrastructure project by definitely executing the plans proposed.

The last review is reflected in the current plans and strategies. However, to ensure the continued development of the JCM, it is important to make a strategic and concrete succession plan as most of senior research scientists will retire in 4 to 7 years

Bioresource Engineering Division

Division Head: Doctor Atsuo Ogura

Achievements

The Bioresource Engineering Division has accomplished numerous outstanding achievements. They developed and improved basic techniques, which have made significant contributions to the infrastructure of the Bioresource. These techniques include cryopreservation, microinsemination (also known as intracytoplasmic nuclear injection or ICSI), somatic nuclear transfer cloning, and the derivation of new stem cell lines generation. The Division's basic research, such as studies on X-chromosome inactivation in somatic nuclear transfer cloning, genomic plasticity (chromatin modification) and DNA demethylation at the pronuclear stage of embryo development has produced results with high academic value. In summary, the division has made remarkable contributions to bioresource infrastructure.

The key to the Division's long-lasting high productivity appears directly related to the synergy the Division head has developed with his team. He makes the most of the members' abilities by combining the right individuals who can work well together and complement each other. He has a good track record of competitive research funding. He and other members have won numerous awards, and many former members have furthered their careers in new posts. He deserves credit for his human development and management skills.

The Division has pursued compelling research that enables one to generate a mouse clone from a drop of blood and in vitro fertilization in as little as one µl of media. Although the public can easily understand such projects, they can also understand that the projects are challenging for scientists. One reason why projects are accomplished in succession within their respective time frames is the Division's highly effective project scheduling.

There is a strong spirit of collaboration between members of this Division and others in the BRC and with other partners in Japan and overseas, as evidenced by projects with over 50 collaborative researchers. A total of 39 papers have been published since 2011, many in high impact journals. Both the number and quality of the papers published is impressive. The members should also be acknowledged for their contributions to a total of twelve review journals and textbooks.

Numerous activities are available to expose high school students to research and the Division's website provides useful information in a user-friendly manner. The Division has issued two press releases, both of which have had significantly high social impacts and they

were of high quality. Continued efforts to engage the media will lead to more positive media exposure.

In response to comments made during the last evaluation, the Division organized and offered more advanced technical training courses. These courses were of a high standard that recognized RIKEN BioResource Center expertise and capability and were a compelling tribute to the BRC. The Division is encouraged to continue these outreach efforts. Following the comments from the review committee the rabbit iPS cell study was terminated even though this project did produce interesting results.

It should be noted that the Division head has consistently delivered remarkable results for many years. As a RIKEN Core PI, he is one of the leading scientists in Japan.

Recommendations

The Division is developing fundamental technology to support the bioresource infrastructure. Projects are classified into two categories: essential projects for operations, and challenging projects. These classifications are useful as they enable one to clearly define project goals.

The challenging projects will obviously make large contributions to the full range of life sciences and their standard is appropriately high for RIKEN as a non-profit national R&D organization. For example, the PDCA project has worked effectively. Projects commensurate with the BRC's mission should also be promoted. Continuing these activities is highly appropriate for reinforcing the development of operations. The Division's current plans include an emphasis on projects that enhance the resource and continue to make it highly compelling and useful to users. For example, there is a significant emphasis on derivation of new ES cells. Mouse ES cells can provide good models for epigenetics and developmental biology.

Although results with significant scientific impacts are expected, we suggest more efforts should be made in the area of public relations.

Technology and Development Team for Mammalian Genome Dynamics

Team Leader: Doctor Kuniya Abe

Achievements

The team is in charge of developing cutting-edge technologies that reinforce mouse and cell resources. After the last BRAC, Dr. Abe reorganized the team to adapt this direction. Along this direction, the team has strived for the development and improvement of sophisticated technologies to characterize genotypes, epigenotypes and phenotypes. The team has made significant achievements in two areas: One is bioimaging technology. The development of bioimaging technology using a three-dimensional internal structure microscope (3D-ISM) through joint research with Dr. H. Yokota, RIKEN, Wako, is of particularly high international originality and of acclaim. The other is a new technology is to study epigenome dynamics. This is a new type of cutting-edge technology aimed at fusing epigenome dynamics with new imaging technology. Although there are still many technical hurdles to overcome, whole-mount meFISH (methylation-specific FISH for detection of DNA methylation status in situ) technology would blaze a new trail for the study of epigenome dynamics at the whole body level as well as cellular level. All these achievements are highly praised, because they add new value for bioresources in BRC.

