The Report

The Forth Advisory Council Meeting of the RIKEN BioResource Center

August 30 – September 2, 2011

Foundation for Discoveries
And
Access to the Future

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[Black: AC members / Gray: BRC members**]**

August 30 – September 2, 2011
RIKEN Tsukuba Institute
and
Okura Frontier Hotel Tsukuba

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Advice and Recommendations from the RIKEN BioResource Center Advisory Council in response to the BRC Director's Terms of Reference

1. On the scope of bioresources to be collected

Background and explanations:

The policy of the BRC on the collection of bioresources has been to focus mainly on those developed by Japanese scientists. In this way, the BRC has been able to establish itself as a unique center among comparable bioresource centers in the world. The variety of bioresources that have been collected so far by each division will be reported on to this BRC Advisory Council. In addition, the BRC's future plans for collecting bioresources has already been repeatedly discussed by a number of bioresource committees of Japanese scientists.

We want our Center to be established as a first class bioresource center and to this end are working to respond to global trends in scientific research. The BRAC is asked to give advice and suggestions from a global perspective on the strategies and planning for improving the BRC's bioresource infrastructure.

It should be mentioned that the BRC has been working on mouse strains, Arabidopsis, human and animal cell lines including various stem cells, genetic materials of animal and microbe origin, and microbes. We do not plan an expansion to other bioresources, since we think the BRC's bioresources are and will be the major bioresources in the life sciences for the next 5 or 10 years to come, unless the needs of the scientific community change drastically. Furthermore, 22 other bioresources are being handled by core facilities at other universities and institutes designated under the MEXT National BioResource Project.

Advice and Recommendations from the BRAC:

Regarding the collection of resources, the BRC already has one of the world's leading collections. We think that the Center already has a very strong collection and does not need to expand into new bioresources for the next *five* years unless there are specific requests, and the Council thinks it is not necessary to expand the collection of bioresources to outside Japan at the present time. The Council would like to emphasize the necessity of having top-quality bioresources rather than having the greatest quantity.

If there are unforeseen request, the director can ask the Council for its opinion and respond flexibly to such requests.

2. On the scope of research and development that are needed for the BRC

Background and explanations:

The BRC needs programs of research and development (R&D) for improvement of its bioresource infrastructure. R&D includes development of technologies for quality control and improvement, and for effective and efficient operation as well as characterization of bioresources and development of novel bioresources. These programs are essential to ensure the trust, sustainability and leadership of the resources and of the Center.

At present, the BRC has one division, four teams, two subteams and one unit dedicated to R&D related to bioresources. In 2008, the R&D capability of the BRC was doubled by the addition of three teams and one unit from the former mouse mutagenesis project oat the RIKEN Genomic Sciences Center（GSC）.

The R&D division, teams and unit are all, however, focused on mouse resources, except for one subteam. Other resources also need R&D programs from various reasons and a number of these will be proposed to this meeting by the BRC.

Furthermore, research trends and the need for bioresources have been changing very rapidly. Both stability and flexibility/mobility are required of the Center. In 2013, all the divisions and teams originally in the BRC will have existed for over 10 years, and even the teams and unit from the GSC will have been at BRC for over 5 years. It is time to re-examine the missions and aims of all the R&D programs.

The Center has provided its R&D components with most of its operating funds to ensure that they can accomplish their missions. The Center has never forced any division or team to obtain external funds, because external funds may induce them to deviate from their primary missions. There has been an implicit agreement that the subject of research

carried out using external funds should be within the scope of the BRC's mission. The BRC would like to keep this current funding policy in place as much as possible. However, given the severe economic and financial situation in Japan, it has become almost impossible to increase the BRC's operating budget provided directly from the Japanese government, except in special cases. If we are to increase the number of R&D projects, it will be necessary to consider an alternative system to establish new teams supported by a mixture of external funds for research and internal funds for limited numbers of personnel. Consequently, there may be R&D teams with two different funding systems in the BRC, one with total support and other with partial support. To establish such systems, the BRC must be attractive enough that teams will be willing to join even with only partial financial support. The BRC has compiled so many interesting and unique bioresources and technologies that it should, hopefully, attract many young and creative scientists from diverse disciplines in the life sciences. Still, the BRC will need to make considerable effort to attract new personnel.

The BRC asks the BRAC for advice and suggestions on the following issues:

1. Cutting-edge and cross-cutting R&D programs to improve mouse and other resources
2. Examination of the existing R&D programs
3. Allocation policies for funding, personnel and facilities for R&D programs, and recommended operational structure for R&D teams

Advice and Recommendations from the BRAC:

In terms of an expansion of research and development projects, it would be advisable for the BRC to adopt new projects, but they should be innovative science, should be integrated into the Center's central mission, and should as much as possible make use of the strengths of the Center.

The director has proposed four new research and development projects: New Cell Materials Obtained by Cutting Edge Technology, an Epigenomic Toolbox for Bioresource Characterization and Promotion of Life Sciences, Research on Plant Genome Dynamics Responding to Environmental Stress, and Integrated Imaging for Biological Process. They all seem to be in line with the missions of the Center and would contribute to the characterization of bioresources.

In the reports on the divisions, we have very positively reviewed the work of the different divisions, and have commented on some of the smaller teams.

3. Other Business

Advice and suggestions on Education & Training, International Cooperation, Public Relations, etc.

Advice and Recommendations from the BRAC:

We have heard many examples of how the BRC is actively expanding its international collaboration. We believe this is a strength of the Center and encourage the management to continue along these lines. In addition, the work the BRC has done in the area of training and education will contribute to the reputation of the BRC and RIKEN as a whole, as well as the nurturing of future generations of scientists, and the Council commends these activities.

The Council notes that the BRC has been quite successful in its public relations activities. A symposium held in July 2011 attracted roughly 500 participants from all over Japan. In addition, the Council commends the Center on its activities to establish and expand Asian bioresource networks.

It was fortunate that no one was injured at the BRC and that there was only minor damage to infrastructure from the recent disaster. Still, this has reinforced the importance of back-up systems for valuable bioresources. We recommend that the BRC accelerate its efforts to establish such systems.

Advice and Recommendations from the RIKEN BioResource Center Advisory Council in response to President Noyori's Suggested Topics

1. Does the Center/Institute have achievements of major scientific significance and/or social impact?

The mission of the BRC is to collect and distribute biological resources. The Center is performing its task in an admirable way. Its resources allow users to publish new scientific findings and these are expected to have a major social impact, as biological science is vital for the further development of knowledge in medical science as well as in other fields such as agriculture and environmental management.

Some examples of BRC research that are expected to have a clear impact are the mouse clinic, reproductive engineering and technologies, work with microbes and plants that can contribute to biomass research, and work on iPS cell cultures. In addition, it is important to consider the distribution of materials developed elsewhere but which cannot be maintained by the laboratories that developed them, as well as the development of resources that cannot be easily created by laboratories that have a specific focused interest. Further, making resources developed in Japan available to the international scientific community should also contribute to making foreign resources available to Japanese science. The central position of the BRC within the National BioResource Project (NBRP) of Japan, which supports research in Japan and throughout the world, is very important.

2. Does the Center have a functioning PDCA cycle? In particular, are the mechanisms for reorganizing, improving or closing laboratories working effectively?

Since the Center has only existed for ten years, no decisions have had to be made so far on the replacement of specific groups by new groups. However two years from now such decisions will have to be made, based on the performance of non-permanent groups in charge of research and development. These decisions will impact the BRC over the next ten years. The director is preparing for this and is also, along with some of the permanent staff, preparing for new research projects at the cutting edge of science that will also fit into the mission of the BRC and/or make efficient use of its resources. The Council therefore concludes that an effective PDCA cycle is in effect for reorganizations as well as for the daily operations of the Center where management decisions are continuously evaluated and adapted when needed.

3. Are the personnel management practices (hiring and employment conditions) of the Center/Institute appropriate to its world class standing? Are the quality and diversity of researchers being maintained at a sufficiently high level?

The Council evaluated the qualifications of the six division heads and found them to be true leaders of their cutting-edge resource units. All are actively publishing in peer reviewed English journals on research and resource issues, and each appears uniquely suited to his/her position, reflecting prudent, thoughtful hiring practices. We feel confident the Center has a fair and open recruitment process at the upper levels. Indeed, the BRAC was asked to give input to the job description being prepared for the proposed head of the Gene Engineering Division. There is evidence of active collaboration between the division heads, with other RIKEN scientists, with those in the Japanese university system and within the international research and resource community. Each division head is a well recognized Japanese scientist and one is a woman. Their units are extremely productive suggesting the positive interaction of the division heads with their researchers, technicians and other laboratory staff and with the small population of postdoctoral scientists and graduate students in their midst. Dr. Obata discussed the RIKEN Initiative Awards, and similar BRC awards to recognize the work of young scientists, noting the qualities of the BRC awardees from this year.

4. Evaluate the Center/institute's collaborative activities within and outside RIKEN, as well as its efforts to promote international collaborations.

The evaluation of collaborative activities, both within RIKEN and outside, has always been considered an important issue in previous evaluations of the RIKEN BioResource Center's divisions and teams. This point has again been seriously considered this year and the Council noted with great satisfaction that several cooperative projects have been solidly established with European, North American and Asian countries. The Japan Mouse Clinic, for example, one of the newest divisions, is involved in the International Mouse Phenotyping Consortium (IMPC), and Dr. Obata is a member of the consortium’s governing board. Similarly a great number of collaborations have been established with other Asian countries and North America. Students from other Asian countries are trained at the Center and scientists from RIKEN have ongoing cooperative projects.

There are also many instances of collaborations with other Japanese institutions or universities. The Experimental Animal Division, for example, has close connections with several universities, and the Cell Engineering Division with Kyoto University in particular, in the field of pluripotent stem cells.

Specific Comments and Recommendations to the Center, Divisions and Teams on Policy and Practice from the 4th Advisory Council Meeting of the RIKEN BioResource Center

Progresses and achievements

The RIKEN BioResource Center Advisory Council (BRAC) noted with great satisfaction that **substantial progresses were achieved by the Center over the last two years**. At the same time the BRC has also expanded into a **wider variety of research** and **is definitely stronger and more solid than before**.

The Council wishes to address its **warmest congratulation and great satisfaction to the Director, Professor Obata, and his staff**. During the Advisory Council Meeting, Prof. Obata provided precise and concise explanations on the general activities of the BRC. It is clear that most of the divisions now have coherent and well-structured projects and most are developing interesting, often outstanding research activities, which are in most instances complementary to their service activities. The opinions of the distinguished Japanese colleagues who participated in the evaluation of the Divisions' activities in December 2010/January 2011, were highly valued by the international members of the Advisory Council while assessing the overall activities of the BRC.

The BRC has made significant advances in acquisition, preservation, archiving and distribution of high quality collections in the 2.5 years since the last AC meeting and the Advisory Council unanimously agrees that the BRC is **a unique research resource** that has contributed significantly to the advancement of basic and applied life sciences in Japan and elsewhere. The achievements in the fields of mouse genetics and mutagenesis, phenotypic analysis, reproductive biology, microbiology, and protection and distribution of resources have had and will continue to have a substantive positive impact on Japanese society. The quality of BRC science and resources, as reflected by ISO 9001 accreditation from the Japanese Accreditation Board (JAB), is a testament to the value and importance of the BRC.

As a result, the BRC is securing an admirable reputation and credibility among the scientific community worldwide. The BRC should continue to pursue excellence in order to ensure an even higher level of achievement in the future.

Compared to similar resources worldwide, **the Advisory Council agrees that RIKEN BRC ranks highly as a unique and important life science resource.** Because of the

diversity and value of its collections, distribution of biological resources, and research collaborations and partnerships, the "BRC brand" has earned respect and admiration worldwide. This achievement is particularly noteworthy considering the modest level of financial support, crowded space, and limited manpower compared to other resource centers, such as ATCC and The Jackson Laboratory in the USA. Further, the unique diversity of scientific areas, from genes to cells, animals, plants and microorganisms sets the BRC apart from other institutions throughout the world. Thus, the BRC is a world-class biological resource center that serves a valuable and necessary function in the support of life science research for RIKEN, Japan and the world. To continue this level of achievement in the future, the BRC should continue to seek valuable and unique collections, develop useful and informative technologies, and promote broad utilization and distribution of its resources and services within and outside Japan. The BRC should pursue integration into the world-wide network of resource centers. **In addition, the BRC may want to consider more flexibility in its policies, such as its Material Transfer Agreements (MTA), in order to increase distribution to a broader research community.**

In general, the quality and quantity of publications, and the number of accessions, depositions and distributions, are evidence that BRC scientists actively seek and engage in collaborations with their colleagues within the BRC, throughout Japan, and internationally. Through their own research activities and by enhancing the research programs of collaborators and users, the BRC has had a positive impact on the advancement of Japanese society. **The Advisory Council considers that additional efforts to enhance research collaboration and cooperation are warranted.** Specifically, there are likely great opportunities to develop synergistic relationships between the BRC and other RIKEN scientists on research areas that will enhance the BRC's resource activity, performance, and output. Similarly, the outstanding reputation and infrastructure of the BRC can be used to promote collaborations with scientists throughout Japan, as well as with Asian neighbors. Following the example of AMMRA (Asian Mouse Mutagenesis and Resource Association), the BRC can enhance their international research collaborations using mice, plants, and microorganisms. Further, the BRC **should work to increase recruitments,** and to **enhance the training and education of scientists who work at the BRC.** Developing international collaboration can also help this recruitment effort.

Preparing for the future

With an ever-increasing amount of genetic diversity, it is clear that **the demand from the national and international research communities that will be addressed to the RIKEN BRC is likely to increase substantially in the forthcoming years.** For this reason, the Council warns the management of the BRC as well as all the Division leaders, that they must be prepared to this change. Many techniques, which are routine nowadays, will prove to be insufficient in the (near) future because of increased demand.

The BRC should be prepared for such new scientific developments and new technologies. For example, several projects with the aim of generating many new mutations in the mouse (ideally one in every gene of the genome) are on-going worldwide, and will probably have a profound impact on the activities of the BRC. Other important techniques, including *in vivo* and molecular imaging at the cellular level are also rapidly developing. The Advisory Council suggests these developing technologies should be watched and fully exploited at the BRC.

The availability of new mutants will dramatically expand the use of mice in biomedical research, especially in the development of systems biology and translation to new clinical applications. For the Japanese national research effort to remain competitive, these resources must be made available to both academic and industrial biomedical researchers. In addition to the considerable logistic challenges this entails, these new efforts will require innovative and expanded capabilities in bioinformatics. We therefore encourage the Director to anticipate further developments of this nature in other model organisms. The science of genomics is in a revolutionary period, presenting both enormous challenges and enormous opportunities.

Basic research for improving infrastructure should also be conducted in collaboration with universities and other research institutions. Because of limitations of expertise and manpower, development of new resources and characterization of the existing resources may not be possible within the BRC alone. In this context it may be worth building “satellite” groups to exploit and develop new resources.

For the operations of such “satellite” groups, we suggest:

- pursuit of pilot projects in novel and new areas of research under the direction of the BRC in specialized laboratories,
- immediate feedback of the results of their activities to the BRC so that the resources and information can be made available to the research community,
- regular evaluation to determine whether the activities of these groups should be

continued as they are or directly integrated into the BRC.

Developing collaborations

The BRC is to be congratulated for its **efforts in developing international cooperation with similar institutions in the neighboring Asian countries (China, Taiwan, Korea, Singapore and others).** This will definitely have a positive influence on the progress and importance of the RIKEN BRC and will presumably enrich the various resources as scientific research progresses in these countries. However, this activity increases the load of responsibilities for the RIKEN BRC.

Cooperation with similar organizations in other Asian nations is of especial importance, though there may be some difficulties that must be overcome to develop these relationships.

Researchers seek new types of resources for their research, and the development of such new resources is an imperative for the BRC. Moreover, in harsh times, renewal and rebirth of scientific activity requires preserved scientific resources.

As often stated in former Advisory Council reports, **there is no research without resources.** Further development of BRC's international role, especially in Asia as well as coordination with European and American organizations in the same fields is recommended. In addition, collaboration with Africa, South America and Eastern Europe should be promoted where possible.

Problems related to the funding of BRC activities

A major issue that should be mentioned in this report is **the funding of the RIKEN BRC**'s activities. The Advisory Council insists on the fact that **this is essential for the development of Science,** not only in Japan but also at the international level.

The consensus feeling of the Advisory Council is that it is absolutely necessary that stable funding be insured at an optimal level to guarantee the future of the activities.

Suggestions for such action might be:

- Seek funding from multiple sources,
- Seek increased funding from RIKEN and from MEXT,
- Charge more for resources supplied to users whenever appropriate,

- Seek competitive funding and apply for patents,
- Organize a system by which donations are sought from an industrial network,
- Avoid duplication of resource maintenance among ministries and centers.

