Evaluations and Comments

3rd Meeting of the RIKEN BioResource Center Review Committee

(Mutagenesis and Genomics Team)

April 3, 2014

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?**

- 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 next-generation sequencer. 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 next-generation sequencer is worth mention. If the team can explain about the role of their research on a global scale, we believe it will further enhance their reputation. 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 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 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). Their attitude is praiseworthy. The research of the team, which is conducted systematically, is the right kind of work for collecting and disclosure of basic genetic information that BRC should pursue. Progress is steadily and surely being made with mutation cataloging and disclosure.
- Although their attitude toward research may seem to be excessively aggressive, that is what is important for this project. In this sense, the team is judged to have made sufficient contributions to the bioresource I-infrastructure.

(2) Other matters

- **Collaborations within BRC and within RIKEN**
- **Collaborations inside and outside Japan**
- **Public relations activities**

- 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 participated in an international conference on mouse germline mutagenesis.
- 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.

(3) Response to previous year's evaluation and advice

- It was pointed out before that it is important to show some successful applications of

ENU-induced mutant resources from the results of the team's joint research with organizations inside and outside Japan. In response to this suggestion, the team showed some successful cases. Three papers written by the team staff, including one or two that have already been submitted, are scheduled to be published in 2014. This result is a good start, but it is not sufficient. In particular, there are still issues to resolve about the presentation of the results by the team staff. However, the team responded well to the previous recommendations about improving mutation detection throughput and acquiring external funding.

- The team has taken various actions to reduce analysis costs. Particularly noteworthy are its great efforts to resolve the cost-related problems pointed out by the previous review. The team has continued to acquire funding for its research, which means it is making an effort to continue its research.
- The team has properly responded to the previous recommendations.

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?**

- 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. This explanation, however, does not sound particularly persuasive. 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.

- The team has genetic resources that are unique in the world, and which thus can give RIKEN's BioResource Center (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.
- 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.
- 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.
- 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.
- It is a project worth being conducted by a non-profit national R&D organization. However, the team is poor at providing sufficient explanations. 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.

(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?

- 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. The team is also asked to nurture next-generation researchers.
- The team's responses to the previous review have been incorporated into the results to some extent. However, as mentioned earlier, future plans will have to be formulated based on the fact that the CRISPR/Cas System has been developed.