Another achievement to be emphasized is development of a method for epigenome (DNA methylation) analysis using a minute amount of cells, i.e. 100 cells. Using this technology, the team discovered large, germ cell-specific hypomethylated DNA domains on the X chromosome. This is a significant finding in the field of epigenetics.

A variety of research collaborations have been carried out within BRC or RIKEN, as well as inside Japan to develop advanced technologies. These collaborative efforts have produced successful results. A good example is the three-dimensional internal structure microscope (3D-ISM). This technology has the potential to benefit many researchers who are interested in observing the internal structure of organs or even the whole body. This technology could be used in the Japan Mouse Clinic and Experimental Animal Division in BRC. On the other hand, collaborations outside Japan are limited, so it is necessary to make further efforts for international cooperation.

In terms of public relations activities, the team's achievements are mainly provided through academic papers and are not sufficiently conveyed to the public. However, it might be better for RIKEN BRC to publicize its activities in a systematic manner as an organization, rather than by the team.

The committee previously commented that the research subjects the team worked on were too broad, and therefore suggested that the team should focus on more restricted fields, such as technology development for bioimaging and epigenome analysis. Addressing these suggestion and recommendation, the team has developed a variety of new technological solutions focusing on epigenome analysis and imaging, and its efforts should be praised. The previous recommendations and suggestions have been fully incorporated into future plans to improve the technologies of bioimaging and stem cell/epigenome analysis.

Recommendations

The team plans to go further with the improvement of imaging and stem cell-related technologies from the whole body level to the cellular level. 3D-ISM is a particularly innovative technology, because of its high resolution. EpiSC technology is also a very promising theme. In particular, the team discovered that a Wnt-inhibitor suppresses the heterogeneity of gene expression in EpiSCs. Based upon this finding, the team may be able to establish stable stem cell lines with high reproducibility. It might make great contributions to a wide range of stem cell biology. The improvement of EpiSC technology is also important not only for enhancing stem cell biology but also for reinforcing the value of cell materials as bioresources.

Overall, these research plans are commensurate with the new organization of RIKEN, and will be of high importance to the BRC.

Technology and Development Team for Mouse Phenotype Analysis (Japan Mouse Clinic: JMC)

Team Leader: Doctor Shigeharu Wakana

Evaluation

Phenotypes are fundamental properties of mouse strains and mutants, and a key area for research and activity in a leading bioresource. Platforms for comprehensive mouse phenotyping have been established at the JMC to acquire systematic mouse phenotype information. This essential work enhances the significance of the BRC as well as the value of its bioresources.

The team's collaborations and involvement with international organizations such as IMPC are applauded. These joint efforts create standardized and robust methods for mouse phenotyping leading to the development of a global standard rather than just a local Japanese standard. The active participation of JMC in various international bioresource projects, including IMPC, as well as with AMMRA, facilitates the internationalization of basic bioresource research in the mouse in Japan.

While phenotyping of ENU mutant mouse strains continues to make a contribution to the number of phenotyped strains, the growth of phenotyping in the JMC will increasingly reflect the enormous increase in knockout and CRISPR/Cas9 mutants, which overall will prove to be a significant contribution to mouse bioresource data. The data obtained from the comprehensive phenotyping of mutant mice is one of the few types of bioresource information that is highly standardized and widely accessible not only to scientists and the public in Japan, but worldwide. This achievement enhances the purpose and mission of the center.

The team's academic achievements, including numerous published papers, are increasingly highly recognized, and if the team realizes its goals, it will make a substantive and important impact on the IMPC program. Both the national and international cooperative projects are being delivered to a high standard. The mouse phenotyping project, conducted within the IMPC framework, is particularly noteworthy for its international cooperation where the JMC works closely with its international partners in terms of mouse production, mouse phenotyping, data capture and analysis, and data dissemination.

There has been some success in publicizing these activities, though there is more that needs to be done in this sphere to spread the work both across biomedical sciences and within wider scientific and public domains. It would be worthwhile to increase the efforts being made to

enhance and improve media exposure to bring this important work to the public's attention.