It is noted that this world-leading BRC program has been established despite a consistently lower budget each year (approximately 1% decrease per annum). The request for a comparison with the budget and personnel at the other major BRCs in USA and Europe produced results, but the numbers provided cannot be used for comparison because they were for support of whole institutions that also did things other than providing resources.

This level of effort should be sustained and consideration of an increase in staff and budget in specific areas and improvement of the BRC facilities is highly recommended. For example, for the international efforts to succeed, a budget to support travel, exchange of personnel and the significant administrative and legal activities necessary for resource distribution, are required.

The Japanese government is encouraged to support the activities of RIKEN BRC **at least at the present budget level.** In the same way, and even if it is not easy under the present circumstances, increase of manpower is needed to support the mission of the BRC.

Many of the activities at the BRC, if not all, have a substantial although indirect impact on the funding of biological research worldwide and seriously contribute to the reduction in cost of the global research effort. Phenotyping, which is achieved by the Japan Mouse Clinic, is a good example of this because it is accomplished in a systematic and efficient manner by BRC specialists in contrast to the less efficient, non-standardized characterization achieved at much higher cost in separate academic laboratories. Similarly, the cryopreservation of mouse strains and mutants, which is achieved with a high degree of confidence in the Experimental Animal Division, saves money from the budget of individual Japanese laboratories.

Experimental Plant Division

Division Head: Doctor Masatomo Kobayashi

Achievements

The Experimental Plant Division continues to provide both the Japanese and international community with seed and DNA resources that are essential for modern biology. Because these resources are often developed in large programs (e.g. collections of full length cDNA clones, knockout lines, etc) these cannot and will not be developed in most cases by biologists interested in one or a few genes.

The position of the BRC plant division as one of the 3 main *Arabidopsis* resources in the world has been emphasized and is internationally recognized as shown by the enrollment of Dr. Kobayashi in the multinational *Arabidopsis* steering committee, which together with the organization of the International *Arabidopsis* Congress (ICAR21) in Japan in 2010 increased the international visibility of the Division.

The genotyping of their natural accessions using the same set of SNP markers as used by the other centers for the description of such accessions allows the comparison and the integration of the Japanese collection with the international collection. It may also provide indications about the phylogenetic position and origin of Japanese accessions. By starting the phenotyping of this collection and by providing cell cultures and the development of technologies for the long-term preservation of the cell cultures, **the BRC is ahead of the two other *Arabidopsis* resource centers.** High quality of seeds and clones distributed from the BRC are guaranteed and appreciated.

The *Brassica rapa* full-length cDNA collection provided an important contribution to the international *B. rapa* genome sequencing project, which led to co-authorship of a recent *Nature Genetics* publication.

Developing resources for *Brachypodium*, a species that is increasingly used as a small genome grass model fits in the mission of the group to provide resources for basic plant research, although working with this species is relatively novel in Japan where few groups work with this species.

Recommendations

The BRAC recommends continuation of the phenotypic and genetic characterization of the natural accessions, which if possible, should be extended with more Japanese accessions and wild relatives. For the latter it might be useful to collaborate with Prof Kentaro Shimizu from the University of Zurich and Prof Hiroshi Kudo from the Center

for Ecological Research, Kyoto University, who are specialists of *Arabidopsis* relatives. Furthermore collaboration within Asia might be achieved by collaboration with Prof Hongya Gu at Peking University, who maintains a collection of natural accessions from China that are not yet in the US and English stock centers.

The activities of Dr. Kobayashi to collect miscellaneous resources from Japanese laboratories are strongly encouraged, now that the generation of resources by the RIKEN Plant Science Center is reduced and their resources have been and are taken care of in the Division for further distribution.

Since there seems to be no community in Japan that requires *B. rapa* resources and because it will be difficult to develop these (transformation is difficult), the decision not to continue developing additional resources for this plant species is supported.

For *Brachypodium* in addition to resource development that should be done in close interaction with the international *Brachypodium* community, there will also be a need for instruction and public relations within the Japanese plant science community. The BRAC supports the direction of *Brachypodium* study examining basic mechanism on stress-resistance for the purpose of enhancing the character in the meadow pasture.

Microbe Division (Japan Collections of Microorganisms: JCM)

Division Head: Doctor Moriya Ohkuma

Achievements

The Division has been functioning very well with respect to scientific, social and international aspects. It has achieved a strong position as one of the three most important international resource centers for microorganisms. The latter is despite its smaller size compared to the other two big centers.

Recommendations

The AC strongly supports the initiatives to update the infrastructure of the Division as well as the continuing efforts to collect biological material present in research organizations where such collections are endangered due to retirements. It will be important to prevent a gap from forming between the more traditional microorganism taxonomy and modern microbiome activities. This might require additional investments in staff familiar with these developments. This may also include a discussion with other

organizations in maintaining and providing data sets coming from microbiome projects. Where possible the opportunity to use the know-how present at BRC should be exploited after moving to the Tsukuba campus. However, it will be very difficult for the Division to maintain its high level and present scale of operation when it needs in addition to exploit and pioneer new resources and to implement the modern microbiome in their activities. The latter will be especially useful for Environmental and Health Sciences. To deal with these new developments the size of the Division needs some expansion. Thus, the allocation of additional staff and time to achieve this should be considered. It is important to take into account new developments in the field when recruiting new staff to ensure sustainable development of this Division.

Experimental Animal Division

Division Head: Doctor Atsushi Yoshiki

Achievements

The Experimental Animal Division is among the very first divisions that were established at the RIKEN BioResource Center at Tsukuba, and accordingly, its activities have already been evaluated several times. The conclusions of all previous evaluation committees were that its work was excellent and those of the present Advisory Council are the same: excellent! The presentation of these activities and on-going projects by the team leader Dr. Yoshiki was outstanding, clear and comprehensive and the ensuing discussion provided answers on all aspects. The Division is to be commended for its impressive list of achievements and successes under the leadership of Dr. Yoshiki.

Suggestions that were formulated after the second and third meetings were all taken seriously and great progress was made. The Experimental Animal Division has succeeded in all of its missions, and consequently, it has contributed to the high reputation of the "RIKEN brand" as a supplier of top quality biological material. This is the result of continuous efforts to collect, maintain and distribute mouse strains with excellent quality both from the genetic and microbiological point of view.

The collection of genetically defined strains and stocks is growing steadily. The number of strains and mutant mice that are stored and exported abroad is increasing year after year indicating *i*) that the BRC is well known in the scientific community and highly appreciated, *ii*) that the collection is rich in terms of genotypes in *iii*) that the community trusts the quality of the exported material.

The Advisory Council noted with great satisfaction that internal collaborations with other groups on the Tsukuba campus are numerous and fruitful. Collaborations have also been established outside the Tsukuba campus with other RIKEN divisions, for example, with Professor Tonegawa's group for the production and subsequent use of a number of tissue-specific *Cre* mouse strains as tools to produce genetically modified mice with conditional gene expression and modification. The development of *Cre* drivers has been a very successful and important activity of this Division. It will be important to maintain the interface and complementarity of the activities with the CREATE and EUCOMMtools consortium.

The Council also noted with great satisfaction that this Division is interacting with the rat resource group in Kyoto (Professor Serikawa), in particular by storing deep-frozen embryos for this institute. This is a good example of highly synergistic cooperation where competences are optimized, which was a strong recommendation of the last Advisory Council Meeting. The Council also notes with satisfaction the remarkable progress in international collaborations as well as the integration of the Experimental Animal Division as a member of the Federation of International Mouse Resources (FIMRe), for example. Some consideration might be given to the integration or unification of data outputs from the RIKEN and European efforts. Importantly, the dialogue should be maintained.

Recommendations

The scientific and societal value and importance of the mouse collections is corroborated by the number of published papers reflecting the impact of the Division as a supplier of top quality mouse models (approximately 300 research papers were published by scientists making use of the resources provided by the RIKEN BRC, some of the latter in prestigious journals, such as *Nature* or *Science*). The Advisory Council recommends that records be kept of the mouse strains and stocks that have been distributed worldwide with reference to publication.

The evaluation committee recommends that modernization of the facilities be seriously considered with **some equipment being refurbished or replaced by new equipment with higher performance.**

The Advisory Council also recommends that distribution fees be periodically revised and updated where necessary with different charges for national non-profit organizations, national for-profit organizations and foreign institutions.

Because they are part of Japanese input in the field of mouse genetics, the Advisory Council recommends that the collection of wild-derived mice be expanded, some of these strains being part of the "RIKEN brand".

A good case is made for the new imaging subproject being located in this Division. However, the Division should continue to focus in this area on key questions such as:

- What are the new technologies here?
- The opportunities for whole animal imaging for gene expression.

The Council would like to emphasize that the dramatic events that occurred in Japan last March 2011 are a strong reminder for the Division head of the importance of risk management practices to protect valuable collections, such as by duplicating the archive at a distant site.

Finally the Council recommends that Dr. Yoshiki, the Division's head, visit other centers with similar functions, preferably but not exclusively in Asian countries, where the competences and skills of the Experimental Animal Division might possibly be applied in collaborations.

Bioresource Engineering Division

Division Head: Doctor Atsuo Ogura

Achievements

The mission of this Division is to develop techniques essential to the development and delivery of high-quality bioresources and their transfer to the scientific community. They planned to address six major areas: cryopreservation, nuclear transfer, technology transfer, micro-insemination, stem cells and resource development in mouse ES cells classifying their attacks into practical applications (A), development of existing areas (B) and exploration of new areas (C).

They made a movie of the protocol for embryo cryopreservation, now submitted to *J. Visualized Experiments* (PubMed), made further practical advances, by using cryotubes rather than straws for embryo distribution and showed they could transfer vitrified embryos nationally and internationally with good survival on dry ice rather than the far more expensive use of dry shippers. Another practical advance was made when they showed that the use of inhibin antiserum increased the yield of oocytes after superovulation. In the area of nuclear transfer they found that they could improve the

efficiency of nuclear transfer by correcting aberrant *Xist* expression, and published this very well in *Science*. In a more speculative mode they were able to analyze imprinting in by germ cell nuclear transfer and devised a carrier ChIP method for allele-specific histone modification in embryos. Breakthrough technologies resulted from transplanting male and female gametes to the kidney capsule, and live mice were born from sperm obtained from testicular tissues cultured *in vitro*, also very well published in *Nature*. In the area of stem cells they found that they could improve germline contribution of mouse ES cells by using Austin Smith's 2i-culture techniques, and they were able to improve the culture conditions of rabbit ES cells and to prepare rabbit iPS cells. They also made strides in transferring these techniques to the scientific community by running a series of courses on gamete cryopreservation, on mouse ES cells and on Intra Cytoplasmic Sperm injection (ICSI). Since their space for trainees is limited they increased the number of courses and also gave these courses in various Japanese universities and also in Taiwan. This group made sure their advances were well publicized not only to the scientific community through 25 publications in the scientific literature but also in press releases and in *RIKEN News*.

Though it had been hypothesized previously that male gametes did not have to mature in the gonad itself, the work of this group showed that normal development could take place in extra-uterine sites and *in vitro.* This result has far-reaching societal implications. The group is also trying to develop methods to study imprinting and epigenomics.

The achievements of this Division reach well beyond their purpose of resource development and distribution and penetrate into the essence of mammalian reproductive biology. Their work with rabbit iPS cells opens the door to experimental work in a larger model organism.

Because of the dual role in research/resources and the nature of the biological material, i.e. gametes, stem cells, rabbit and mouse, there is no other division or team in Japan or internationally with such a scope.

The depth of the research, the scope of the resources and the dissemination of the findings of this group are simply outstanding.

Internal collaboration – the development of new twists on old techniques greatly improves the ability of this resource to be able to distribute resources rapidly and with assurance regarding quality. Dr. Ogura is very well supported nationally, collaborates with the international mouse repositories and is an internationally recognized scientist.

The Division has made efforts to disseminate the developed techniques relating to preservation, nuclear transfer, micro-insemination and stem cells technologies providing

multiple courses in house and nationally and also internationally.

Recommendations

Continuous scientific and public advertisement of the achievements of this Division should be made nationally and internationally. The movie publication should be usable to great advantage.

This Division will continuously play an important role as core structure of the BRC, taking care of preservation and resource transfer system in connection to the Experimental Animal Division (Dr. Yoshiki's group), as well as pursuing basic reproductive biology. Because of his vast achievements, it may be not easy for this Division to set out new objectives that will be resolved in near future. However, Dr. Ogura suggests his future work will involve the identification of next-generation factors of genomic plasticity and pluripotency. He will abandon one or two projects that proved intractable and will turn over some of his work to collaborators.

Technology and Development Team for Mouse Phenotype Analysis

Team Leader: Doctor Shigeharu Wakana

Evaluation of the activities

This Division is recent since it started its activities only about two years ago. It is however **a critical and growing activity for the BRC that has made enormous progress and deserves full support.** Its aim is to develop an in-depth phenotyping platform, a so-called "*Mouse Clinic*", for mice created all over Japan, and even throughout the world, that will be equivalent although not identical to the other existing mouse clinics elsewhere, namely in England, Germany and Canada. There is no doubt that the contribution of this platform will be of major interest (and already is!) to the research community as a whole because stringent and rigorous phenotypic examination is tightly correlated to the harmonious development of genomics by **associating a phenotype to a genotype.** This is even more important considering that genotype/phenotype analysis often provides feedback for **the elucidation of human diseases and the development of potential animal models,** which are invaluable for the development of treatments. In this respect, this Team is a very important component for enhancing the scientific significance and social impact of RIKEN BRC. Accelerating the disclosure of the phenotypes obtained so far will be an effective way to

promote functional genome science in Japan. Here again, the Japan Mouse Clinic will clearly contribute to the establishment of the "RIKEN brand".

The Advisory Council was most impressed by the large and diverse number of parameters that are routinely checked by the platform (around 400). This indicates that progress has been remarkable over the last two years under the highly dynamic leadership of Dr. Shigeharu Wakana.

The establishment of this platform for mouse phenotype analysis and the acquisition of the data of standard strains of all kinds (including mutant strains, inbred strains, recombinant strains of all kinds and wild derived strains) will be of great importance in the future.

The Advisory Council noted with great satisfaction that the Japan Mouse Clinic at Tsukuba is to be networked with the homologous mouse clinics in Europe and the USA and Canada. The request for the Division's participation in the International Mouse Phenotyping Consortium (IMPC) suggests successful achievements of this Team in the future and must be considered a strong contribution to the IMPC.
The Japan Mouse Clinic can process around 50/60 different genotypes per year. This is comparable with the best performances of the other phenotyping units world-wide, although there is still an enormous unmet demand.

The activities of this Division are certain to be of **great interest to the pharmaceutical industry** particularly since the development of some Standardized Operation Procedures (or SOP) is often oriented towards the discovery of new biologically active molecules.

Peripheral technologies for operation of the mouse clinic, such as speedy congenic production, molecular genotyping, etc…, have been established, and progress is being made as scheduled.

Recommendations for the future

The Division needs **strong financial support,** in particular for the next two years, for two main reasons: *i*) because it is still in its expanding phase and accordingly needs to buy expensive equipment to sustain its performance, and *ii*) because of the commitments made by this Team in parallel with its integration into the IMPC network. A substantial budget will then be essential for the full establishment of the scientific infrastructure of this Division.

The Advisory Council also considers that service charges should be calculated carefully, keeping in mind the need to balance the Division's achievements and results with

considerations related to the affiliations of the institutions (academic or private) requesting the services. The service charge system does not seem to be fully established yet, but it will certainly be necessary to design it as soon as possible. It will then be important to talk to users when determining the structure of charges. In addition, it will also be important to solicit financial support from various domestic and foreign organizations.

Cooperation with Dr. Masuya's Unit will be key to managing the obtained phenotype data information. Development of comprehensive analysis that includes environmental factors should also to be considered.

The new imaging subproject should be closely allied with this program – the role of new imaging modalities in the IMPC pipeline will be an important area for consideration and technology development.
Finally, the possibilities for commercialization might also be examined. Market surveys concerning service charges, inspections, licensing and other such matters are absolutely necessary.

Public relations activities should be intensified. It would for example be important to consider how the IMPC may help publicizing the activities of the BRC?
What further opportunities are there for the BRC to lead across Asia in terms of developing a wider contribution to IMPC is another issue to be considered by the team leader.

