Evaluations and Comments

3rd Meeting of the RIKEN BioResource Center Review Committee

(Team for Advanced Development and Evaluation of Human Disease Models)

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?**

- The achievements of the team are largely divided in two parts. One is identification of the causal genes of mutant mice obtained from ENU-mutagenesis and the contribution made by detailed phenotyping to the value of the disease model. The other is the establishment of human cancer cell line xenograft models through the Project for the Development of Innovative Research on Cancer Therapeutics (P-Direct) to blaze a trail for establishing the foundation for future cancer research. For the former, papers were published on two of the eight systems of mutation, and the results, which were in accordance of the expectations of the previous Review Committee, were released as a disease model. On the other hand, the human cancer cell xenograft model is a new research theme, and its results are expected to trigger the growth of resource development in the future. Overall, it was concluded that the team has made remarkable contributions to bioresource infrastructure.
- The research results were covered by the media, which had a social impact.
- It is indicated that development of the research about P-Diect is under way. The xenograft model, which helps to instill awareness of the importance of bioresources, has been integrated into that project, and it can be seen that it also helps to enhance the reason for the team's existence.

- For the patient-derived xenograft (PDX) model, innovative results are yet to be achieved. However, the discovery that the gene mutations in the xenograft system are mainly silent mutations, which is greatly different from the cultured cell system, could trigger new discoveries about the biology of cancer cells.
- Regarding analysis of APC mutant mice, it has been found that the phenotype of mutant mice can change, depending on changes in the truncation length of the APC resulting from the position of the mutation. This discovery is a major academic achievement that suggests much potential when the mouse is considered as a model for evaluating disease.
- The data that contain the progress of analysis of ENU-induced mutants are invaluable. They help to enhance the reason for the existence of the BioResource Center and contribute to bioresource infrastructure. High-quality academically important research is being conducted for each of the eight disclosed mutants. It may be nearly impossible for BRC alone to handle all these phenotypes. For a project like this, perhaps it would be more efficient and effective to disclose useful mutants to the academic community at an early stage and let many researchers freely use them.
- The team has been producing academic results that are of the highest class in the world. The level of their academic contribution to the BRC is also high. The team is also engaged in bioresource research projects which are generally difficult for academia to conduct. In this sense as well, the team is making great contributions.

(2) Other matters

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

- At the Center, cooperation with the Japan Mouse Clinic has been very significant. The cooperative relationship with the Cancer Institute of JFCR has provided effective support for the infrastructure project in P-Direct. For analysis of ENU-induced mutant mice, the team has worked with the Institute for Virus Research at Kyoto University.
- There was nothing noteworthy in regard to international cooperation.
- When results are presented in papers, it helps to promote cooperation and coordination both inside RIKEN and with relevant organizations in Japan.

・ Joint research activities were sometimes covered by the media, but no conspicuous P.R. activity was conducted.

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

・ 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. However, the team has presented papers on two mutations and disclosed them as bioresources since that Review Committee met. In addition, the team now has a clear schedule for paper publication and will release the results as they become available. These actions indicate that the team is fully capable of taking corrective measures in response to previous comments and recommendations.

・ Although there have been cooperative activities within Riken and inside and outside Japan, they have only been limited. In particular, the team needs to work harder for international cooperation. Regarding cooperation with the Japan Mouse Clinic and the need to make the financial burden more equitable, it seems that no effective measures have been taken since the last recommendation. These are issues that should be addressed by the Center as a whole.

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?**

- It seems that the most difficult part about analysis of ENU-induced mutant mice has been accomplished. We believe they need to focus on the PDX model, which is a promising new resource in cancer translational research. When doing this, it is necessary to pay sufficient attention to the ethical issue of handling bioresources derived from specific individuals. Overall, their research plan is so promising that it is expected to have large social impact and make significant contributions to the bioresource infrastructure.
- 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 is expected to produce results that can lead to innovative development of new anticancer drugs. Certain successful results have already been obtained, and concrete results are expected in the near future.
- While it is certainly the top priority for Riken's BRC to enrich mutant mouse resources, it is strongly recommended to disclose their use at an early stage and let free competition among researchers take its course. It is considered one of the fundamental issues for Riken's bioresource infrastructure to ensure the neutrality and equality of resource use.
- The stage of infrastructure development has already ended, and now it is time to consider how to let the society use bioresources widely and wisely. The team is requested to make a sufficient review of the direction this is to take.
- The 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. However, would the team be required to clearly explain how to differentiate the results of the Cancer Institute from those of BRC?

(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?

- For analysis of ENU-induced mutant mice, the previous comment suggested that papers be published or resources be disclosed on a timely basis without delay. The team properly responded to this suggestion, and their current plan is to finish the research. 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.

- It is determined that the PDCA cycle is being properly implemented. About 50% of the data on ENU-induced mutants has been released. This has been achieved as a result of drawing in a line in the research.
- The team leader plays various roles. It is probably difficult time-wise for him to continue serving as the team leader. We expect new leaders to emerge from the team staff.
- The team should present more of their papers.