Although some expenses are charged to the users of the JMC, we recommend that the charging system be regularly reviewed. While a charging system may be controversial if the team continues to use public funding to maintain its activities, it is not unreasonable for the JMC to consider recovery of a portion of the costs. It will be important to consider long term stable funding for JMC's contribution for IMPC and the committee were pleased to hear that the Director is making vigorous efforts to persuade the government to invest in this important international effort (see also below).

Recommendations

Proposals to enhance the mouse phenotyping platform and to introduce additional sophisticated behavioural platforms associated with psychiatric disorders are very welcome and should continue to be given high priority. In addition, the proposal to investigate Developmental Origins of Health and Disease (DOHaD) is imaginative and innovative and will benefit from the enhanced behavioral phenotyping.

The council was also pleased to hear that other systems likely to be affected by the fetal environment such as diabetes, obesity and cardiovascular disease would not be ignored. Moreover, such research will benefit from close collaboration and cooperation with BRC groups working on epigenetic modifications. Overall, malnutrition in pregnant women remains a serious problem and establishing a mouse model system to assess the effects of maternal malnutrition on phenotypes throughout the organism's lifetime could be of considerable significance for both academia and society and is worthy of significant support.

The Japan Mouse Clinic has both the infrastructure and the expertise to investigate the various issues associated with interactions between genes and environmental factors. A nationwide framework, with the Japan Mouse Clinic as a core facility central to this enterprise, has the ability to tackle such challenges and should be established. In this respect, the Japan Mouse Clinic operation is strategically important for RIKEN.

The JMC is the only team in Japan that is intensively using the accepted international standardized protocols in mouse phenotyping; therefore, this work is indispensable for life sciences and medical research using mutant mice in Japan. The center should continue to host and support the team and its mouse phenotyping work for the foreseeable future.

Following the widespread development and introduction of the CRISPR/Cas9 mutagenesis system, there will be a significant expansion in the production of null mutant mice. The team's

intention to meet the challenges from the expansion of CRISPR/Cas9 work and to apply internationally standardized phenotyping platforms is to be welcomed.

The team's phenotyping techniques and approaches are fundamental for increasing the value of the BRCs bioresources. This work also has wide academic significance. In this regard, the facility should continue to develop mechanisms to enable the JMC to gain more public recognition. Thus, the proposal to use the phenotyping pipelines to investigate DOHaD and to elaborate and improve the breadth and depth of phenotyping platforms, such as those linked with behavioral-neural systems, is to be applauded.

It will be important as the phenotyping work expands that the team focuses on accurate estimations of the increasing number of mice to be phenotyped and finds solutions for the current insufficient capacity for mouse maintenance. Efficient project management and stable funding are crucial for the continuation of this work. It is critical to secure a sufficient budget that will allow the Japan Mouse Clinic to maintain and expand its operations since the clinic will play a crucial role in Japan's leadership in the area of gene function studies for the next decade or more.

The introduction of international standardization at the JMC and the development of its own unique technologies are essential for the continued success of the clinic, and a budget that reflects the future growth in work should be allocated.

Unlike many other IMPC member countries, no public funding for projects is directly allocated in Japan. Rather, the Director allocates a budget from within core resource. The Council welcomed the Directors support for the JMC and was pleased to hear that he was seeking a direct allocation of funding to support the IMPC project.

Education and training of the next generation of scientists in the importance of mouse phenotyping, its value for translational research, and the role and impact of programs such as IMPC should be part of the outreach of the JMC and, more widely, the BRC.

The previous evaluation results were well reflected in the current work and future proposals.

Team for Advanced Development and Evaluation of Human Disease Models

Team Leader: Doctor Tetsuo Noda

Achievements

The achievements of the team are in two areas. One is identification of the mutated genes in mice obtained from an ENU-mutagenesis protocol and their detailed phenotyping to show they are suitable disease models. As this previously active part of this program will be sunsetted the papers documenting these mutants as models for specific human conditions are in the publication process, (2 published, 1 submitted, 3 in draft, 2 in preparation). The goal is to finish these papers now or as soon as possible. For example, analysis of APC-mutant mice, showed the phenotype of the mutant mice can change, with the length of truncation of the APC gene, resulting from the position of the mutation, an academic achievement to be considered in evaluating human disease. Findings such as these enhance the existence of the BioResource Center and its phenotyping capabilities. Further, efficient and effective disclosure of such mutants to the academic community should attract researchers to use them in their own cancer work.