Evaluation of Mammalian Cellular Dynamics

Team Leader: Doctor Kuniya Abe

Achievements of major significance made by the Team over the last two years

The aim of this Team is to develop technologies and tools for genotyping, phenotyping and epigenotyping the resources of the BRC. In the last two years, they developed a B6/N BAC library, mapped the BACs onto the B6/J genome and they also established a website to access this information. They published one paper using a BAC clone from the MSM BAC library they constructed earlier to rescue a mutated gene for positional and another using MSM BAC to clone the pseudo-autosomal region in these mice. This powerful resource was thus announced scientifically and information about it was made readily available on the www. They also established a method to detect global DNA methylation on ~2ng of genomic DNA, using it to classify different categories of stem cells (e.g. ES/EG/iPGC/GS/testis). They also developed a novel FISH method to detect

methylated DNA sequences in osmium-treated samples. Further they are developing technologies for intravital imaging that should have good long-term potential. Each of these contributions has a dual potential to develop a bioresource and to generate information for the scientific community. Since the last review they have published and/or submitted 24 peer-reviewed papers in English, 6 reviews, some in Japanese and have presented data 73 times at various meetings. **Their work shows excellent persistence and perspicacity a fact also echoed in their external funding rate.**

In the long run the ability to differentiate the X-chromosome regions that are subjected to X-inactivation from those in the pseudo-autosomal region that are not, may reveal insight into the mechanism for dosage compensation/Lyonization in mammals.

Dissemination of the BAC resources is great contribution to the mouse community and will aid the field of biomedical science as the function of each gene is unraveled in the mouse.

Dr. Abe's Team appears unique in that they not only develop methods and tools for the resource, but they are involved, either individually or through collaborations, in the use of these technologies to solve biological problems. This is an important achievement as it turns the scientific community to the resource, where they can obtain reagents, information and training to use them.

They have produced a practical BAC resource and the methods they developed have potential for producing biological information of long term importance in biomedicine.

There is evidence of firm collaborations within the BRC in the Mouse Phenotype Analysis group, with other centers in RIKEN and with other researchers in the Japanese scientific community. Indeed, **the Me-FISH system established under the collaboration with RIKEN ASI and Kyushu University is an outstanding achievement,** with potential to contribute to many different studies of epigenetics and epigenomics. To their credit, the Team tried to engage Olympus and, though unsuccessfully, another pharmaceutical company in its work but has an active collaboration with a biotech company that produces BAC transgenic mice and rats.

There was no direct evidence presented, but the BAC resource comes with an instructive website of information. Attention to this resource in the world-wide scientific community should develop as word gets out as to its availability.

Recommendations and suggestions for possible improvements

Three different subjects have been approached, all of which are important and interesting. Because of the limitations of personnel, budget and the state of completion

of the projects, prioritization should be considered. **The Division's future scientific strength may be in epigenomics and imaging technologies.**

The application of intravital imaging may prove to be of diagnostic potential in humans and if properly developed can perhaps be used by the mouse phenotyping team.

Since the BAC resource has been revealed in publications, others should be engaged to use this resource and contribute to the web site. Interesting future work to understand the boundaries of the pseudo-autosomal region should and can be done by collaboration with others. Their efforts will now turn to BAC library preparation and genome analysis of wild strains, collaboration with the international scientific community.

Detection of methylation by microscopy may be modifiable to detect specific differentially methylated regions, perhaps with the new ultra high resolution microscopies. This could be a powerful collaborative project with broad scientific and societal implications. On a more practical level they can apply their expertise to quality control of different populations of distributable iPS and ES cells.

In collaboration with others in the resource center, they are trying to market a package of resource-related activities, i.e. the BAC library, genome data, ES cells, mice, to help researchers thereby directing their attention to BRC and how it can help them.

Mutagenesis and Genomics Team

Team Leader: Doctor Yoichi Gondo

Achievements of significance made by the Division/Team over the last two years

This Team has generated an enormous collection of mouse mutations through gene-driven mutagenesis using the potent mutagen ethyl-nitroso urea (ENU). These mutations have been stored at (virtually) no cost in liquid nitrogen tanks and can be retrieved when desired by simply thawing up the semen samples. The collection is steadily increasing, and the Council believes that in the very near future, nearly all mouse genes will be potentially affected by one or more mutations of this kind. The annotation of the mouse genome will benefit greatly from this strategy, which must be seen as complementary to the generation of mutations in ES cells by genetic engineering rather than alternative to it.

The Team has succeeded in introducing a new-generation sequencer that makes it possible to efficiently screen for mutations and to obtain mutant mice. The current

thinking on the application of NGS to the whole library characterization would be useful to consider, and to plan for. It seems likely that over the next 2-3 years, sequencing costs will come down to the point where it is conceivable to contemplate whole genome sequencing of the entire ENU archive.

The Team has also successfully analyzed phenotypes in its own lab. **Thus, the achievements of this Team are clearly visible.**

Although the gene-targeting system is not yet fully understood by the community of mouse geneticists, **the Council believes it is a powerful tool.** The mutagenesis and gene-targeting system will surely contribute to the advancement of biology. In addition, as the team leader insisted, the new protocol for mouse modeling of oligogenic traits is highly original and has great potential. There are important opportunities for this program for exploiting the ENU archive through NGS and it is an approach that is certainly worth trying, whatever the ultimate results may be.

There are no similar units today in Japan, but similar projects have been established in the UK and (perhaps) other countries as well. This Team led by Dr. Gondo is, however, well ahead of the others in its work.

The Advisory Council noted, with satisfaction, the positive internal collaboration with Dr. Yoshiki's team.

Recommendations and suggestions for possible improvements:

The Advisory Council considers this Team to **be a major addition to RIKEN's existing bioresources.** The strategy developed by the team leader will enormously benefit the mouse community, since a collection of 10,000 samples of G1 sperm cells and associated DNAs has made it possible for researchers to access mutations of many kinds (and not only knockouts). It has also increased the visibility of the BRC as an important research center for mouse genetics worldwide.

The council encourages further collaborations with other centers, both inside and outside RIKEN, particularly to enhance the efficiency of the detection of mutations at the DNA level. Since the Team only recently settled in Tsukuba, **the council strongly recommends an increase in funding to allow the rapid development of its projects.** It is also recommended that the delivery of mutations at specific loci be made, at least in part, at the expense of the requesting laboratory unless it is in the framework of a cooperative project.

The Council hopes for the early publication of the results of 247 mutations identified with the high-speed sequencer.

The proposal for making possible analysis without backcross is favorably evaluated by the Council. The Council also commends the Team for reaching the stage at which genetic modifiers may possibly be identified. The Council believes that further work is necessary in particular with regard to the following items:

- The Team should work to demonstrate the effectiveness of the variant mouse identification system and publish results showing this.
- The Team should identify variant mice corresponding to particular phenotypes, since the value of the results will vary if evaluated from this viewpoint.
- The screening of mutations should be continued together with participation in phenotype analysis work for the remaining period.
- The acquisition of users and public relations are critical tasks for the Team.

The research themes appear promising and the progress has been steady. The Team's positive attitude toward closer collaboration with other departments and teams is favorably evaluated, and the Advisory Council positively notes the collaborative studies with Kawaoka ERATO and Agilent. Looking toward the future, a proposal to encourage past users to make use of the high-speed sequencer system would be a positive step forward. The **establishment of the system is a laudable achievement,** and its use value could be positively demonstrated through collaborations with organizations outside the Center.

In summary, Dr. Gondo's team has developed a strong system, and it should be selectively promoted. The Team should work to demonstrate the effectiveness of the system first by **analysis using model cases.** The strategy developed is wonderful and it should make a strong contribution to the core mission of the BRC. This should make it possible to promote and dramatically accelerate collaborative studies. It would also be interesting to have more information on obtaining 3rd generation sequencers such as PacificBio.

Subteam for BioSignal Integration

Team Leader: Doctor Takahiro Doi,

Achievements of the Team

The mission of this Subteam is to characterize bioresources and to demonstrate their best use in order to increase the value of the bioresource. In the last two years this small

Subteam focused on the bioresponses resulting from activation of NF-kB, focusing specifically on the RelA family member. Contrary to the original hypothesis that RelA knockout mice would be important in the induction of inflammation, they found the phenotype of the B6 RelA knockout mouse they prepared was characterized by a paucity of lymphocytes, autoimmunity, anemia and osteoporosis. Dr. Doi was able to elicit many collaborators, some with the RIKEN Research Center for Allergy and Immunology, some within the Japanese university system to work on this problem with him. His work resulted not only in the distribution of a good number of NF-kB family member knockout mice nationally and specifically RelA and TNF/RelA double knockout mice both nationally and internationally. In the last 2 years he has co-authored 10 papers, some in top journals, 5 specifically about the mechanism of action of NF-kB. Some achievements of significance have been made by the Subteam, though the review committee expected more.

The mice this Subteam has produced can be considered as the harbingers of those necessary to model specific human diseases.
The function of this group may be seen as a way to popularize the use of knockout mice to understand the pathways involved in dissecting the pathways involved in differentiation of the various cell types involved in hematopoietic cell differentiation.

At the Jackson Laboratory, Dr. Len Shultz has focused on the use of the Lab's genetic resources to prepare immunologically compromised mice. Such mice have been used by many laboratories around the world to study many different aspects of biomedicine. He achieved success by making crosses and providing these mice to others for collaborative projects. His great knowledge and reliability were of enormous benefit to many fields. It is too soon to judge whether Dr. Doi will prove to be a researcher/resource of this caliber **but it is a desirable model.**

Competition is strong because there are many research groups in Japan and in other countries, because NF-kB is a very important and well-known protein in Immunology and Cancer biology.

The Subteam is making mice, distributing them and publishing papers. These are all criteria of success.

Currently the list of internal and external collaborations looks good, but a more long-term look is necessary in order to make a critical judgment. Ultimately one should consider the Subteam's ability to garner outside support, both independently and with their outside collaborators, as the long term worth of the Subteam. It is important to publicize the use of the resources to scientists.

More collaboration seems to be necessary for further study and development, especially with other teams in BRC.

Recommendations and suggestions

Continue, strengthen, and gather new collaborations. The Subteam should seek to make collaboration with other teams in the BRC to contribute to development of new BRC bioresources. This process may help its own research.
The future plan of the Subteam, and rightly so, is to initiate crosses of NF-kB family members with a series of other knockout mice, to determine the pathways in which RelA, or the other family members act.

This Subteam should be regarded as a public relations group for the BRC by promoting good basic research. To maintain itself as a functioning unit within the BRC some grant money may be required, obtained through collaborators or from individual grant applications.

There is some need for the Division's leader to discuss with the BRC's director about the future of this Subteam.

Team for Advanced Development and Evaluation of Human Disease Models

Team Leader: Doctor Tetsuo Noda

Achievements

The mission of this group is to develop advanced phenotype analysis of mouse models for human disease.
Work over the last two years has continued on 4 or 5 loci that are involved in mouse strains affected by deafness; development of pre-symptomatic phenotypes using several promising, sophisticated techniques including NMR metabolome analysis of mice fed ^{13}C-labeled compounds; developing information regarding transcriptome changes in pancreatic cancer models distributed by the resource during carcinogenesis; and describing the molecular changes in medically relevant phenotypes among the collection of ENU-mutants.
There seem to be many achievements of significance made by the Team. However, most of them are still ongoing and not yet finished. So, they are not visible.

Though promising results appear to be coming, there is no current impact because there have been no publications and few obvious collaborations, and the details on the mouse models have not been divulged to the community. That aside, and perhaps a premature comment, pre-symptomatic phenotyping of mouse models could hold great promise of application to human disease.

This group appears to be extremely competent in developing advanced methods for determining the molecular basis of the mutants, an extremely important activity for the BRC. The technologies for phenotyping of mutant mice have the potential to generate human disease models.

It does take time to work up the molecular basis of diverse mutants as well as to develop new methods and apply them to resource animals. There are very few groups in the world to compare this Team with. The repository team at The Jackson Laboratory has worked over the years to describe the molecular basis of diverse mutants. This is a slow process but it makes the mouse models of great utility.

The opinion of the Advisory Council is that the scientific contribution of the Team is promising and that forthcoming achievement may have a social impact.

The plans of the Team for human disease models have the potential to contribute to science and BRC resources. At present however it is difficult to answer this question.

Perhaps this group could have established collaborations to help in this characterization but since the aim is to characterize the mutants in the bank, this might not have been possible.

The Team has collaborations with other teams in the BRC. However, the way of collaboration should be made more efficient.

It would be important to know whether there is a role for imaging development in this Team, and how phenotyping technologies of the Japan Mouse Clinic have developed, allied to the work of this Team. The planning, development and future of this Team would benefit from being closely coordinated to the work of the mouse clinic.

The development of biomarkers is potentially an important role for this Team, e.g. NMR metabolomics analysis

Recommendations and suggestions for possible improvements

Publish, publish, publish: 15 papers are in the wings. Make this data available as quickly as possible on the BRC website.

Perhaps the organization of the group could be improved to ensure completion of the projects to publication and to get the data into the database of Information on Mouse Strains, the Phenome Database and perhaps the Protocol Database. This Team has a

very important function, it is urgent that its worth be proven soon.

Cell Engineering Division

Division Head: Doctor Yukio Nakamura

Achievements

Much progress has been made during the past two years on the collection of new cell lines, including iPS cells. Over the last two years, under the direction of Dr. Nakamura, the group has gained international recognition for its world-leading program in the collection of various types of stem cells. Dr. Nakamura has without doubt made a huge contribution to the rapid expansion of the deposition of human stem cells, including embryonic stem (ES) cell lines and many induced pluripotent stem (iPS) cell lines. The Division has collected eight ES cell lines, and more than 50 normal iPS and 59 disease-specific iPS cells. These iPS cells have the **potential to make a major contribution to the development of new disease models and new drugs.**

Supplying high-quality cells is critical for the advancement of research in life sciences. The collection of disease-related iPS cells has great value for understanding the etiology of diseases. Dr. Nakamura is a member of the International Stem Cell Initiative (ISCI) and International Stem Cell Bank Initiative (ISCBI) and can contribute to the standardization and characterization of pluripotent stem cells. A consensus guidance on the banking and supply of human embryonic stem cell lines for research purposes was published by the group in 2009. In addition, the group has collected and distributed many stem cell lines in Japan.

This project's work is highly relevant to the modern context of biomedicine. The cells that are preserved as cell lines in the BRC have gained recognition for their added value. The group's recent **efforts for quality control of cells are very important and have been highly evaluated.**

This Division has become a leading world supplier of cells. Its new facility for cell biology is functioning at world standards. There are many research groups supported by the Ministry of Health, Labor and Welfare, such as Kumamoto University and the RIKEN BRC Cell Engineering Division. RIKEN BRC is collaborating with these groups to collect cells and resources after reevaluation. Participation in collaborative projects with the ATCC in the U.S. and DSMZ in Germany on STR polymorphism analysis and cell standardization is highly appreciated. RIKEN BRC is also contributing

to the standardization of pluripotent stem cells internationally as a core member of ISCI and ISCBI.

This Team has made a major contribution to cell biology. The main contribution of the conventional cell banks has been in the field of basic sciences. With the advent of human ES and iPS cells, contributions can be expected in not only basic science but also in applied sciences through activities such as disease modeling and discovery of new drugs.

The Council believes it is essential for the Division to continue to collaborate with national and international biomaterial centers. Otherwise, it will be nearly impossible to deal with a nearly unlimited number of potential materials. The Division's collaborative activities with the Japanese and international research community are highly evaluated.

The group has launched a teaching and training course for preparing human ES cells and iPS cells. This project is highly relevant to the handling of these cells.

Recommendations and suggestions for possible improvements:

Maintaining a proper balance between service, on the onehand, and research and development on the other, is very important. **Research is essential for ensuring the high quality of materials.**

The Council anticipates that there will be increasing demand for iPS cells and disease-related cells in the future. Once iPS technology is firmly established, it will become possible to obtain many kinds of tissue-specific cells through iPS cells or the direct conversion of cells from various somatic types. **The Council believes it will be important for the RIKEN BRC to obtain this cutting-edge technology.**

Subteam for Manipulation of Cell Fate

Team Leader: Doctor Hiroyuki Miyoshi

Achievements

Significant achievements have been made in the past two years especially in iPS cell biology.

The achievements of significance made by the Subteam are works on new iPS cell

generation and good collaboration with use of lentivirus vectors. The study of iPS cells provides important information on programming/reprogramming and cell senescence. The study on hematopoietic stem cells (HSC) has potential for clinical application.

Even though this is a small group of scientists, **the activities of this Subteam are important to the understanding of key issues of modern biology.** The Subteam appears to be working to contribute to a paradigm shift in iPS research.

This question is difficult to answer, because the Subteam is a conventional and standard group of scientists, not much different from other research groups in universities in Japan.

Still, though we do not have comprehensive information to make an accurate comparison, it does seem that over the past two years, this Subteam has attained a level of achievement on a par with other world leading laboratories.

The scientific contribution of this group is its finding that ATP is required for HSC activity. This has helped in the understanding of stemness in adult stem cells.

Recommendations and suggestions for possible improvements:

The external collaboration with the Center for iPS Cell Research and Application, Kyoto University is particularly essential for iPS cell study. There is still some room, however, for more internal and external collaborations. Such collaborations will help the Subteam to work more efficiently.

In-house collaboration is essential for the future of this Subteam. It may be helpful for the Subteam to discuss its plans and activities with other teams and divisions and also the BRC director. The Subteam may do well to reconsider plans to study iPS cells and lentivirus vectors.

