The 15th Committee for Experimental Animal Resource
Evaluation and Suggestions

(April 4, 2016)

Experimental Animal Division
Division Head: Atsushi Yoshiki

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

◎ *1-1a. Have sufficient results been achieved? (The BRC's standing in the world, contribution to society)*

- From the following perspectives, the Division should be evaluated as meeting or exceeding expectations:
    1. In spite of limited budgets, the Division has achieved goals for collection and distribution of mouse strains. Quality control and technology development are also worthy of acclaim. In terms of the scale of projects and the quality of those resources, the Division has become an international core facility for mouse resources second to the Jackson Laboratory.
    2. The Division has participated in the International Mouse Phenotyping Consortium (IMPC) and set the mouse production on track by genome editing and already supplied the Japan Mouse Clinic genetically mutated mice. The achievement exceeded expectations.

- The Committee has advised as below for the Division to achieve sufficient outcomes in future:
    1. The effort to gain new depositors is important for this project.
    2. With regard to the international status and evaluation, it is desirable to evaluate the Division with objective evidence, not just by self-evaluation.
    3. The policy regarding the acceptance and distribution of genome edited mice should be documented and disseminated to demonstrate the leadership of the Division.

4. With spreading CRISPR/Cas9 technology, a quicker distribution of resources will become important to increase the future utilization of mice. The criteria for choosing whether a strain should be maintained alive or cryopreserved should be clarified, and the Committee should recommend increasing live strains in response to users' needs.
5. Questionnaire surveys and other means for grasping users' needs should be implemented more actively. Ingenious measures to boost the response rate might be considered, such as providing a credit for distribution to questionnaire respondents. This kind of activity would also provide an opportunity for promoting the BRC.
6. For tissue-specific Cre drivers, human disease models, and strains that cannot be readily produced using genome editing, more specific guidelines regarding collection methods should be indicated.
7. Knowledge regarding the quality of resources obtained by means of strict quality management operations is important, and it should be published in *Experimental Animals* or other specialist journals.
8. Regarding the duplicate efforts of rederivation being done on transfer of mice from the BRC to other institutions, the Division should let animal facility managers know such wasted works unnecessary.

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

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

- The Committee points out and advises for further improvement as follows:
    1. In order to expand users, it will be necessary to collaborate also with Cell Engineering, Microbe, and other divisions.

2. There is a need to prioritize strains that should be prepared based on the results from surveys of user needs.
3. It will be necessary to develop methods for speedy expansion of living stock in a short time.

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

- From the following perspectives, it can be evaluated as adequately analyzed. The Committee points out and advises for further improvement as follows:
    1. It should be evaluated as a major progress in terms of supporting the resource foundation for life sciences in Japan that the number of live strains can be restored up to 500 with partial recovery of the budget.
    2. For further gaining trust and increasing use, the Division should strengthen public relations activity. It is important to send messages on the necessity and the importance of the BRC to the mouse research community to secure sustainable funding, as well.
    3. Increasing the live strains, starting up a new team for disease model development, and improving information technology are all important issues. It is necessary to clarify cost estimates of personnel, equipment, and operation, and to create roadmaps accordingly.
    4. Disease models that incorporate human disease genome information are being developed at numerous other medical research institutions. It would be desirable to explain how to differentiate the BRC from other institutions and how the BRC is unique.

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

- From the following perspectives, it can be evaluated as generally reasonable:
    1. Establishment of resources to serve as models for rare diseases and diseases for which risk is increasing with ageing is correct as a direction that addresses society's needs.
    2. The following directions for collection are adequate. Firstly, mice that cannot be produced using CRISPR/Cas9 should be collected. Secondly, for mice produced using CRISPR/Cas9, the first generation genome-edited founder mice are not accepted for deposition due to mosaicism. Only the genetically-defined mice of the second or later

generations which have been published in research papers should be collected.

- The Committee points out and makes suggestions for further improvement as follows:
    1. Regarding resource development, it would be strongly recommended to pursue implementation in collaboration with other divisions and development teams.
    2. Regarding the development of disease models with human mutations, it is necessary to clarify which genome information will be used, collect related information, and confirm the validity of methods.
    3. The most important mission of the BRC is to distribute mouse strains of high quality by advanced quality management. Development of even more highly precise and rapid quality management methods and improvement of phenotyping platforms are necessary.
    4. It would be desirable to provide explanations of specific research themes and measures regarding relationships with epigenomes and diseases.

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

- From the following perspectives, it can be evaluated as appropriate:
    1. Quality management will remain important as a mission of the Division and the steps should continue to be taken to prioritize it in future.
    2. For the BRC as a whole, founding a Next-generation Human Disease Model Development Team responds to growing demand from the research community. This response is reasonable as an initiative.

- The Committee points out and makes suggestions for further improvement as follows:
    1. Quality management is a most important field. The Division is expected to properly conduct quality control of transgenic mice which will increase even more rapidly in future. The Division should also play an educational role in the quality management.
    2. It should be appropriate for the Division to closely collaborate with the new model development team and to act as one group in developing resources. At the same time, if coordination with existing development

teams is less than sufficient, steps should also be taken to review and improve that situation.

3. Developing mouse models with human disease mutations is correct as the direction for future, but it will be necessary to select proper human disease mutations of which we can expect users.
4. It would be advisable for this resource project to emphasize continuity over novelty.

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

- From the following perspectives, it can be evaluated as generally appropriate:
    1. The BRC should also aim to make a contribution toward overcoming the issues of an aged society. The policy of preparing and improving disease models for rare diseases and age-related diseases is worthy of approval.
    2. New technology development for quality management of resources should be included.
    3. With regard to technology development, the necessity for improvement of genome editing technology, live imaging, information analysis technology, and other technology is clear. It is recommended that technology development should be original, not merely following the path tread by others.

3-3. Innovation hub

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

● *(ii) Collaborations within the BRC*

- This is largely adequate, which is commendable, but those portions that are deemed insufficient are pointed out and advice is given in the following.
    1. With regard to industry-academia-government collaboration, it would be desirable to explain the objectives with the corresponding achievements.

2. It is understood and accepted that collaboration has been done frequently within the BRC, but specific explanations of these collaborations were lacking.

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

- From the following perspectives, it can be evaluated as sufficient:
    1. The BRC takes steps to actively pave the way for both collection and distribution of resources, and it is important that this approach be maintained. The plans for collection of next-generation disease model mice, of transgenic strains produced by genome editing, and of new reporter mouse strains, as well as related activities, are all appropriate.

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

- It can be evaluated as sufficiently presented, but for portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
    1. The BRC has been jointly organizing a Mouse Resource Workshop with Nanjing University, and the plan to continue this in future is commendable. The plan to continue participation in the University of Tsukuba Life Innovation Degree Program and take on a share of the Introduction to Bioresources for graduate students is also excellent.
    2. However, organizing international workshops and international summer school does not by itself constitute "developing internationally-oriented human resources." Feedback from course participants on the subsequent results of their participation will probably also be necessary.
    3. It would also be preferable to develop plans for future human resource development projects that collaborate with research institutions in Europe and America.
    4. It is necessary to clarify the definition of internationally-oriented human resources.

● *4. Collaborations among the RIKEN Centers*

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