The second achievement is in establishing human cancer cell line xenograft models, and also Patient-Derived Explants (PDX), which are biopsied directly from patients and placed into mice, through the Project for the Development of Innovative Research on Cancer Therapeutics (P-DIRECT). This area will be the foundation for future cancer research of this team, a new research theme, and its results could trigger the growth of resource development in the future. These two xenograft technologies (cancer cell lines and PDX) have are being to explore pharmaceutical compounds in a library of thousands of compounds in hopes of identifying new drugs.

Overall, it was concluded that the team has made remarkable contributions to bioresource infrastructure and it may have a real social impact. The potential for contribution to the academic medical community is also high because the team engages in bioresource research projects which are generally difficult for the biomedical community to conduct without assistance from the resource community.

This kind of work promotes cooperation and coordination inside RIKEN, with relevant organizations in Japan, and with the medical and industrial communities. The cooperation with the Japan Mouse Clinic has been very significant, the cooperative relationship with the Cancer Institute of Japanese Foundation for Cancer Research (JFCR) has provided effective support for the infrastructure project in P-DIRECT and the team has worked with the Institute

for Virus Research at Kyoto University for analysis of ENU-induced mutant mice.

Although there have been cooperative activities within RIKEN and inside and outside Japan, they have been limited. In particular, the team needs to work hard on international cooperation. There is international competition in the cancer xenograft area and the value of collaboration will come after publication.

Regarding cooperation and financial arrangement between the BRC and the Cancer Institute, it seems that no effective measures have been taken since the last recommendation to work this out. These are issues that should be addressed by the Center as a whole.

Recommendations

It seems that the most difficult part, complete analysis of ENU-induced mutant mice has been accomplished and is in the publication process and this will wind down this team's activities in this area. Publication and release of the characterized mutants is important. However, it is time now to focus on the xenografts models, a promising new approach in cancer translational research where the BRC may be of some real help. Overall, their research plan is so promising that it is expected to have large social impact and make significant contributions to the bioresource infrastructure. While doing this, it will be necessary to pay sufficient attention to the ethical issue of handling bioresources derived from specific individuals.

As maintained by this team, the transplant model of patient-derived cancer tissues is considered most appropriate for evaluating drug efficacy at the individual level and should be promoted by the Center in order to encourage Japanese cancer research. It could produce results leading to innovative development of new anticancer drugs. Certain successful results have already been obtained, and concrete results are expected in the near future.

One of the comments made by the previous Review Committee was that the team did not present papers on ENU-inducted mutant mice in a timely manner. The team has now published papers on two mutations and disclosed them as bioresources and has a clear schedule for paper publication of the other six. Publication is important so that the characterization of the mutants and their release to the scientific community is intertwined. While it is certainly the top priority for RIKEN's BRC to enrich mutant mouse resources, it is strongly recommended to disclose them at an early stage in the investigation so as to encourage their usage amongst academic researchers. Ensuring the neutrality and equality of resource use is one of the fundamental issues for RIKEN's bioresource infrastructure.

The stage of infrastructure development has ended, and it is time to consider how to let

society use these bioresources widely. The team is requested to make a sufficient review of the direction this is to take. The emphasis of the future plan is to transform the PDX model into a bioresource, and the project is being organized as part of the overall plan. The proposed research is very high in academic value and is considered to be a project to be handled by a non-profit national R&D organization. From this point onwards the team the results of the Cancer Institute from those of BRC appears to be a collaborative study. The team should thus press forward to publish their papers in a timely fashion so that the resource can be utilized by all.

Mutagenesis and Genomics Team

Team Leader: Doctor Yoichi Gondo

Achievements

The team has developed a unique library of ENU-mutagenesis derived F1 sperm and corresponding DNA. For the library of the mutant mice induced by ENU, it is worth noting that the team remarkably improved the efficiency of DNA mutation detection by introducing the AB Ion Proton device. Using a mouse strain with the mutant genes identified in this strain, the team conducted joint research with external organizations and published some impactful papers about the joint research. The team therefore made contributions to the bioresource infrastructure. The team's technical development of the mutation detection by AB Ion Proton is worth to mention. Exome analysis data are very rare and are something to be proud of in the world. The team helps to enhance BRC's reason for existence. Their contribution to the bioresource infrastructure is also high. We believe that only BRC has the ability to obtain such resources and corresponding data.