The fit and interface between this Team and the Cell Engineering Division are worth exploring, and clarifying.

This Subteam needs more help and support from RIKEN management. The BRC director should better define the position of the Subteam within the BRC and the expectations of its activities. This kind of support will help the Subteam to work more efficiently.

Gene Engineering Division

Division Head: Doctor Yuichi Obata (*acting head*)

Achievements:

This Division has mainly served as a gene bank in the RIKEN BRC and has been keen on collecting new and unique research materials, e.g. adenoviral vectors and newly developed BAC libraries of MSM and C57BL/6N mouse strains. The number of distributed samples was 137,217 out of 3,803,191 materials stored in the bank since 2008. Around 70% of the consignees for these samples were Japanese universities, but it is noteworthy that about 30% of consignees were in foreign countries. Publications using the resources provided from this Division were 347 in the past 10 years. This Division has also been engaged in developing novel biotechnologies that may have an impact both inside and outside of the BRC. The activities of this Division have been highly evaluated as mentioned in the report laid by the Resource Committee held in January 18, 2011.

Recommendations and suggestions for improvements:

Considering that the primary mission of the BRC is the preservation and distribution of unique and important resources, one can consider that this Division has made a highly appreciated contribution in the BRC, while the position of the head of this Division has been vacant for these two years. Appointment of an appropriate person for this position should be essential to maintain the activity of this Division given the rapid progress being made in life science.

Technology and Development Unit for Knowledge Base of Mouse Phenotype

Unit Leader: Doctor Hiroshi Masuya

Achievement

This Unit is now **internationally recognized for its unique research program** within the RIKEN BRC's IT strategy. The core technology constructed by this Unit is unique and applications with their technology will become only one result in the world. The integration of databases with such programs as SciNetS or the upper-ontology

YAMATO-GXO may break new ground in information technology. Steady progress has been made in the integration of databases in many research areas and in collaborative activity. Also to be highly evaluated is the Unit's aggressive participation in a cooperative program, the IMPC.

Progress and recommendation

In general, appropriate plans were made, such as for the expansion and verification of the usefulness of the resource database using SciNetS, and the development of retrieval systems. It is be highly evaluated that the Unit is internationally recognized through its collaborations. Its uniqueness and technological advantages may come from its studies of upper ontology, an important activity that may trigger an increase in the use of mouse resources. We look forward to continued efforts in these directions.

The Unit has taken the initiative to actively collaborate with international consortiums, for example, by holding an International Phenome Integration Meeting RIKEN/InterPhenome/ CASIMIR in Kyoto, Japan. The Unit also participates in projects concerning human disease information, such as the Disease Ontology Project of the Ministry of Health, Labor and Welfare, in which a number of universities also participate. Furthermore, the Unit has established close ties with the Experimental Animal Division and the Technology and Development Team for Mouse Phenotype Analysis in developing information infrastructure (e.g. phenotype date integration, protocol database) in anticipation of its participation in the IMPC. The proposal for deeper collaboration with the IMPC-IT working group for data integration is also to be commended.

The Unit is encouraged to continue efforts to participate in the international cooperative program of mouse functional genomics, and to advertise its upper ontology-based database to propagate its unique phenotype data integration worldwide.

The continuing rapid development of the BRC's efforts in IMPC places an important responsibility on this Unit in terms of the informatics support that will be required. There are strong interactions between this Team and the Harwell Centre which will continue to be strengthened with the formation of the IMPC Data Coordination Centre (DCC) at Harwell. It is sure the current Unit has the expertise and energy to play an important and successful role.

At the same time, it will be important that higher level work on ontologies will continue.

Bioresource Information Division

Division Leader: Doctor Kaoru Fukami

Achievement

The amount and quality of the information currently provided are top class, and the database stores an enormous amount of content. These alone are significant scientifically, socially and are to be highly evaluated. Should the retrieval system ever break down, almost all BRC services will stop. **It is essential therefore that the activities of this Division be maintained.**

Progress and recommendation

Based on the new distribution system, a balance of service and research has been proposed and measures have been initiated to achieve this balance. Careful consideration should be given over the next two years to **devising a specific roadmap for renovation, improvement and enrichment of the web catalog.** We hope to see the development of a more user-friendly interface for the web catalog. Information required by users of RIKEN BRC services and that required to sustain BRC's activities should be managed in close collaboration with the other BRC divisions. It is imperative to establish a daily decision-making platform to set priorities and determine the urgency of the various tasks requested of this Division.

Priority should be given to the maintenance of user information, but also recommended is the urgent construction of systems for analysis of the access log and for calculation of useful statistics related to the distribution of information. A part of the access log analysis has already been done. Further improvement is expected of internal usage of the system, including an automatic system for detecting papers published by the users of BRC resources, for example.

Consideration should be given to using outside data centers or a cloud system. Research themes associated with service tasks should be considered.

This Division will have an important role in ensuring fundamental operational issues and also, importantly, ensuring network and hardware support for IMPC and interactions with the DCC.

The Fourth Meeting of the RIKEN BioResource Center Advisory Council

Date: August 31- September 2, 2011

Venue: RIKEN Tsukuba Institute and Okura Frontier Hotel Tsukuba

Day 0: Aug. 30

Time	Subject	Presenter	Venue
15:00-17:30	Laboratory Tour		RIKEN Tsukuba Inst.
17:30-19:00	Move to Okura Frontier Hotel Tsukuba		
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 Staffs		

Day 1: Aug. 31

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 Tsukuba Inst.
9:05-9:10	Remarks from Chairperson	Dr. Jean-Louis Guenet	
9:10-9:30	An Introduction to RIKEN	Dr. Maki Kawai, Executive Director, RIKEN	
9:30-10:00	Q&A		
10:00-10:30	Activities of the RIKEN BioResource Center	Dr. Yuichi Obata	
10:30-11:00	Q&A		
11:00-11:10	***Break ***		

Time	Subject	Presenter	Venue
11:10-11:25	Experimental Plant Division	Dr. Masatomo Kobayashi, Head Dr. Kiyotaka Okada, Chair	RIKEN Tsukuba Inst.
11:25-11:40	Q&A		
11:40-11:55	Microbe Division	Dr. Moriya Ohkuma, Head Dr. Makoto Watanabe, Chair	
11:55-12:10	Q&A		
12:10-12:40	Closed Discussion by BRAC Members		
12:40-13:30	*** Lunch ***		
13:30-13:45	Experimental Animal Division	Dr. Atsushi Yoshiki, Head Dr. Hiromichi Yonekawa, Chair	
13:45-14:00	Q&A		
14:00-14:15	Bioresource Engineering Division	Dr. Atsuo Ogura, Head Dr. Toshihiko Shiroishi, Chair	
14:15-14:30	Q&A		
14:30-14:45	Technology and Development Team for Mouse Phenotype Analysis	Dr. Shigeharu Wakana, Team Leader Dr. Toshihiko Shiroishi, Chair	
14:45-15:00	Q&A		
15:00-15:30	Closed Discussion by BRAC Members		
15:30-15:40	***Break ***		
15:40-15:55	Technology and Development Team for Mammalian Cellular Dynamics	Dr. Kuniya Abe, Team Leader Dr. Toshihiko Shiroishi, Chair	

Time	Subject	Presenter	Venue
15:55-16:10	Q&A		RIKEN Tsukuba Inst.
16:10-16:25	Mutagenesis and Genomics Team	Dr.Yoichi Gondo, Team Leader Dr. Ryo Kominami, Chair	
16:25-16:40	Q&A		
16:40-17:10	Closed Discussion by BRAC Members		
17:10-17:20	***Break ***		
17:20-17:35	Subteam for BioSignal Integration	Dr. Takahiro Doi, Subteam Leader Dr. Ryo Kominami, Chair	
17:35-17:50	Q&A		
17:50-18:05	Team for Advanced Development and Evaluation of Human Disease Models	Dr. Tetsuo Noda, Team Leader Dr. Ryo Kominami, Chair	
18:05-18:20	Q&A		
18:20-18:50	Closed Discussion by BRAC Members		

Day 2: Sep. 1

Time	Subject	Presenter	Venue
8:30-9:00	Move to RIKEN from Hotel		
9:00-9:15	Cell Engineering Division	Dr. Yukio Nakamura, Head Dr. Tatsutoshi Nakahata, Chair	RIKEN Tsukuba Inst.
9:15-9:30	Q&A		
9:30-9:45	Subteam for Manipulation of Cell Fate	Dr. Hiroyuki Miyoshi, Subteam Leader Dr. Ryo Kominami, Chair	

Time	Subject	Presenter	Venue
9:45-10:00	Q&A		RIKEN Tsukuba Inst.
10:00-10:15	Gene Engineering Division	Dr. Yuichi Obata, Head Dr. Jun-ichi Miyazaki, Chair	
10:15-10:30	Q&A		
10:30-11:00	Closed Discussion by BRAC Members		
11:00-11:10	***Break ***		
11:10-11:25	Technology and Development Unit for Knowledge Base of Mouse Phenotype	Dr. Hiroshi Masuya, Unit Leader Dr. Toshihiko Shiroishi, Chair	
11:25-11:40	Q&A		
11:40-11:55	Bioresource Information Division	Dr. Kaoru Fukami, Head Dr. Satoru Miyazaki, Chair	
11:55-12:10	Q&A		
12:10-12:40	Closed Discussion with BRAC Members		
12:40-13:30	***Lunch***		
13:30-13:50	Discussion on Terms of Reference from the President of RIKEN	Dr. Yuichi Obata	
13:50-14:50	Discussion with BRAC Members		
14:50-15:00	***Break ***		
15:00-15:20	Discussion on Terms of Reference from the Director of BRC (1) On the scope of bioresources to be collected	Drs. Obata, Abe, Kobayashi, Yoshiki, Nakamura	
15:20-16:00	Discussion with BRAC Members		
16:00-16:10	***Break ***		

Time	Subject	Presenter	Venue
16:10-16:30	Discussion on Terms of Reference from the Director of BRC (2) On the scope of research and development that are needed for the BRC	Drs. Obata, Abe, Kobayashi, Yoshiki, Nakamura	RIKEN Tsukuba Inst.
16:30-17:30	Discussion with BRAC Members		
17:30-17:50	Discussion on Terms of Reference from the Director of BRC (3) Any Other Businesses: Education & Training, International Cooperation, Public Relations and etc	Drs. Obata, Abe, Kobayashi, Yoshiki, Nakamura	
17:50-19:00	Discussion with BRAC Members		

Day 3: Sep. 2

Time	Subject	Presenter	Venue
9:00-11:00	Closed Discussion among BRAC Members and Summarizing a Report		Okura Frontier Hotel
11:00-11:30	Reporting from the Chairperson to Director of RIKEN BRC	Dr. Jean-Louis Guenet	
11:30-11:40	Closing Remark	Dr. Yuichi Obata	

The List of the RIKEN Participants

Dr. Maki Kawai	Executive Director, RIKEN
Dr. Yuichi Obata	Director Head, Gene Engineering Division
Dr. Kazuo Moriwaki	Special Adviser
Dr. Kuniya Abe	Deputy Director Team Leader, Technology and Development Team for Mammalian Cellular Dynamics
Dr. Atsushi Yoshiki	Head, Experimental Animal Division
Dr. Masatomo Kobayashi	Head, Experimental Plant Division
Dr. Yukio Nakamura	Head, Cell Engineering Division
Dr. Moriya Ohkuma	Head, Microbe Division
Dr. Kaoru Fukami	Head, Bioresource Information Division
Dr. Atsuo Ogura	Head, Bioresource Engineering Division
Dr. Takahiro Doi	Subteam Leader, Subteam for BioSignal Integration
Dr. Hiroyuki Miyoshi	Subteam Leader, Subteam for Manipulation of Cell Fate
Dr. Shigeharu Wakana	Team Leader, Technology and Development Team for Mouse Phenotype Analysis (Japan Mouse Clinic)
Dr. Tetsuo Noda	Team Leader, Team for Advanced Development and Evaluation of Human Disease Models
Dr. Yuichi 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 Research Promotion Division
Mr. Makoto Murakami	Manager, Head of Planning Section, Tsukuba Research Promotion Division

RIKEN BioResource Center Resource Committees
And
RIKEN BioResource Center Review Committees
December 2010 - January 2011

The Review Sheets and the Responses and Actions by Divisions, Teams and Unit

- Experimental Animal Division (Atsushi Yoshiki)
- Experimental Plant Division (Masatomo Kobayashi)
- Cell Engineering Division (Yukio Nakamura)
- Gene Engineering Division (Yuichi Obata)
- Microbe Division (Japan Collection of Microorganisms: JCM) (Moriya Ohkuma)
- Bioresource Information Division (Kaoru Fukami)
- Bioresource Engineering Division (Atsuo Ogura)
- Team for Mammalian Cellular Dynamics (Kuniya Abe)
- Subteam for BioSignal Integration (Takahiro Doi)
- Subteam for Manipulation of Cell Fate (Hiroyuki Miyoshi)
- Team for Mouse Phenotype Analysis (Shigeharu Wakana)
- Team for Advanced Development and Evaluation of Human Disease Models (Tetsuo Noda)
- Mutagenesis and Genomics Team (Yoichi Gondo)
- Unit for Knowledge Base of Mouse Phenotype (Hiroshi Masuya)

RIKEN BioResource Center Resource Committee of Experimental Animal Division
Review Sheet
(January 17, 2011)

Committee members: Drs. Hiromichi Yonekawa (Chairperson), Ryo Kominami, Toshio Ito, Toshihiko Shiroishi, Ken-ichi Yamamura, Minesuke Yokoyama

Summary

1. Does the Experimental Animal Division have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The Experimental Animal Division has made achievements which exceed expectations. Many researchers can use the mouse resources, and in this way, the Division is contributing to progress of science.

1) Achievements of major scientific significance

Individual Comments

- Deposited mouse strains are maintained and preserved as strains controlled microbiologically and genetically at the highest level and supplied to mouse-user community.
- A number of tissue-specific Cre mouse strains were produced and collected as a tool to produce a genetically modified mouse for conditional gene expression and modification.
- A C57BL/6N BAC library aligned on the reference genome was established and disclosed to the community, and supply of the library has been started in collaboration with the Gene Engineering Division.
- Studies such as SNP analysis of C57BL/6J and N substrains may not be scientifically eye-catching, but contribute to improvement of the value of relevant resources and are also important and highly regarded as a basic genome science.
- 280 research papers have been published by users, based on the resources provided.

2) Achievements of major social impact

Individual Comments

- Presence of a well-managed resource organization in Japan itself is very important and has large social and international impact. In particular, the

Division plays a leading role in Asian region, collecting respects from major organizations in various countries there.

- The Division's bioresource activities such as collection, preservation and provision of mouse strains are considered to be an infrastructure for bioscience and only sustainable operation of it leads to increase users and also recognition of its social significance. When considering the quality and quantity of the mouse strains, the Division's activities are widely known domestically and also internationally and thus contribute sufficiently to the scientific community.
- The Division plays a core role in the establishment of mouse bioresource infrastructure in Japan, and should be evaluated based on its contribution to improvement of the entire level in the life sciences, but not based on the achievement in advanced scientific studies. From this view point and the outstanding publications by users of the resources, the contribution made by the Division would be extremely large.

2. Does the Experimental Animal Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Resource Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  The Experimental Animal Division has taken measures efficiently and adequately.

  Individual Comments

  - It was shown that the facilities were operated very effectively, and outreach and other activities also made sufficiently in response to the comments by this Committee. It is considered that the PDCA cycle was functioning sufficiently and effectively, as judged from the explanation on the measures to the other comments by BRAC and internal evaluation.
  - There is concern that it may be difficult to correspond to all comments in terms of limited time and labor, because there are multiple multi-step evaluation systems currently. Thus, it may be needed to set priority in taking measures to these pointed items in the future.

1) Collection, preservation and provision activities

   Individual Comments

   - In collecting tissue-specific Cre mice, a basic policy to focus on strains for the brain sciences was established.
   - As for preservation of strains, the number of live strains was limited to 600 and

the criteria for selection were established.

- The targeted number of the resource distribution is 2,800. The number of mouse strains preserved is important, but the numbers of strains distributed and the organizations to which they are distributed are also important in evaluating the quality of activities. It is recommended that these numbers are reported in the committee, although they may not be cited as targeted values.

2) Distribution Fees

- Distribution fees for profit organizations and non-profit organizations were revised.

3) Collaboration with other organizations, education of employees for public relations and others

- In the mouse development project, there is currently closer communication with users for exchange of information needed for mouse production.

3. Internal and external collaboration and also international collaboration (activities and achievements of special mention, if available)

- **Conclusion**

There is sufficiently much collaboration in progress both with internal and external organizations.

