The 4th Review Committee
Evaluation and Suggestions

(April 8, 2016)

Mutagenesis and Genomics Team
Team Leader: Yoichi Gondo

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

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

- It can be evaluated as meeting expectations:
    1. This team made scholarly significant achievements, which meet expectation. They include development of a mutation detection system using whole-exome sequencing of the ENU-induced mouse mutants; the estimation of spontaneous mutation rates using a next-generation sequencing of the C57BL/6 strain. There is also the initiative attempting to determine platinum genome sequences using PacBio single molecule sequencing of the C57BL/6 reference genome, which will provide a useful foundation for future mouse genome and genetics analyses.
    2. The creation of a mutation detection system using whole-exome sequencing analysis and the development and cataloguing of the single base replacement allelic series can be commended as contributions to the qualitative improvement of resources provided by the BRC. As to other scholarly results, their direct contribution to BioResource Center operations is rather tenuous.

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

- From the following perspectives, it can be evaluated as adequately addressed:
    1. A large contribution has been made toward improving the quality of the library of ENU-induced mutant mice.

- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
    1. The last time it was pointed out that nowadays CRISPR/Cas9 genome editing has dramatically raised the efficiency of target gene destruction so that it will be necessary to reconsider what kind of value there is in the ENU-induced mutants. With regard to this point, the team stated that the two are complementary and useful, for example, for analyses of gene-to-gene interactions, but this explanation is not sufficient.

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

- From the following perspectives, it can be evaluated as adequately analyzed:
    1. The results from this team have reached a "goal" point, and it appears necessary to examine what kind of new contribution should be made in RIKEN BRC in the future.

- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
    1. As a shortcoming, there was the self-analysis stating that the development of a model mouse for gene-to-gene interactions has not yielded any actual results. Taking the genomic mutation density in the ENU-induced mutant library into consideration, the likelihood that genes in particular genetic pathways or networks will also simultaneously have mutations is probably not very high. Therefore, development of a multifactorial disease model using the present library has a low theoretical probability.

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

- From the following perspectives, these can be evaluated as being generally reasonable:
    1. The basic mutation rates per generation and the differences between strains have been overlooked so far, even though these are basic genetic information. Work to discover related information about these matters by re-sequencing is an important task that can only be performed by RIKEN BRC, and this has the potential power to give rise to new directions in genetics.

- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
    1. It was difficult to tell from the explanation given what output is expected in advance of visualizing the gene variations in experimental animals.

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

- From the following perspectives, it can be evaluated as generally adequate, but for some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
    1. For the reasons cited in section 3, an effort to clarify gene-to-gene interactions by the use of material from the ENU-induced mutant library appears to present methodological problems.

3-3. Innovation hub

● *(ii) Collaborations within the BRC*

- From the following perspectives, it can be evaluated as sufficient:
    1. Projects that are only feasible through collaboration with other units within RIKEN BRC, such as the Experimental Animal Division, the Bioresource Engineering Division, and the Technology and Development Team for Mouse Phenotype (Japan Mouse Clinic), are being pursued, which is commendable.

- For some portions that are deemed insufficient, the Committee points out and makes suggestions as follows:
    1. Explanations of the record of results from use of frozen sperm of mice with ENU mutations and of the outlook for the future appeared to be insufficient. Perhaps it would be better to step up the promotion activities for the database that has been disclosed.
    2. It is possible that discovering users of point mutations in genes that resulted in lethal from knockout mutations will lead to discovering additional users. On the other hand, plans to screen for modification genes and to develop a multifactorial disease model are not clear, and the probabilities of achieving the objectives are not yet apparent.