The resources with ENU mice and sequence information integrated as a set are very rare worldwide, which can help to enhance the reason for the BRC's existence. Epoch-making results have begun to emerge, and even greater results can be expected in the future. We expect that the team will even more actively engage in joint research using these resources. Whole exome analysis of 24 individuals was conducted to clarify the existence of interactive genetic sets by detailed analysis of ENU mutations.

The team is working diligently to take on the biological challenge of complex systems (interaction of genes). We were presented with an experimental approach toward discovery of modifier loci, which after discussion raised serious questions about the likelihood of achieving successful results. There is a certain risk of the approach towards modeling complex "oligogenic" traits. In depth power calculations have to be performed prior to the start of the experiment. The outcome of the power calculation should drive the decision to start or not to start the experiment. Alternatively the group proposed to focus on homozygous lethal phenotypes and to create allelic series of mice for these loci. This is an important and essential approach toward the understanding of gene function and is greatly appreciated. Progress is steadily and surely being made with mutation cataloging and disclosure. In short the team is judged to have made sufficient and important contributions to bio-resource infrastructure.

Collaboration, such as joint research with Fujiyama Group of the National Institute of Genetics, Pacific Biosciences California, Inc., etc., is under way to develop a DNA mutation

detection system using the next-generation sequencer.

The team is actively involved in international collaboration, including holding international conferences. Although the team has been conducting joint research with organizations inside and outside Japan, such efforts do not seem to have produced many successful results. It is assumed that some information is not disclosed because of confidentiality clauses signed with users. RIKEN must consider how to evaluate such cases.

The team has a good cooperative relationship within the Center and RIKEN, and it has begun to bear fruit. We believe that its collaboration with organizations inside and outside Japan will rapidly grow in the years to come. We have a feeling that the recent trend in the world will guarantee the effectiveness of this activity in terms of public relations.

The team successfully responded to the recommendations made by the previous review, by helping to enhance the BRC and obtaining advanced, innovative, and academic results. They are very unique as genetic resources. This research should be continued by reinforcing the sequence information. However, as mentioned earlier, future plans will have to be formulated based on the fact that the CRISPR/Cas9 System has been developed.

Recommendations

The team has genetic resources that are unique in the world, and which thus can give RIKEN BRC a unique advantage. It is a research theme that should definitely be pursued by RIKEN BRC. It is hoped that greater efforts will be made to release information.

It is a project worth being conducted by a non-profit national R&D organization. However, the team is at the beginning to provide evidence for the new plans. It is necessary to let non-specialists easily understand that the team's research is a very useful. Organization theory will have to be used to explain how project continuity can be ensured.

The concept of resource development of systematic modeling of genetic interactions and interactions with the environment is important. It will be highly useful knowledge even if only a few genetic interactions are revealed. The plan that utilizes whole exome analysis requires muscle power and is the very project that RIKEN should vigorously promote. Systematic analysis of ENU mutant mice and KO mice as the culmination of the model mouse research is important. It stands to reason why RIKEN should do it. In order to make it a viable project to be pursued by a non-profit national R&D organization, it is important to determine the scale and formulate a schedule and plan for its achievement.

The addition of new annotation information that supports estimations of the function(s) of amino acid substitution in the form of the mutant catalog is highly advantageous for users and is a significant plan. According to the team, the frequency of ENU-induced mutations on the genome (up to 5000 mutations/strain) is located between KO mice (one mutation/strain) and polymorphism among strains (million SNPs/strain), which is unique and useful. Furthermore, the usefulness and feasibility of the said resource for the analysis of intergenetic interaction is not particularly clear at this stage. The team should continue exploring new applications of ENU mutants. For example, since ENU mutations are characterized by single amino acid substitution, one idea would be to reinforce a line of allelic series such as hypomorph mutation targeted on the protein functional domain by focusing on some important genetic cascades. Another idea would be to target the gene clusters that cause fatality to KO mice.