Individual Comments

- As for external collaboration, collaboration with domestic research organizations as well as European and U.S. organizations is sufficiently under progress. In addition, the Division plays a leading role sufficiently as an Asian mouse resource-providing organization.
- It is significantly recognizable that the Division is making collaboration eagerly with external relevant projects and programs, such as collaboration with NBRP Fundamental Technology Upgrading Program and MRC Mary Lyon Centre and possible participation to the International Mouse Phenotyping Consortium (IMPC), in addition to collaborations with the relevant teams within BRC. It is expected that the Division will make significant international contribution, as a representative of BRC and Japan, in IMPC in the future.
- Although collaboration with some teams was described, it was recommended to indicate the current status of collaboration with other divisions and teams briefly as well. Apparently, the Division has favorable collaboration with Gene and Cell Engineering Divisions, and it would be highly valuable to indicate the fact.

4. Others

- The Experimental Animal Division will maintain its effort to manage quality-controlled, high value-added and characteristic mouse resources in the future, publish its research accomplishments and make its advanced technology used more extensively.
- It is needed to make effort to find out hidden resources, for example by retrieval of research papers and abstracts of academic societies. A retrieval program for that purpose should be developed and a system for evaluation of the resources retrieved should also be established.
- Public Relations Activity program for education of microbial and genetic control should be established. In addition, in-house inspection kits for control of test animals in the user organizations should be developed.
- A questionnaire study should be made for the identification of the mouse resources demanded in the research community and the results are reflected in the resource activities in the future.
- The collection of strains developed in Japan has been almost accomplished and resources derived from them (such as BAC, ES, iPS and others) should be developed more intensively.
- Summary of the hearing study concerning bioresource upgrading strategy: The targeted number of the resources provided and others may be influenced by the trend of the studies based on animal experiments in general, if the problems of research budget and animal welfare are considered. The targeted values may not be achieved only by the effort of BRC. It is necessary to make a survey on the trend of the R&D's by using live mouse resources in Japan.
- It is needed to discuss how to use gene trap ES cells in the future. It is needed to decide whether the gene trap ES cells are used only by general users or more positively by BRC itself. For example, possibility of BRC conducting screening of genes that are important but, the KO mice of which are not commercially available, and publishing the results should be discussed. It will be useful as own resource development.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Experimental Animal Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Experimental Animal Division have achievements of major scientific significance and/or social impact?

1) Achievements of major scientific significance

- On the comment that the Division should be evaluated based on its contribution to improvement of the entire level in the life sciences by the establishment of the infrastructure.
  - With regard to standards for evaluation of our contribution to raising the level of the life sciences by means of our provision of mouse resources, we will compile opinions on this matter as a shared issue of concern with other divisions and domestic and overseas institutions, and we will take every opportunity to lobby the government on that basis.

2. Does the Experimental Animal Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

- On the Resource Committee's impression that there are comments which are difficult to respond or with which the Committee members did not necessarily reach the same understanding.
  - With regard to comments indicated by the Resource Committee members, we will not simply respond to every issue, but we will respond efficiently, following an order of priority considering time and labor.
- On the recommendation to survey both of the number of strains distributed and the number of organizations to which distributed for evaluation of the quality of the distribution activity and to report the both parameters to the Committee.
  - As indexes for the evaluation of the Division's collection, preservation and distribution activities, in addition to the number of strains collected and the number of instances of distribution to organizations, we will compile and analyze other statistical parameters that express the quality of distribution, including the number and type of the strains distributed, the form in which they were distributed, and the number of organizations to which they were distributed, and report to the Committee on that basis.

3. Internal and external collaboration and also international collaboration

- On the comment of the Committee's strong expectations in relation to the Experimental Animal Division making an international contribution as a representative of Japan in respect of the International Mouse Phenotyping

Consortium (IMPC).

- We will establish production pipelines for chimera mice and knockout mice to enable us to participate in and contribute to the IMPC as a production facility.

- On the recommendation to indicate the current status of all collaborations with other divisions and teams.
  - We will continue to engage in collaborations that enable us to make use of the expertise of other divisions and teams, and we will report each of these collaborations to the Committee, etc.

4. Others

- On the recommendation to make greater efforts to publicize research outcomes and disseminate advanced technologies in addition to working to produce quality-controlled, high value-added, and distinctive mouse resources.
  - We will conduct searches of papers, abstracts of academic conferences, etc. in order to collect and publish useful information that makes it possible to evaluate the scientific value of the strains we have collected.
- On the recommendation to unearth hidden invaluable resources by searching papers, abstracts of academic conferences, etc., the development of a search program for that purpose, and the creation of a system for the evaluation of the academic value of resources that come up as hits.
  - In addition to collecting publications generated by users via a Web search program, we will also collect publications by directly querying users.
- On the recommendation to establish a publicity program to increase awareness concerning microbial and genetic controls, and the development of an in-house test kit to enable these controls to be conducted at the recipient organizations.
  - With regard to the results of microbial and genetic monitoring of deposited mice, we have ensured that the domestic status is widely known by means of papers, academic newsletters, etc., and we also provide information on our website to increase awareness of the importance of quality control. Regarding an in-house kit to enable users themselves to test microbial and genetic qualities at the same level as the BRC, we will conduct a survey of users' demand and formulate a development plan.
- On the recommendation, given that the collection of unique Japanese strains has been nearly completed, to focus effort on developing their derivatives such as BAC, ES cells, and iPS cells.
  - We will collaborate with other divisions in the creation of BAC clones and ES cell lines, iPS cell lines, etc. derived from the collected unique strains.

- On the concern that the fulfillment would be difficult based on the efforts of the Division alone, without knowing trends in domestic research using laboratory mice.
  - We will survey domestic users concerning the status of use of experimental animals and trends in animal experiments, and reflect the results in our operations.
- On the recommendation to consider how to use polyA-gene trap ES cells in future and the possibility of screening trapped genes for which knockout mice are unavailable, and publishing the results.
  - With regard to polyA gene trap ES cells developed by the NBRP, we will screen useful clones that trap genes unable to be trapped using conventional trapping methods, and publish this information on our website, and we will further publicize and disseminate these as unique knockout resources.

RIKEN BioResource Center Resource Committee of Experimental Plant Division
Review Sheet
(January 7, 2011)

Committee Members: Drs. Kiyotaka Okada (Chairperson), Yasunari Ogihara, Hiroshi Kamada, Makoto Kawase, Nobuharu Goto, Kazuo Shinozaki, Satoshi Tabata

Summary

1. Does the Experimental Plant Division have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The Division promotes projects quite actively, and has made the achievements steadily.

  The excellence in the quality of resources is highly evaluated.

1) Achievements of major scientific significance

Individual Comments

- Among the various plant materials, Arabidopsis resources are the most important infrastructure for whole plant research. The RIKEN BRC has become recognized as one of the three core centers of Arabidopsis resource in the world, as the Division provides resources and information essential for all researchers from basic to application/commercialization studies; this is a significant achievement. In addition to the collection and distribution of resources, the Division promotes user-friendly activities, which is highly evaluated. It is also favorable that the Division is concentrating its efforts on the collection of plant resources inherent to Japan, as well as those supplemental to overseas resources provided from other centers.
- Users of Arabidopsis resources are expanding from basic researchers to agricultural, engineering, and medical researchers. This is obvious judging from the users list of the Division. Further effort to increase the number of users is important. Specifically, the Division tries to expand its collection to Chinese cabbage (*Brassica rapa* var. glabra), a plant in Brassucaceae to which Arabidopsis belongs, and to establish a system that can provide its technology and information in the form applicable to crop plants. This effort is highly evaluated. In addition, the project for application of *Brachypodium distachyon* to plastic production, as a new raw material for green innovation, is a novel

activity.

- The Division leads the world particularly in studies on the response of Arabidopsis to biological and non-biological stresses.
- Disclosure of activation tag lines, transposon tag lines, Chinese cabbage EST clones, FOX lines and etc. is considered to be great contribution to basic and applied studies on plants.

2) Achievements of major social impact.

Individual Comments

- It is contributing to the world with its own resources such as Arabidopsis mutants and FOX lines. Participation and leadership in organizing ICAR2010 was a significant achievement, which leads to improvement of the international presence of the RIKEN BRC resources.
- This Division continues to collect resources inherent to Japan and such an attitude is highly supported by researcher community. The fact that much effort is directed to quality control of the resources is noteworthy, and is becoming recognized as a unique characteristic among the domestic and foreign resource centers. However, we may wait for some time until social influence of the efforts by the Division becomes visible.

2. Does the Experimental Plant Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Resource Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  The PDCA cycle is functioning sufficiently in the fields of technological development on quality as well as strategies for information, international collaboration and public relations. The Division's aggressive approach is highly evaluated.

  Individual Comments

  - There were comments indicating the needs for establishment of resources higher in value and usability in various evaluation phases internally and externally, and there were sometimes also demands that cannot be achieved in a short period of time, but the Division is making every effort to take measures. The Division is also trying to improve its operation, including improvement in efficiency, and has taken measures also in international collaboration, information

dissemination and public relations more efficiently than expected.

- Measures taken, such as development of novel cultured cell lines, consideration of *Brachypodium distachyon* as a possible new resource, and recruitment of new users by information dissemination, are favorable.
- Collaboration with various organizations through SABRE will be monitored carefully. The scientific background and achievements of the collaboration counterpart together with the mutual understanding including on diversity of organisms will be the key factors.
- The Division is eager to incorporate and develop new resources and the number of plant resources therein is increasing. Public relations in academic meetings and others are effective for increase in the number of users. It is important to collect individual resources prepared in Japan.
- The Division is trying actively to appeal to the general public.
- More specific explanations for why *Brachypodium distachyon* was selected as strategic resource in the RIKEN BRC or in Japan may be required.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

- **Conclusion**

  The Division is contributing to domestic and international collaborations.

  Individual Comments

  - The Division is very active in the international collaboration through ICAR and also in leading domestic plant bioresource community. Its promotion of collaborative activities is highly evaluated. Measures for its initiative in the world as a representative of Japan are desirably discussed in relation with the Biodiversity Treaty.
  - Its international collaboration, especially with Asian countries, is highly evaluated. In principle, strategies should be described at the policy level. Policy proposal as well as discussions and efforts based on the broad horizons to bring the favorable strategy are anticipated.
  - Based on the improvement of the infrastructure for NBRP's plant-related resources, leadership in the mutual information exchange and the classification of subjects to be discussed is desired to set up the project for next 10 years.

4. Others

Individual Comments

- The RIKEN BRC's resources will continue to grow consistently. Development and application of preservation technology should be promoted furthermore to reduce labor and cost for storage.
- Along with the development of plant research, resources should be re-characterized from the viewpoints of evolution, ecology and diversity researches. Similarly, convenience of users in such research field would be considered in the collection and distribution of resources and information.
- Collection and development of resources based on the social seeds are more and more important for application studies. It is noteworthy that much consideration is paid in the aims of the Division to contribute application studies. Establishment of an infrastructure allowing cross-sectional studies in combination with other applicable resources is desired.
- A system that can accept requests from various research fields is desired to be established.
- Events held for next-generation citizens, such as poster presentation by super science high-school students in ICAR2010 and "Tsukuba Chibikko Hakase" in the RIKEN BRC-sponsored meeting, would be important.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Experimental Plant Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. **Does the Experimental Plant Division have achievements of major scientific significance and/or social impact?**

- On the comment that social influence will become visible after certain period:
  - We will make efforts based on a medium- to long-term perspective, looking towards the period when social spillover effects become apparent. In the meantime, we will attempt to work effectively to ensure that no opportunities for public relations activities targeting ordinary laypeople are missed.

2. Does the Experimental Plant Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

- On the comment that careful monitoring is needed for the collaboration with various organizations through SABRE:
  - We believe that it is important at the very beginning to establish a mutual understanding and shared awareness with organizations and communities on the outside. Exchanges of opinion have been already conducted for the past several years on this basis. We will continue the efforts in future to further deepen our collaborations.
- On the recommendation to collect individual resources created in Japan:
  - The Experimental Plant Division has commenced collecting every Arabidopsis resource created in Japan, and will continue in these efforts.
- Necessity of explanation for selecting Brachypodium as a resource to be strategically stocked:
  - Discussion of the importance of Brachypodium is deepening within the project itself, but we believe that its value will become clear if we make an example for the outcomes in the area of large herbaceous plants.

3. Internal and external collaboration and also international collaboration

- On the comments that considering strategies for international collaboration:
  - The BRC promotes international collaboration with a focus on Asia, and is responding to the Convention on Biological Diversity. We will continue the efforts while collaborating with relevant organizations. In addition, we will attempt to formulate strategies that enable us to assume a leading position in Asia, and make proposals to the government on this basis.
- On the recommendation to play central role in the collaborative network of plant resources in NBRP:
  - We are proposing to the NBRP the implementation of public relations activities on the plant topics at international and domestic conferences scheduled for 2011, and will promote practical collaboration aiming towards the ongoing enhancement of cooperation.

4. Others

- On the comment that the further development and application of preservation technology is advisable:
  - We have measured an order of priority based on the importance and the scarcity of the resource, and make every effort to maintain the resources of the

highest priority. We are proceeding with the development of technologies to enable us to reduce the cost and manpower involved in the preservation of other resources.

- On the recommendation to consider the view points of evolution, ecology and diversity researches in the collection and distribution of resources and information:
  - In relation to research related to evolution and diversity, we have continued collection of natural accessions and closely related species, as well as improving the appended information of these resources. We will take the Convention on Biological Diversity into account and continue our efforts to ensure the convenience of researchers to use
- On the recommendation to establish a system to take requests from research communities of different fields.
  - For several years we have been continuously supplying information to the applied research community. We will continue to proceed efficiently with these activities at meetings and conferences in various scientific fields.
- On the comment that the events for next-generation citizens are important:
  - We will continue our efforts to promote the events as well as considering other strategies, for example, preparation of useful materials such as manuals and photographs for school education.

RIKEN BioResource Center Resource Committee of Cell Engineering Division
Review Sheet
(January 18, 2011)

Committee Members: Drs Tatsutoshi Nakahata (Chairperson), Toshihiro Akaike, Toru Imamura, Yoshiki Sasai, Kyoichi Shimomura, Namho Huh

Summary

1. Does the Cell Engineering Division have achievements of major scientific significance and/or social impact?

- **Conclusion**

  Deposition of ES and iPS cells is in progress and their provision is also favorably in progress. There are made various achievements such as deposition of disease-specific iPS cells, international collaboration on cell misidentification test, and initiation of service for quality control analysis depending on the user's requests.

1) Achievements of major scientific significance

Individual Comments

- The Division plays an important role as a basis for life science. Future continuation of the activities and development of the RIKEN BRC is essential for life science.
- It is highly evaluated that the Division is catching up advanced cell banks in the world and passing them both in quantity and quality.
- Addition of cells for use in genome analysis and also stem cells for use in regenerative medicine research to conventional general-purpose cells in the collection was a significant achievement. As for the quantity, the number of the cell materials preserved increased almost 3 times and the number of the cells provided also increased 1.5 times. There were also an increased number of research papers made based on the cells provided, indicating the Division's large scientific contribution. Measures for improvement in quality were also taken intensively, and the Division obtained ISO9001 certification finally after its examination.
- It is desirable, although difficult, to evaluate the current status of the entire cell-using research community, specify the contribution possibly made by the Division therein and thus, determine the future strategic direction of the Division.

2) Achievements of major social impact.

Individual Comments

- It is recognizable that the work in the cell bank is less eye-catching labor, but pursuit of scientific achievements, particularly high-grade research papers, made based on the preserved cells and also based on the technical advantage obtained by cell preservation is desired. Scientific achievements highly contributing socially to regeneration medicine and medicine development are desirably pursued.

2. Does the Cell Engineering Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Resource Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  Targets were favorably specified, and the measures to the targets were established and executed. Further improvement was pursued, based on evaluation results, and thus, the PCDA cycle is functioning sufficiently.

  Individual Comments

  - Measures to the respective items cited in BRAC and Resource Committee are taken properly. Cells, which are preserved as cell lines, are being recognized to have additional value. In addition, preparation for initiation of deposition of disease-specific iPS cells is in progress according to the proposal, and in this way, measures are taken sincerely and effectively to the items cited. In particular, the new effort for quality control of cells is very important and highly evaluated. Practical targets are proposed from the self inspection within the Center and measures suitable and effective for the targets are taken.
  - A more effective system is desirably established for public relations, staff education, dissemination of scientific results, contribution to the society and improvement of the cell technology level of Japan with the strategic brains available in the Center in the future (the effort is highly evaluated and further progress is expected).
  - With limited capacity, priority was given to these measures, and collection and preservation of iPS cells was pursued particularly eagerly. The service of quality control analysis for users started this year, and a large-scale cell culture

apparatus (automatic culture apparatus) will be installed next year for large-scale culture.

- The reported number of research papers accomplished by using the cells provided does not reflect the actual state and may be too small. The number of papers published or presented should be determined more accurately, for example, by modification of the investigation method or by providing incentives.
- Further discussion is needed on foster personal of staffs.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

- **Conclusion**

Collaboration activities including sponsorship of ANRRC meeting were active, and the Division's contribution to the research community is highly evaluated.