Now that destruction efficiency of target genes has been greatly improved by the CRISPR/Cas9 system, it may be necessary to reconsider what value the genetic resources of the mice that have random mutation by ENU mutagenesis have.

It may be difficult to materialize the complex system biology, which is the ENU mutation and gene set, within a time frame of five years or so. This is because the team may have to focus its analyses on individual diseases or specific genes. When considering the gene set, it might be necessary to also use point mutation that uses the recently reported CRISPR system, even though ENU mutation is taken as the gateway. This project itself, which includes the materialization of a $1,000 sequence in its outlook, is sound and is expected to produce advanced results.

The team successfully responded to the recommendations made by the previous review, by helping to enhance the BRC and obtaining advanced, innovative, and academic results. This research should be continued.

As mentioned earlier, future plans will have to be formulated based on the fact that the CRISPR/Cas9 System has been developed.

Technology and Development Unit for Knowledge Base of Mouse Phenotype

Unit Leader: Doctor Hiroshi Masuya

Achievement

Generating appropriate tools for data capture of mouse mutant phenotypes, their analysis and dissemination is a key issue for promoting the use of bioresources. The unit has begun to make significant progress in three areas:

-Developing appropriate LIMS systems for the capture of phenotype information from the JMC

-Beginning to establish the statistical tools for the analysis of phenotype data and the identification of significant outliers

-Addressing the very wide issues of phenotype descriptors i.e. ontologies, and employing ontological structures to facilitate data integration across diverse datasets, including those between species. All of these areas are keys to underpinning the successful development and integration of phenotype information that is a critical pillar for the success of the BRC.

The first area in particular has been successful and it is clear that capture of phenotype data is underway, and data upload to the DCC for the transfer of phenotype data for the IMPC has been successful. Other areas are under development and while some progress has been made the Council questions the breadth of work that is proposed for the future, and whether or not there is sufficient focus in the plans looking forward (see below), recognizing that resources to the Unit are limiting.

In terms of the overall activities, the BRAC welcomes the efforts that have been made to integrate the activities with other partners internationally, particularly the IMPC. However, more attention needs to be paid to similar activities underway at institutions worldwide in the development of ontologies and statistical tools.

The team has a very significant focus on the development of ontologies and database integration. This is an important area, not only linking the mouse datasets being generated to human disease databases, but also illuminating connections between model organisms. Successful efforts in data integration are exemplified by the "recommended mice" function that has been developed for the phenotype database. It is clear that the team is focused one extending such functionality.

As the phenotype database grows, and links are made with human diseases, the Unit should take the very many opportunities that will arise to promote the utility of the work for the wider biomedical sciences community and health.

Although the Unit has presented fewer papers than other groups, it is still a respectable number considering there are fewer people in the Unit and given the nature of informatics work, which does not necessarily lend itself to a high publication output.

The Unit has worked well with the Technology and Development Team for Mouse Phenotype Analysis (JMC) within the center and with the Database Center for Life Science in Japan. Clearly the interface with the JMC is critical for the success of phenotyping programs at the BRC, and the success of this interface is reflected in the fact that the data capture LIMS systems are working well. Also there has been a recent enhancement of the LIMS system. At the international level, the Unit has played an active role in IMPC. For example, it is a member of the Statistics Technical Group of IMPC. It has also participated in the Cell Line Ontology Consortium, which was established for international standardization of cultured cell information. This activity has contributed to the creation of a standard format and is well regarded.

The rapid increase in visitors to the website indicates that there is considerable interest within the scientific community on the phenotype data being produced at the JMC. Moreover, we can expect that this activity will have a positive impact on the wider public perception of the work of the Unit and of the JMC. Nevertheless, there are opportunities to continually review the outreach of the Unit and the JMC and the dissemination of the utility of the work that is being done for medicine and human health.

The responses to most of the comments in the last evaluation were appropriate. One comment highlighted the need for improvements in user-friendly aspects of the database. The Unit has as a consequence developed a "recommended mice" interface, which allows users to browse other mice with similar phenotypes in an organized way. This effort is highly applauded and the Council expects to see a continuing effort towards data integration that focuses on the ability to move seamlessly amongst similar phenotypes both within and between species. As discussed above, there should be a continuing effort to gain public recognition of the importance of database development and data dissemination to the wider scientific community. As part and parcel of this, more effort should be made to illustrate the functionality of the database to diverse users as the database continues to develop.