Individual Comments

- Efforts to collaborative projects in progress with ATCC in U.S. and DSMZ in Germany on STR polymorphism analysis, cell standardization and others are highly appreciated.
- The RIKEN BRC is contributing to standardization of stem cells internationally as a core member of ISCI and ISCBI.
- Further efforts to become an intellectual hub to the cell bank projects in Korea and other Asian countries are desired.
- A plan to accept foreign postgraduates is discussed and future progress of it is expected.
- The initiative of the Division at the world level is important.

4. Others

Individual Comments

- In general, recent efforts and the results are highly evaluated.
- If a one-stop shop for provision of cell materials is constructed for common online resource retrieval in cooperation with the databases of other typical resource centers such as ATCC and DSMZ, it will lead to increase in the number of the resources provided from the Riken BRC, allowing fulfillment of the goals of increased contribution to research community and increased advertisement of

the RIKEN BRC.

- When considered from the point of social importance, further intensified, more efficient efforts (for example, redistribution of labor by education of staffs, automation, partial subcontracting, etc.) may be needed, although it may be very hard to practice with limited capacity.
- Congratulation to construction of the Bio Resource Building for Cell Research. Establishment of a new system and effective use of it are desired.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Cell Engineering Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Cell Engineering Division have achievements of major scientific significance and/or social impact?

- On the recommendation that future orientation of the Division should be determined after taking an overview of the research community that utilizes cell materials as a whole and clarifying the degree of contribution made by the Division:
  - The main contribution of the conventional cell banks has been in the field of basic sciences. With the advent of human ES and iPS cells, contributions can be expected in applied sciences such as regenerative medicine. Disease-specific iPS cells are capable of making a contribution in areas ranging from the basic research of disease to the applied field such as that of drug discovery, and expectations are therefore strong for these cells. As recommended, we will attempt to grasp the needs of the research community, and proceed with our work based on the order of priority it determines.
- On the comment that representative scientific results such as superior papers based on the cell materials and technologies provided by the Division should be collected, in particular, social contributions such as those to regenerative medicine and the development of pharmaceuticals are important:
  - It will be important to compile papers produced by users. We will make efforts towards improvement by increasing the number of personnel assigned to this

task.

2. Does the Cell Engineering Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

- On the recommendation that public propaganda, the fostering of human resources, the dissemination of research outcomes of users, social contribution, and improving the level of cell technology in Japan should be carried out with strategic thinking of all stuffs in the BioResource Center towards more effective systems:
  - It is important to engage in public relations activities that can be understood even by the general public. New public relations activities will be necessary in addition to the open house sessions, acceptance of visits by high school students and other activities that we have conducted to date. While it is essential to consider the cost/performance ratio, it might be useful to utilize the mass media.
- Presumably more papers have been published based on research using cell materials supplied by the Division than those actually reported to the Division, and thus its contribution risks being undervalued. On the recommendation that promotion of a clearer grasp of the number of published papers should be carried out by refining survey methods, providing incentives to users, and so forth:
  - It is important to compile research outcomes generated by users. Efforts will be made towards improvement such as by increasing the number of personnel assigned to this task.
- On the comment that fostering of human resources is very critical for the Division:
  - The Center has no option but to cease competitive tendering for temporary staff due to social conditions (the crisis in national finances). However, it is important to secure human resources of a specific level of skill on a continuous basis.

3. Internal and external collaboration and also international collaboration

- On the comment that further efforts to become an intellectual hub of the cell bank business in the Asian region should be carried out:
  - We intend to take initiatives and play a central role in promoting cooperation between cell bank businesses in Asia through involvement in organizations such as the Asian Network of Research Resource Centers (ANRRC) and the Stem Cell Network of Asia-Pacific (SNAP).
- What extent can initiatives be taken at the global level?
  - At the global level, we are working towards the creation of a shared common database concerning short tandem repeat polymorphism analysis for human cell lines in collaboration with ATCC, DSMZ, and other cell banks. We believe that

we can promote initiatives that produce a win-win situation.

4. Others

- On the recommendation to create cooperative systems such as a shared online resource search system unified with the databases of ATCC, DSMZ and other representative cell banks:
  - We wish to enhance cooperation with ATCC, DSMZ and other global cell banks on a variety of fronts, not restricted to the creation of a shared common database concerning short tandem repeat polymorphism analysis for human cell lines.
- On the suggestion that the work should be carried out more effectively, e.g., Division of duties through the fostering of human resources, mechanization, partial outsourcing, and so forth:
  - We are planning to introduce a large automatic cell culturing system. If the operation of this system works well, an increase in work efficiency can be expected to some extent.
  - Some kinds of quality control analysis could presumably be outsourced. We will examine this option with consideration of the cost/performance ratio.

RIKEN BioResource Center Resource Committee of Gene Engineering Division
Review Sheet
(January 18, 2011)

Committee Members: Drs. Jun-ichi Miyazaki (Chairperson), Izumu Saito, Sumio Sugano, Mamoru Hasegawa, Hirohumi Hamada, Koji Matsushima, Ryouzaburo Mukai

Summary

1. Does the Gene Engineering Division have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The Gene Engineering Division has made significant spreading effects by promoting research collaboration among scientists and accelerating progress of scientific research in Japan. Altogether, the Division has made meaningful achievements as a scientific infrastructure.

1) Achievements of major scientific significance

Individual Comments

- There are important achievements by paving the way for the future, for example, distribution of DNA samples reaching 1,000 items annually, increase in the number of published and submitted research papers using these samples, collection of quality-controlled clones, and total collection of 3.5 million genetic material stocks. In particular, preparation of C57BL/6N BAC library (construction of 124,000 clones and sequencing of both ends of clones) is a very promising important achievement.
- It is evaluated very favorably, as the Division demonstrated the usefulness of adenovirus vectors by the fact that adenovirus vectors harboring iPS inducing genes can transform mouse embryonic fibroblast cell to iPS. Collection and preservation of termite's enteral protozoa-derived "cellulase" genes should be highly evaluated from the viewpoint of biomass production.
- As results of distribution of many useful and unique genetic materials, the number of published research papers that were accomplished by using the materials has been increasing. This shows large spreading effects of this Division's efforts.

2) Achievements of major social impact.

Individual Comments

- If the Gene Engineering Division did not exist, it would have been impossible for many research laboratories to obtain genetic materials. Consequently, it is most likely that many important studies could not have been started. Therefore, its social impact is considered to be large.
- Although social recognition is not enough, the important function of this Division in domestic and foreign sciences is obvious, for example, by the fact that about 1,000 DNA items are distributed annually as described above.
- Under the circumstances which acceleration and competition on development from bioresource into scientific and/or technological output have been increasing, genetic materials distributed by this Division have been contributing to improvement of efficiency of research and this role will continue to increase in the future.
- With appropriate plans, for example collection of genes of enzymes for biomass production, the Division will be able to contribute to establishment of an infrastructure for biomass engineering in the future.

2. Does the Gene Engineering Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments by the previous BRAC and Resource Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  The Gene Engineering Division has taken measures very sincerely to all evaluation points and comments made by BRAC and this committee. It is objectively judged that the PDCA cycle is functioning well.

  Individual Comments

  - The PDCA cycle is steadily functioning every year, especially the followings are noteworthy: public relation activity at meetings of the academic society, increase in efficiency of preservation of genetic materials and collection of valuable genetic materials scattered in various universities in Japan.
  - Proper measures have been taken sufficiently to individual issues made by committees, such as investigation of the achievements by users such as published papers obtained through the use of the genetic materials provided.
  - It is recommendable that the Gene Engineering Division shall communicate with depositors on the distribution of deposited DNA samples every 3 to 5 years.

Since preservation and distribution are very costly, it is important to evaluate upon receiving a DNA sample whether the sample is worth enough for preserving.

- Necessity of examination of the preservation method has been pointed out several times by this committee. Measures have been taken properly. The improvement of preservation method has big impact and the effort should be made continually.
- Not all comments made by the BRAC or this committee may be appropriate. For example, there was a comment that the number of published research papers using genetic materials distributed by this Division was insufficient. However, as described above, the comment is considered not to reflect the current contribution of this Division accurately.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

- **Conclusion**

International collaboration and also collaboration with other RIKEN centers are in progress, which is favorably evaluated.

Individual Comments

- In particular, this Division is one and only provider of adenoviral vectors of the world and promotion of collaboration with foreign researchers on this subject will be valuable.
- Collaborations with other divisions are also actively pursued and, in particular, cellulase clones are very interesting. However, this collaboration may be quite different from the traditional activities of this Division. The outcome should be monitored carefully.
- Technology transfer through collaborations with other resource facilities including those of National Bioresource Project, seminars and technological training courses has been conducted actively. Examples are preservation technology of large-scale genome clone set and preservation method of plasmids in DNA solution at -30°C.
- Collaboration should be promoted strategically from the viewpoint of secure use of resources in the Asian region.
- The ratio of foreign distribution is as high as 30%, and further international collaboration is recommended. In addition, efforts to resolve problems of

intellectual property rights such as patents on clones, vectors and others should be made. Negotiation at the national level would be needed in the future.

4. Others

Individual Comments

- Facilitation of genetic material to many users by further improvement of deposited materials will be important for expansion of the spreading effect.
- The effort for "standardization of genetic materials" will be very significant.
- Although there are seemingly disputes over rights on retroviral and lentiviral vectors, distribution of these materials is desired.
- Further improvement of public relations concerning genetic materials is recommended.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Gene Engineering Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Gene Engineering Division have achievements of major scientific significance and/or social impact?

2) Achievements of major social impact

- On the comment that social recognition is not enough:
  - We will actively publicize our work to the general public. Press coverage provides the greatest number of opportunities for us to make contact with the public, and we will actively publicize noteworthy outcomes of our users in basic and applied research. In addition, we will provide easy-to-understand explanations of our activities and our role in the society at our open house events during Science and Technology Week which represent opportunities for us to make direct contact with the public. To contribute to efforts to prevent young people from drifting away from science, we will also conduct educational activities by actively participating in laboratory visits by middle and high school students and the Tsukuba “Doctor Kid” program.

2. Does the Gene Engineering Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

- On the recommendation to contact depositors every three to five years to report the status of distribution of their resources:
  - We will periodically report to depositors on the numbers of distribution and research papers using on their genetic materials.
- On the comment that it is important to review the value of genetic materials prior to deposit, given the high cost of preservation and distribution:
  - Prior to accepting the deposit of large-scale resources, we examine whether a research community actually uses these resources or not, and decide whether to accept the resources on this basis. We will continue to apply this principle in future. With regard to quality control for large-scale clone sets, we first preserve all of them after their deposit, and conduct quality inspections only when the clones are requested. Distribution is delayed by about one week, compared with quality inspection in advance, but it significantly reduces costs. On the contrary, in the case of resources from individual researchers, we conduct quality inspections immediately following their deposits.
- Necessity of examination of preservation methods has been pointed out several times by this committee, and the Division is responding appropriately. On the recommendation of continuing efforts to improve the preservation methods:
  - Currently, we use -80°C preservation methods, which mean the level of dependence on electric power is high. We will seek to make the transition to preservation methods with a lower level of dependence on electric power. First, we will continue to monitor the viability over time of glycerol stocks preserved at -30°C.
  - Other core facilities of the NBRP are also very interested in resource preservation technologies, and we will therefore disseminate our technologies by means of seminars.

3. Internal and external collaboration and also international collaboration

- On the recommendation, given that the Gene Engineering Division is the sole provider of adenoviral vectors in the world, that there would be value in pursuing collaborations with overseas researchers in this area:
  - Although no specific collaborators have been selected, we intend to seek researchers with whom we can collaborate to promote the use of adenovirus vectors.
- On the comment that, while clones of cellulase genes are of great interest, it will be

necessary to measure outcomes in this area closely, since this activity is significantly different from the Division's previous activities:

- We will show our collected resources sequentially in our catalogues. We will decide our future direction by comprehending research trends and needs.

- On the comment that, from the perspective of securing resources in the Asian region, it is particularly necessary to proceed strategically:
  - We believe that the securing of resources and the sharing of information are most effectively pursued within the framework of an Asian network. We will use the framework of the Asian Network of Research Resource Centers (ANRRC). Within the ANRRC, there are virtually no institutes outside of Japan that handle genetic clones. We will make a strategic plan by which the Division will play a leading role in this area.
- On the recommendation to pursue further international collaborations, and on the comment that negotiations at the intergovernmental level will also become necessary, as the high (30%) ratio of distribution of resources to overseas.
  - While we have not yet decided on particular collaborating partners, we think it is necessary to take consideration of the Convention on Biological Diversity when pursuing mutual agreements with specific governments and institutions.
- On the comment that some mechanism will be necessary for clearing patent right issues in the area of clones, vectors, etc.:
  - We will continue negotiations regarding the academic use of clones that are produced by using technologies licensed by companies.

4. Others

- On the comment that the further improvement of deposited genetic materials in order to make them more convenient for a larger number of users is important from the perspective of ripple effects:
  - The collection and distribution of resources that have been modified and improved by the users will create a positive cycle of added value and promotion of further use, and is extremely effective and efficient. We will collect resources by asking for deposition to users who have published research results using our resources.
- On the suggestion of "standardization of genetic materials":
  - We have formulated a standard operating procedure (SOP) for quality control (tests for antibiotic resistance of recombinants, restriction enzyme mapping, and terminal sequencing of the inserted genes) of each category of resource (plasmids, BAC, viruses, etc.). We will adhere with these SOP strictly. We

intend for this initiative to provide a de facto standard.

- On the comment that while intellectual property rights issues exist in relation to retroviral and lentiviral vectors, their distribution would be desirable:
  - It is necessary to negotiate with a large number of companies and universities in relation to intellectual property rights associated with lentiviral and retroviral vectors. This has been making progress difficult. We will search a variety of possibilities to expand academic use.
- On the comment that further improvement of public relations concerning genetic material is needed:
  - It is necessary to modify the content and method of the public relation program depending on the target (researchers, the general public, young people, etc.). We think that at times it will be necessary to seek advice from outside professionals in order to conduct the most effective programs for each target.

RIKEN BioResource Center Resource Committee of Microbe Division

Review Sheet

(January 7, 2011)

Committee Members: Drs. Makoto Watanabe (Chairperson), Susumu Itoh, Sumio Shinoda, Ken-ichiro Suzuki, Seizo Sumita, Katsuhiko Kamei

Summary

1. Does the Microbe Division have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The Division with the current number of staffs and funding has been functioning well to the maximum degree and making sufficient achievements.

1) Achievements of major scientific significance

Individual Comments

- It is highly evaluated that the Division is making achievements as one of 3 major microbial bioresource centers in the world along with ATCC and DSMZ. However, the capacity is limited with the current staffs, and the collection should be focused at least on the current targets, resources for academic and research use and those for academic research pursuing mainly environmental sciences and health sciences.
- As for microbial bioresources, the Division plays a role sufficiently as one of central institutions in the world in academic research, mainly with standard type strains.
- The Division has been publishing high-quality research results, for example on classification of microbes and discovery of symbiotic microbes in mammalian gut-associated lymphoid tissues, although these achievements may not be flashy.
- The number of papers published based on the microbes provided by the Division rose to more than 800 in 4 years, indicating that the contribution to the advancement of the field of science involving microorganisms is significant.

2) Achievements of major social impact.

Individual Comments

- It is necessary to conduct active public relations widely to the government and to

the society in general that the Division (JCM) is playing a role as one of 3 major microbial bioresource centers in the world along with ATCC and DSMZ. When advertizing its activity, it is necessary to point out that there are still issues to be solved for sustainable operation of the Division by comparing with ATCC and DSMZ.

2. Does the Microbe Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Resource Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  Intensive efforts have been made to the issues, and the PDCA cycle is functioning very well.

Individual Comments

- The system for repository of resources and the capacity of processing may be at the top class in the world. In addition, close attention should be given to the resources and associated information that is needed by research community, such as those for compliance with the Convention of Biological Diversity.
- The ability to preserve microbes that are very difficult to be cultured is very important for discriminating the Division from other resource centers (including those in foreign countries) and this has made the Division superior to other centers.
- Relocation of the facility to the Tsukuba Institute will be a big project. This may be an occasion for selection and concentration of the resources. Relocation should be carried out carefully without damaging on precious strains.
- Measures so far taken to comply with the Convention of Biological Diversity are highly evaluated. As the Nagoya Protocol will be ratified, some guidelines for the implementation of it (e.g., special consideration to the use for non-commercial purpose) will be necessary. By participating in an international group from the academic side, collection of information and exchange of opinions are recommended.
- An international congress of International Union of Microbial Societies (IUMS2011) will be held in Sapporo in September this year. Involvement in the meeting by many ways is recommended.
- Care should be given to preservation of the scientifically important strains that

are currently held by retiring researchers. Otherwise they would be lost by their retirement.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

- **Conclusion**

  Vigorous efforts for domestic and international collaborations have been made even with a limited number of staffs. As a result, active collaborations inside and outside the RIKEN BRC and international collaborations are in progress.

Individual Comments

- Establishment of ANRRC and holding its Tsukuba meeting, and participation and contribution to the All Species Living Tree project and the Microbial Earth project are highly evaluated. The efforts should be made to keep playing a leading role in the world with emphasis on the uniqueness of Japan and to stay ahead of rapidly catching-up Asian counterparts.
- There are differences between collaboration with large institutions in advanced countries and that with institutions in developing countries in south east Asia. Current collaborations are mainly with the former institutions. Maintaining activities at the level similar to that of these institutions are highly evaluated, considering the scale of the Division. While keeping these collaborations consistently at the current level, it is necessary to establish a network with the Asian institutions by taking much consideration for what should be done in Asia.
- There have been many reports of research achievements that were made by using the JCM strains. Among them, what are the achievements by foreign countries? If possible, classification of achievements by foreign researchers into those in Europe, U.S., Asia and other regions, is recommended.

4. Others

Individual Comments

- The Division has been operated at the highest levels of activity and quality. It is no doubt that the Division is one of the three core microbial resource centers in the world. It is necessary to indicate objectively that there is a limit to the possible improvement merely by optimization of efficiency in the Division. Measures for further improvement of the Division should be taken.

- Analysis of collection of strains (species) that may become important in the future is recommended in addition to important strains at present.
- Although various efforts have been already made, further measures to cope with increase in the number of deposited strains will be needed (for example, selection of strains or collaboration with other culture collections).
- The Division is facing a big problem in changing generations of soon retiring curators. It would be very difficult for the Division to maintain the level and scale of the current achievement and to exploit pioneering new resources at the same time. It may be necessary to chose only one of them, unless the scale of the Division is expanded. Thus, the allocation of staffs and time suitable from this viewpoint should be analyzed. Earlier planning and recruiting suitable staffs are recommended for the future of the Division and the management of its unique resources in addition to the future plan similar to general research laboratories.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Japan Collection of Microorganisms will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Microbe Division have achievements of major scientific significance and/or social impact?

- On the comment that the capacity is limited with the current staffs and that the collection should be focused on the current targets:
  - We will continue to take seriously our mission of microbial resources that are important from the perspectives of academic and scientific research and those that contribute to research in the areas of environmental and health sciences.
  - We will also continue our policy of collecting microbial resources that are difficult to cultivate for the purposes of division of roles and cooperation with other institutes.
- On the comment to the necessity to point out that there are still issues to be solved for the sustainable operation by comparing with ATCC and DSM:
  - We will work to publicize the fact that we are one of the world's three leading institutions in terms of collections of bacterial and archaeal type strains, taking into consideration of objective comparisons between our institution and other

institutions such as the DSMZ and ATCC.

2. Does the Japan Collection of Microorganisms have a functioning Plan-Do-Check-Action (PDCA) cycle?

- On the comment that the relocation should be carried out carefully without damaging on precious strains:
  - With regard to the relocation to Tsukuba, ensuring that no important microbial strains are lost will be uppermost in our minds, and we will work to minimize any delays in our activity as a microbial resource center. We will also treat the relocation as an opportunity to consider the realization of increased efficiency and the establishment of future systems.
- On the comment to the recommendation for collecting information and exchanging opinions by participating in an international group discussing about Convention on Biological Diversity (CBD):
  - We will focus on the trends entailed by the ratification of the Nagoya Protocol to CBD, in particular special considerations such as the use of resources for academic and non-commercial purposes, and will make a calm and reasoned response, while working to gather information and exchange opinions in cooperation with the BRCs and other institutes. One of our staff will join the next conference for CBD as a representative of academic researchers.
- On the comment to the participation in various forms in the 2011 Congress of the International Union of Microbiological Societies (IUMS 2011):
  - In addition to hosting a symposium at IUMS 2011 in September, we are planning to conduct public relations activities.
- On the comment to the preservation of scientifically important microbial strains of retired professors:
  - We will gather information of microbial collections of retired professors that are in danger of being lost, and we will work to transfer those considered important from an academic or scientific research perspective to enable their sustainable use.

3. Internal and external collaboration and also international collaboration

- On the comment to the efforts to keep playing a leading role in the world with emphasis on the uniqueness of Japan and to the necessity to establish a network with Asian institutions
  - We will work to enhance our present collaborations with BRCs in Europe and the U.S. and with the Asian network, and we will attempt to demonstrate Japan's

originality and play a leading role in the world.

- On the comment to the classification of achievements using JCM strains by foreign researchers depending on their countries:
  - We will demonstrate research outcomes (publications) achieved with JCM strains, classifying them into those from overseas such as Europe, the U.S., and Asia, and those achieved by domestic researchers.

4. Others

- On the comment to the necessity to indicate objectively the limit to possible improvement merely by optimization of efficiency:
  - Considering the comparison between our institute and others, we will demonstrate objectively that there are limitations under the present system, and seek to realize improvements to the system.
- On the comments to the important collection in future:
  - In future, we will make continuous efforts to the present targets particularly with emphasis on the resources useful for research in environmental and health science. For this purpose, we will work to understand the trends in future research fields as well as the needs of researchers.
- On the comments to the measures to cope with increase in the number of deposited strains, the choice of our future plan, and the recruiting suitable staffs:
  - We will make continuous efforts to increase the efficiency in order to be able to respond to the increasing deposits of strains. Bearing generation changes, the fostering of human resources, and cooperation with other institutions in mind, we will consider the direction for a future sustainable JCM system based on a balance between a system maintaining the present scale and activities and a system able to pioneer new resources.

RIKEN BioResource Center Resource Committee of
Bioresource Information Division
Review Sheet
(January 26, 2011)

Committee Members: Drs. Satoru Miyazaki (Chairperson), Takeshi Itoh, Yoshihiro Ugawa, Shun-ichi Kikuchi, Yoko Satta, Yasukazu Nakamura, Kozo Matsumoto, Nobumoto Miyashita

Summary

1. Does the Bioresource Information Division have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The activity in Bioresource Information Division is essential for the existence of bioresources, and continuation of the activity itself is "significant achievement." The Division is contributing to scientific research inside and outside of the RIKEN BRC. The amount and quality of the information currently provided are at the top class in the world, and the database stores an enormous amount of contents. The fact itself is significant scientifically and socially and highly evaluated. Increase in uniqueness of the database with addition of a new information retrieval system is recommended for further improvement.

Individual Comments

- Renewal of the website is important from the viewpoint of social impact. However, that is not accomplished yet. Efforts to improve in convenience and efficiency of the web catalog should be continued in the future. Some additional manpower may be needed.
- Information, which is an essential element in distribution of bioresources, has a large impact, regardless whether it is good or bad. The new distribution system established by this Division last spring would have had a large spreading effect, if it were functional as expected, however, the troubles that occurred are regrettable.
- Based on self realization that the Division is a part of social system, opening of a home page for general public and delivery of e-mail news to researchers had a social impact and these efforts are highly evaluated.

2. Does the Bioresource Information Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Resource Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  Based on the new distribution system, balance of service and research was proposed, and measures to each issue were started to be taken according to this proposal.

Individual Comments

- Efforts to improve efficiency and rationalization by alteration of the configuration of resource database were made. The reduction of the cost for operation and improvement in efficiency are highly evaluated.
- There were many "initial troubles" observed when operation of the new distribution system started (March, 2010), but most of the problems were identified and corrected at this point of time, and the system had achieved its initial objective. Measures including follow up were taken adequately. In addition, management of the troubles by using the Issue List seems to be functioning well.
- Not much improvement was achieved yet from the point of easiness to view.
- Re-assignment of the personnel is recommended for the best outcome.
- It may be necessary to outsource some of the tasks such as functional design of the fee accounting page and the web catalogue. Such outsourcing, however, should not be done by the Division alone, but only by agreement and cooperation of the entire RIKEN BRC.
- There may be weakness in making plans. There is an impression that the Division did not have room to make its plans and furthermore it lost further when the problems occurred. It is doubtful whether the Division had set a target for reduction of operational cost and whether the reduction of budget could not be foreseeable in advance.

B. Strategy and implementation plan in the two remaining years in the current mid-term plan.

- **Conclusion**

  Planning of selection and dissemination of information that can be provided only by

the Bioresource Information Division is recommended.

Individual Comments

- "Information needed for the users of RIKEN BRC" and the "information needed for sustainability of the RIKEN BRC" should be managed in collaboration with the other Divisions of BRC.
- Priority should be given to maintenance of the user information, and then urgent construction of systems for analysis of access log and for calculation of useful statistics of distribution information is recommended.
- A specific roadmap for renovation, improvement and enrichment of the web catalog is recommended. An easily using system such as Amazon.com, is requested to develop.
- It is already known what the problems are, and thus, a specific targeted period and the extent of the measures to correct the problems should be proposed.
- There is a problem in recruiting staffs. The number of staffs in the Division was cut back and now recruitment based on the experience is recommended. If the staffs are to be employed on the contract basis, care should also be given to the staffs' carrier path.
- A specific plan for "literature curation" should be proposed.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

Individual Comments

- Information should be accumulated in the Center and the leadership of the director of the RIKEN BRC is strongly recommended.
- Collaborations with inside and outside of the RIKEN BRC and also international collaboration are recommended.
- Incorporation and initiation of the service of Microbe Division (JCM) are highly evaluated.

4. Others

Individual Comments

- Self realization that the Division is a part of "social system" is strongly needed.
- Re-examine whether there were any defects in the plan of replacement of the distribution system.

- Cost reduction made by internal improvement should be evaluated higher, although it is less visible to the users.

Responses and Actions by the Division to the Evaluation Conclusions and Comments

For issues that received positive evaluations, the Bioresource Information Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Bioresource Information Division have achievements of major scientific significance and/or social impact?

- Changes to the website are important from the perspective of social spillover effects. Concerning the fact that few changes have been made to date.
  - We will seek to enhance our initiatives in this area, engaging in discussions with each of the resource divisions in order to clarify precisely what needs to be done to increase convenience for users. We will increase our manpower as required to enable us to do so.
- Concerning the faltering start of the resource distribution system, etc., given the fact that when these systems are functioning effectively, there is a significant social spillover effect.
  - When we commence operation of a new system in future, we will cooperate sufficiently with the relevant divisions in the BRC, and commence operation on the basis of a 100% complete plan.

2. Does the Bioresource Information Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Concerning the status of responses to items indicated as requiring attention in the previous reviews conducted by the BRAC and the Committee, and the Center internal self-inspection and evaluation.

- Concerning the fact that few improvements have been made in the area of user-friendliness, more efforts will be needed to refine the functional design of the Web catalogues, etc.
  - We will enlist the aid of external professionals in implementing large-scale system development projects – improving user-friendliness, refining functional

design, etc. We will take measures including 1) increasing our manpower for formulating specifications, and 2) formulating Requests for Proposals (RFP) in order to enable us to proceed effectively with the required system development.

- Concerning the necessity for reconsideration of the plan for optimal deployment of personnel.
  - We will consider the appropriate deployment of personnel to enable us to improve the present situation, in which we are exclusively pressed by daily "Dos," and establish a functioning Plan-Do-Check-Act (PDCA) cycle by also implementing Plans and Checks.
- Concerning the Committee's feeling that the planning ability of the Division is weak; the impression that there is no margin for planning, and when problems have arisen, the margin has been further eroded.
  - We will foster and enhance our human resources for the formulation of plans, to enable us to address our weakness in planning within the Plan-Do-Check-Act (PDCA) cycle.
- Concerning the question as to whether targets for reductions in operating costs were set, and whether the Division was aware in advance that there would be a significant decrease in the budget.
  - In future, we will obtain an adequate understanding of the annual budget, and request increased allocation as needed in order to ensure the continuation of sound operation.

B. Concerning guidelines and action plans for the remaining two years of the current mid-term plan.

- Concerning the recommendation to cooperate with the resource development divisions in efforts to organize the information required by the BRC's customers and the information necessary for the continued existence of the BRC.
  - We will engage in cooperation with the resource development divisions in both of these areas. In respect of the latter in particular, it will be necessary to organize the distribution data currently scattered in each division in one location, and the cooperation of the other divisions will be essential in this.
- The organization of user data is an essential condition; concerning the recommendation to create a system enabling analysis of logs of supplied information and the calculation of useful statistics.
  - We see the priority of this measure as just behind that of redesigning the Web catalogues. We will implement this measure following the redesign of the Web catalogues, or will attempt to put both measures into effect simultaneously by obtaining the requisite manpower.

- Concerning the recommendation to formulate a concrete roadmap for the redesign, improvement and enhancement of the Web catalogues, and to develop an easy-to-use system like Amazon.com.
  - We will formulate a draft roadmap, and refine it by taking opinions from each of the relevant divisions.
  - There are various conditions that prevent us from modeling the system precisely on the Amazon.com system (the necessity of handling paper media such as MTA, etc.), but that system will represent one of our target models.
- Concerning the recommendation, given that the location of the problems is known, to clarify when they will be rectified by and how far efforts in that direction will proceed.
  - There are uncertain elements such as our ability to secure manpower, but we will attempt to clarify these issues to the degree possible.
- Issues remain in terms of securing manpower. Concerning restructuring, etc. based on the experience of having considerably downsized.
  - We will secure the necessary manpower, taking into consideration, in addition to our existing manpower that is necessary for the bare minimum operation of the Division, the manpower necessary for enhancing security, preparing hardware, conducting developments to achieve the minimum level of in-house production, formulating specifications for orders to external companies, etc., and also manpower to provide for the risk of tendering for temporary staff.
- Concerning clear indication of the details of a concrete plan for literature curation.
  - We will define our plan, and will commence discussions with each resource development division concerning the division of roles, etc.

3. Internal and external collaboration and also international collaboration

- Concerning, given the need to centralize information in the BRC, the recommendation to proceed in this area under the leadership of the Center's Director.
  - We will proceed on the basis of top-down decision-making, under the leadership of the Director.
- Concerning the need for cooperative activities within RIKEN and external to the organization, and for internationalization of activities.
  - We will promote cooperative activities within RIKEN and external to the organization, in addition to internationalization of our activities.

4. Others

- Concerning the recommendation to bolster the Division's awareness of itself as a "social system."
  - We will attempt to proceed with our operations in future with a greater awareness of our Division as a "social system."
- Concerning the recommendation to conduct a thorough review in order to determine whether there are any deficiencies in plans for system replacement.
  - We will identify any deficiencies in our plans when we introduced new systems, and make use of the improved plans in our future system replacement operations.

RIKEN BioResource Center Review Committee of
Bioresource Engineering Division
Review Sheet
(December 16, 2010)

Committee Members: Drs. Toshihiko Shiroishi (Chairperson), Fumitoshi Ishino, Masaru Okabe, Hiroaki Yamamoto, Keiji Wada

Summary

1. Does the Bioresource Engineering Division have achievements of major scientific significance and/or social impact?

- **Conclusion**

  This Division has made great contribution, as all research technological developments are well in progress.

1) Achievements of major scientific significance.

Individual Comments

- High-quality achievements, such as the paper on Xist published in Science, were obtained.
- The Division made contribution to the progress of science by facilitating its achievement to many researchers.
- All four target projects are scientifically at the most advanced level. This Division is essential for establishment of the infrastructure of the RIKEN BRC.
- In three research levels, which is categorized into A, B and C, multiple research projects were advanced. The Division as a whole has made noteworthy progress compared to that reported in the review committee two year ago. There has been also great progress in the reproductive engineering technology for embryo cryopreservation of wild-derived mouse strains, which are unique resources to the RIKEN BRC.
- There has been progress in research fields of cryopreservation, microinsemination, nuclear transfer cloning, and establishment of novel stem cells. In particular, identification of a gene responsible for genomic reprogramming by nuclear transfer may have a far-reaching effect to all fields of biology.
- Transportation of vitrified embryos with dry ice is extremely important in the field of bioresource. It is also highly evaluated that the feasibility of this

technique has been assessed by international collaborations.

2) Achievements of major social impact.

Individual Comments

- Every scientific achievements in the four projects have reached to the level at which achievement can be applied to many fields of science and also return the fruits to the society. More aggressive public relation activities of these achievements by a PR section of BRC are recommended.
- Technical training courses have been given constantly. The Division is recommended to make a clear strategy for future training courses, including scaling-up of the present courses.
- The Division has a clear vision that the research results will be extended to the human studies. Active public relation activities emphasizing this vision are recommended.
- It would be important for this Division to describe clearly what the outcomes of this Division are.
- As for rabbit iPS cell production project, the significance of this research should be shown clearly.

2. Does the Bioresource Engineering Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Review Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  With many achievements made by this Division, it was evaluated that the PDCA cycle is functioning well.