Recommendations

While the three key areas of 1) data capture 2) data analysis 3) data integration and dissemination are all appropriate for RIKEN and will have significant impacts on both academia and society, the Council questions the focus of the Unit’s work overall and proposes

a re-prioritization across each of these work areas.

The highest priority should be given to continuing to underpin data capture systems for the JMC. Second, we welcome the innovative efforts that are being made in the field of ontologies with regard to data integration (and thus dissemination). However, very importantly, the Unit should carefully consider the relationship of their work and proposals in this area to other work that is being undertaken in mouse genetics in ontological structures, such as those underway at MGI (the MPO) and within IMPC. It is critical that the ongoing developments at BRC are integrated with and take account of developments in phenotype ontologies at other institutions, and that every effort is made to ensure that there is not duplication of effort.

While BRC and JMC clearly require tools for statistical analysis of phenotype data, we are concerned that insufficient consideration has been given to accessing tools that are being developed elsewhere for phenotype data analyses, particularly within the IMPC and IMPC institutions. Moreover, given the limited resources at the Unit's disposal, to move forward with and develop high quality systems in all areas is unwise. Rather the focus should be on the development of the strengths of the Unit in ontological systems (aligned with efforts being made in ontologies at other centers), and to acquire and implement statistical tools that are being developed elsewhere particularly within the IMPC consortium.

This is a highly successful Unit, and with some realignment of priorities and focus as indicated above, the Unit has excellent opportunities to make a pivotal contribution to the development of disease models and their relevance to human diseases. We recognize that the Unit is short of staff for this work and as a consequence we recommend increased focus as well as ensuring that the Unit takes the opportunity to import appropriate tools where possible. It is not possible for the Unit to undertake successfully the full breadth of development work that is proposed.

The comments made in the last evaluation are reflected in the current work that is proposed. However, given the resources that are available to the group there is concern that the future plans are overambitious and need focus. Clearly, more could be done with increased funding. We make some critical suggestions for areas of focus in our comments above.

The Unit has made an excellent start in support of the JMC and the mouse phenotyping programs at BRC. This is a critical and important area for Japanese genetics research both nationally and internationally. Careful consideration of future plans will assist in ensuring that

the Unit delivers a world-class system for the data capture, analysis and dissemination of mouse phenotype data.

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The Fifth Advisory Council Meeting of the RIKEN BioResource Center

Date: June 8 - 10, 2014
Venue: RIKEN BioResource Center and Okura Frontier Hotel Tsukuba

Day0: June 8 (Sun)

Time	Subject	Presenter	Venue
19:00-19:30	Mission of the RIKEN BioResource Center and the BioResource Center Advisory Council (BRAC)	Dr. Yuichi Obata, Director, RIKEN BioResource Center	Okura Frontier Hotel
19:30-19:45	Introduction of BRC Members and Supporting Staff		
19:45-21:00	Informal Reception		

Day1: June 9 (Mon)

Time	Subject	Presenter	Venue
8:30-9:00	Move to RIKEN from Hotel		
9:00-9:05	Opening Remarks	Dr. Yuichi Obata, Director, RIKEN BioResource Center	RIKEN BioResource Center
9:05-9:10	Remarks from Chairperson	Dr. Barbara Knowles	
9:10-9:30	Introduction to RIKEN	Dr. Maki Kawai, Executive Director, RIKEN	
9:30-10:00	Q&A		
10:00-10:15	***Break ***		
10:15-10:50	Experimental Animal Division	Dr. Atsushi Yoshiki, Division Head Dr. Hiromichi Yonekawa, Chair	
10:50-11:25	Bioresource Engineering Division	Dr. Atsuo Ogura, Division Head Dr. Toshihiko Shiroishi, Chair	
11:25-12:00	Technology and Development Team for Mouse Phenotype Analysis	Dr. Shigeharu Wakana, Team Leader Dr. Toshihiko Shiroishi, Chair	
12:00-12:35	Cell Engineering Division	Dr. Yukio Nakamura, Division Head Dr. Tatsutoshi Nakahata, Chair	
12:35-13:30	*** Lunch ***		
13:30-14:05	Gene Engineering Division	Dr. Yuichi Obata, Division Head	

Time	Subject	Presenter	Venue
14:05-14:40	Technology and Development Team for Mammalian Genome Dynamics	Dr. Kuniya Abe, Team Leader Dr. Toshihiko Shiroishi, Chair	RIKEN BioResource Center
14:40-15:15	Team for Advanced Development and Evaluation of Human Disease Models	Dr. Tetsuo Noda, Team Leader Dr. Toshihiko Shiroishi, Chair	
15:15-15:50	Experimental Plant Division	Dr. Masatomo Kobayashi, Division Head Dr. Kiyotaka Okada, Chair	
15:50-16:05	***Break ***		
16:05-16:40	Microbe Division	Dr. Moriya Ohkuma, Division Head Dr. Makoto Watanabe, Chair	
16:40-17:15	Mutagenesis and Genomics Team	Dr. Yoichi Gondo, Team Leader Dr. Toshihiko Shiroishi, Chair	
17:15-17:50	Technology and Development Unit for Knowledge Base of Mouse Phenotype	Dr. Hiroshi Masuya, Unit Leader Dr. Toshihiko Shiroishi, Chair	
18:40-19:10	Move to Hotel from RIKEN		
19:30-21:00	Official Reception Hosted by Director of RIKEN BioResource Center	All BRAC and BRC Members	

Day2: June 10 (Tue)

Time	Subject	Presenter	Venue
8:30-9:00	Move to RIKEN from Hotel		
9:00-9:20	Discussion on Terms of Reference from the Director of BRC (1)	Dr. Yuichi Obata	RIKEN BioResource Center
9:20-10:20	Discussion with BRAC Members		
10:20-10:30	***Break ***		
10:30-10:50	Discussion on Terms of Reference from the Director of BRC (2)	Drs. Obata, Abe, Kobayashi, Yoshiki, Nakamura	
10:50-11:30	Discussion with BRAC Members		
11:30-11:50	Discussion on Terms of Reference from the President of RIKEN	Drs. Obata, Abe, Kobayashi, Yoshiki, Nakamura	
11:50-12:30	Discussion with BRAC Members		
12:30-13:30	***Lunch ***		
13:30-14:50	Discussion with BRAC Members		
14:50-15:00	***Break ***		
15:00-15:50	Preparing reports		
15:50-16:50	Closed Discussion among BRAC Members and Summarizing a Report		
16:50-17:20	Reporting from the Chairperson to the President of RIKEN and Director of RIKEN BRC	Drs. Knowles, Kawai (TV) and Obata	
17:20-17:30	Closing Remarks	Dr. Yuichi Obata	
17:30-18:00	Move to Restaurant		
18:00-19:30	Working Dinner	All BRAC and BRC Members	

The List of the RIKEN Participants

Dr. Maki Kawai	Executive Director, RIKEN
Dr. Yuichi Obata	Director Division Head, Gene Engineering Division
Dr. Kuniya Abe	Deputy Director Team Leader, Technology and Development Team for Mammalian Genome Dynamics
Dr. Atsushi Yoshiki	Coordinator Division Head, Experimental Animal Division
Dr. Masatomo Kobayashi	Coordinator Division Head, Experimental Plant Division
Dr. Yukio Nakamura	Coordinator Division Head, Cell Engineering Division
Dr. Moriya Ohkuma	Division Head, Microbe Division (Japan Collection of Microorganisms: JCM)
Dr. Kaoru Fukami	Division Head, Bioresource Information Division
Dr. Atsuo Ogura	Division Head, Bioresource Engineering Division
Dr. Shigeharu Wakana	Team Leader, Technology and Development Team for Mouse Phenotype Analysis (Japan Mouse Clinic: JMC)
Dr. Tetsuo Noda	Team Leader, Team for Advanced Development and Evaluation of Human Disease Models
Dr. Yoichi Gondo	Team Leader, Mutagenesis and Genomics Team
Dr. Hiroshi Masuya	Unit Leader, Technology and Development Unit for Knowledge Base of Mouse Phenotype
Mr. Hiroshi Imaizumi	Director, Tsukuba Administrative Division