Individual Comments

- Development of technologies are made stepwise in the order of feasibility; exploratory research → improvement → practical use. Development of a method that is also applicable to wild-derived animals is a significant progress and highly evaluated.
- Significance of the researches aimed at technological development of reproductive technology of mammals other than mice needs further explanation.
- The five-year objects and the road map based on the mid-term plan were ambiguous in the presentation. Therefore, it was difficult to judge whether the

PDCA is functioning. However, measures to individual issues are taken properly.

B. Strategy and implementation plan in the two remaining years remaining in the current mid-term plan.

- **Conclusion**

  Many projects showed progress. It is expected that the number of projects that are developed to the practical use level will increase.

Individual Comments

- Important projects of practical level (the rabbit project, production of chimera animals from iPS cells) and a scientifically epoch-making project (identification of genomic plasticity gene of 129 mouse strain) have been planned. The impact will be enormous, if either project is accomplished successfully. In particular, the latter project will revolutionize somatic cell cloning technology and trigger international development of regenerative and reproductive medicines.
- Although it may be difficult, interesting new projects (level C) are planned including a project for identification of the genetic factor determining the genome plasticity of 129 mouse strains. The study may give a significant impact on the regenerative medicine in the future and is urged to be carried out. Other projects are also well thought through.
- These projects are recommended to be carried out, after the expected outcomes of these projects are clearly set.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

Individual Comments

- The Division is already at the most advanced level in the world, and has conducted international collaboration continuously. However, international collaboration dose not seem to be of the highest activity, probably because the Division has already established a leading position internationally in the relevant field.
- The plans of the Division should be in accordance with the direction of the

governmental policy concerning iPS and others. At the same time, the Division should play a leading role in the field.

- The Division has already established a leading position in the world. With this advantage, a strategy should be made more clearly and active public relation is recommended.

4. Others

Individual Comments

- Excellent progress is accomplished, and these studies are wonderful. Future progress is very hopeful.
- Very high quality achievements were obtained as research seeds. A business plans including technology transfer and advertisement should be strengthened.
- The Division is considered to become one of the cores of the RIKEN BRC. Its originality, uniqueness and superiority should be emphasized.
- The Division is definitely one of the world's top runners in the field of reproductive engineering research. The Division is expected to make a large contribution to the field continuously.
- In the cell differentiation research using iPS cell, research subjects that only this Division can approach, such as an "organ" construction retaining its higher functional structure, should be challenged.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Gene Engineering Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Bioresource Engineering Division have achievements of major scientific significance and/or social impact?

- Concerning publicity regarding scientific outcomes and the scale-up of the Division's technical training courses.
  - Due to the physical limitations of the laboratory, we are only able to accept three to four individuals for each training session. So we will increase the number of sessions to respond to the number of applications. Training does not simply involve technology transfer, but can also be expected to have an effect

in increasing awareness of the BRC's high technological capability. We will also make training sessions available in a visual form. As one example of this direction, we submitted a movie file on embryo freezing and thawing technologies to the *Journal of Visualized Experiments* (Pubmed), the most widely subscribed video journal. It will be published as an open access paper soon...

- Concerning applications of outcomes to humans, especially the significance of the rabbit iPS project.
  - The characteristics of the cardiovascular, metabolic, reproductive and other systems of rabbits are similar to those of humans, and rabbits are therefore superior to mice in some iPS cell researches for human regenerative medicine. We will attempt to make the public more aware of the significance of research using rabbits by public lectures, our website, the mass media, scientific papers and conference presentations. For example, our article was introduced by several newspapers as "iPS cells produced from a rabbit: The leap towards clinical applications."

2. Does the Bioresource Engineering Division have a functioning Plan-Do-Check-Action (PDCA) cycle?

- Concerning explanation of the significance of the development of reproductive engineering technologies for animals other than mice.
  - For rabbits, we will publicize its significance for the study of reproductive engineering technologies, as indicated above in "Concerning the foregrounding of application of outcomes to humans….".
- Concerning the identification of genetic factors in the genome plasticity of the 129 strain.
  - We are determining RI strains which have the 129-type phenotype by nuclear transfer experiments and will move to the identification of genetic factors in the genome plasticity of the 129 strain. We received a five-year research grant from the government for this project.
- Concerning the clarification of outcome setting.
  - Having responsibility for the BRC's technological underpinnings, we will work towards more efficient mouse strain preservation. With regard to outcome setting, while basically maintaining the status quo, we will modify it according the research trend and related technological development.

3. Internal and external collaboration and also international collaboration

- Concerning the promotion of international collaboration
  - We will actively promote international collaborations for a higher-level technological development. We are now collaborating with more than ten laboratories in Europe, the U.S. and China. For example, we shipped vitrified embryos packed in dry ice to Dr. Kent Lloyd of UC Davis in the U.S and to Dr. Martin Fray of MRC in the U.K. All or most embryos survived after thawing and offspring were obtained from all recipient females. Other international collaborations with the U.S., Netherlands, and the Czech Republic resulted in publications in the journals *Science* and *Stem Cells*.

4. Others

- Concerning the enhancement of the business plan, including public relations
  - We will proceed with this in cooperation with the Planning Section of the Research Promotion Division and the sections in charge of intellectual property. In particular, we would like to make progress in the areas of patents and sales of reagent kits. We are proceeding with consultations with the Technology Transfer Office concerning two patents.
- Concerning research topics that are very difficult in general, such as organogenesis using iPS cells.
  - With regard to organogenesis using iPS cells, we are preparing experiments that combine more undifferentiated (naïve) pluripotent stem cells and interspecies chimeras. If the initial experiments succeed, we would like to proceed with the creation of chimeras with organ-hypoplastic animals.

RIKEN BioResource Center Review Committee of
Technology and Development Team for Mammalian Cellular Dynamics
Review Sheet
(December 16, 2010)

Committee Members: Drs. Toshihiko Shiroishi (Chairperson), Fumitoshi Ishino, Masaru Okabe, Hiroaki Yamamoto, Keiji Wada

Summary

1. Does the Technology and Development Team for Mammalian Cellular Dynamics have achievements of major scientific significance and/or social impact?

- **Conclusion**

  Valuable achievements by the effective strategy which combines three major studies of genotyping, phenotyping and epigenotyping with imaging are highly evaluated.

  The results of the studies should be reflected in research papers. The lack of attached achievements lists made it a little difficult to evaluate properly.

1) Achievements of major scientific significance.

Individual Comments

- The impacts of the achievements described above are potentially very significant, because they constitute the basis for understanding of biology and can be applied to elucidation of all biological phenomena. The Team has accumulated important basic data and has become one of the most important teams in the RIKEN BRC.
- Research and development are very actively carried out, as the Team has focused on three major subjects, (1) genotyping, (2) phenotyping and (3) epigenotyping. Especially in the case of the subject (1), the BAC genomic library of C57BL/6N strain will contribute in the future to the KO Project, such as IKMC which uses ES cells derived from this strain. It is important to use BAC clones with a genetic background completely identical with the ES cell to improve the efficiency of producing knockout mice, and for that reason, the library is considered to have a very large impact. In addition, in the case of the epigenomic study, remarkable progress was observed in development of an analytical system for a trace amount of samples. It is, in general, not easy to

allocate limited resources and researchers properly and effectively to various research projects. We hope this team will make achievement by paying attention to this point.

2) Achievements of major social impact.

Individual Comments

- The studies by the Team are important conducting a research and development associated with the bioresource infrastructure. This kind of technology development activities should be carried out in parallel with the resource business, and its significance is large. In particular, visualization of biological phenomena, which was hitherto impossible, is considered to have a significant social impact.
- Quality control of experimental mouse strains by using the research achievements described above is important as social contribution.

2. Does the Technology and Development Team for Mammalian Cellular Dynamics have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Review Committee and also by internal self-inspection and evaluation.

- **Conclusion**

We give a high evaluation to the fact that PDCA cycle is functioning well: new research targets, such as methylation of a trace amount of DNA, production of B6N mouse BAC clones and their sequencing, were established favorably and are in progress stepwise.

Individual Comments

- External collaboration was demanded to the Team. It is favorably evaluated that analysis of methylation, which is the mechanism for epigenetic gene control that is attracting attention recently, is conducted independently as well as in collaboration.
- With regard to the development for imaging technology, collaboration with other centers in RIKEN (Wako, etc.) is in progress.
- There are many seeds, but some of them are still unpublished, which seem to be preliminary as the responses to the comments made by each committee. It seems PDCA cycle might still not be functioning well in such cases.

B. Strategy and implementation plan in the two remaining years remaining in the current mid-term plan.

- **Conclusion**

  It is expected that newly developed technologies will be spread to general users.

Individual Comments

- Approaches with focused directions are expected. Possibility of external collaborations, including cooperation with private companies, should be considered.
- Imaging of the fluctuation of gene expression in a cell population is an important finding that may lead to the development of an evaluation method of stem cells in the future.
- The Team is developing promising, core technologies that can contribute to many scientific fields. Development of phenotyping and epigenotyping technologies at the individual cell level is encouraged.
- The Team is shifting analyses using microarray technology to the one with next-generation sequencer (SOLiD4) for genotyping and epigenotyping. We hope research throughput will improve greatly by this shift in the future.

3. Internal and external collaboration and also international collaboration of the laboratories and teams of RIKEN BioResource Center (activities and achievements of special mention, if available)

Individual Comments

- A strategy for wide-spread use of the B6N mouse BAC library is necessary in the future and its advancement is expected.
- Although establishment of the BAC library may not be a result of direct collaboration with other organizations, it would give rise to collaborations with many researchers in much wider fields. In that sense, it is highly favorably evaluated.
- Collaboration with organizations inside and outside RIKEN is favorably in progress. Development of the imaging technology is highly evaluated.
- Although domestic collaboration is in progress, international collaboration remains an issue in the future. As for the imaging technology, the technology should be applied not only to the mouse-related research but also other fields including plant biology.

4. Others

Individual Comments

- The level of the achievements by this team is considered high as basic research. The Team should present how their achievements contribute to the activity of the RIKEN BRC, which is confronting external evaluations, for example, such as the program review by the government. It is preferable to differentiate the research themes by making clear what universities can and cannot do.
- We hope new innovative findings emerge out of the accumulated important basic data.
- Imaging is a factor readily recognizable by people outside. Therefore further effort should be made for public relations activities utilizing the imaging technology.
- As for the imaging technology, it may possibly lead to the improvement of mouse phenotype analysis technology in the entire BRC, if the study is carried out in collaboration with Technology and Development Team for Mouse Phenotype Analysis.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Technology and Development Team for Mammalian Cellular Dynamics will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Technology and Development Team for Mammalian Cellular Dynamics have achievements of major scientific significance and/or social impact?

- Concerning the Committee's recommendation to reflect outcomes in papers, etc., and its indication that the lack of an explanation in the attached list made the situation difficult to understand.
  - In the three-year period since the previous review conducted by the Committee, we have published 24 original papers in English (peer-reviewed). In addition, among other efforts, we have also published six review papers (five in Japanese and one in English), and offered conference presentations (54 domestically and 19 internationally). Some of the content that was presented to the Committee

during the present review has already been published, and we have two papers that are presently being submitted and four that are in the process of formulation; we intend to strive as hard as we can for publication in future.

- Concerning the Committee's indication that it is not an easy matter to decide how to allocate effort towards varied research topics, including the deployment of limited human resources, and its recommendation to consider this point and produce outcomes.
  - With respect to how to allocate effort with limited human resources, the Committee has proposed that we direct attention to setting priorities. It cannot be denied that our human resources have diminished in comparison to the situation at the previous Committee review, due to the departure of researchers and technical personnel, among other factors. Given this, in future we will work to conduct our operations with consideration of the order of priority based on the level of progress of the research, etc. Also, in addition to securing competent human resources, we will continue to develop the skills of the personnel who presently make up our teams (for example, by fostering personnel able to perform both wet experiments and dry analyses).

2. Does the Technology and Development Team for Mammalian Cellular Dynamics have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Concerning the status of responses to items indicated as requiring attention in the previous reviews conducted by the BRAC and the Committee, and the Center internal self-inspection and evaluation.

- The seeds are there, but there are still cases in which outcomes have not been published in response to comments made by the members of the Committee. Concerning the suggestion that a PDCA cycle to ensure development might still not be functioning adequately in such cases.
  - The Committee has indicated that the PDCA cycle is functioning effectively overall. The previous Committee review was conducted about two years ago, and in that period we have produced outcomes that have not been published. As indicated in 1. above, we will make further efforts to publish these outcomes as papers. In addition to the publication of papers, we will also work to make outcomes, technological protocols, etc. available via our website and other media.

B. Concerning guidelines and action plans for the remaining two years of the current mid-term plan.

- Concerning efforts to focus the Team's orientation and consideration of the

potential for cooperation with external entities, including private companies.

- As indicated above, we will allocate our efforts and focus our orientation with consideration of factors including the importance and feasibility of the project.
- We are required to make newly developed technologies generally available. First, we will enhance our cooperation within the BRC. To date, we have concentrated on animals (mice), but in future we will also conduct joint research and technology transfers in the areas of cell resources and also plants. For the remaining two years of the Midterm Plan, we will work on actualizing quality control by means of profiling gene expression and DNA methylation in mouse and human ES and iPS cells and other cells using next-generation sequencing.
- With regard to cooperation with external entities, we have been involved up to the present in active cooperation with universities and other research institutions, and we will continue these activities. We are involved in joint research with Olympus in the area of *in vivo* imaging, and we intend to be involved in the development of new *in vivo* imaging lenses, etc. We have also provided DNA preparation technologies for the production of BAC transgenic mice to research institutions including universities and to a private company that produces BAC transgenic mice and rats (PhoenixBio Co., Ltd.), and an outcome has been published as a result (Tomida et al., Nature Genet. 41, 688-695, 2009 : http://www.phoenixbio.co.jp).

3. **Internal and external collaboration and also international collaboration**

- Concerning the Committee's indication that progress is being made in domestic collaborations, but international collaborations are an issue for the future.
  - With regard to the diffusion of the C57BL/6N BAC library, in addition to conducting publicity programs, we are considering a strategy for its supply in a form that can be used by a greater number of users, in a package comprising the gene library, genome data, ES cells, mouse strains, genotyping technologies, etc, as a combined effort of the entire BRC. We will conduct model research for this purpose. Regarding domestic cooperation, we will continue as we have to date with cooperative projects within the BRC and outside the organization. In the area of international cooperation, we have engaged in projects up to the present (producing four coauthored papers), and in future will push ahead with further joint research utilizing newly developed technologies and resources. Specifically, we are planning collaborations in the areas of stem cell characterization analyses of human embryonic germ (EG) cells (with the

Faculty of Medicine of Leiden University in the Netherlands), and the creation of a BAC library and genome analysis of wild-derived mouse strains (with the Massachusetts Institute of Technology and University of Texas at Austin in the U.S.).

4. Others

- Concerning the contribution that can be made by the Team to issues with which the BRC is struggling, for example the budget screening process, and distinguishing what cannot be done at universities and other institutions.
  - The Team's mission is to develop new modes of use of bioresources using new technologies and to append information concerning the characteristics of the resources. We are also engaged in the development of new resources with other divisions of the BRC, seeking by this means to contribute to the Center's operations. As indicated by the Committee, physical proximity to divisions involved in resource operations is a factor of great significance in the ability to undertake organic cooperation programs.
- Concerning more intensive public relations in the area of imaging, given that it is easy to understand for people outside the field.

Because it is difficult to get across the results of live imaging by means of still images, we will consider the use of website and media that mainly use moving images (e.g., Journal of Visualized Experiments).

RIKEN BioResource Center Review Committee of
Subteam for BioSignal Integration
Review Sheet
(January 21, 2011)

Committee Members: Drs. Ryo Kominami (Chairperson), Atsushi Aiba, Minoru Kimura, Naohiro Hashimoto, Satoru Takahashi

Summary

1. Does the Subteam for BioSignal Integration have achievements of major scientific significance and/or social impact?

- **Conclusion**

  More meticulous plan should be made, although it was good for the Subteam that some achievements were made, as there was some abnormality in bone metabolism. However, there were achievements with some spreading effect. That was a significant achievement for a small group.

  Individual Comments

  - It is highly evaluated that there are some scientifically significant findings obtained and excellent results made in collaborating with research groups are published. However if the emphasis is placed on the research achievements as the team, achievements at higher level, for example publications at higher level, are desired.
  - It is important to demonstrate the achievements by publishing the analytical results of NF-KB family KO mice as a research paper after peer review. As for provision of these mice, the number of mice provided was apparently very large in the presentation made by the team, but the exact nature of the collaborating with research groups is not clear. Publication of the results is desired.
  - Identification of the relA-KO mouse as a variant mouse of possible osteoporosis model is interesting. However, the potential of the mouse for use as a human model is still unknown. There was no distinct achievement in the last 2 years.

2. Does the Subteam for BioSignal Integration have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Review Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  Measures taken to the items cited in BRAC, review committee and self inspection and evaluation in the Center were explained and considered to be taken appropriately. However, it is still ambiguous whether the explained measures were taken effectively.

  Individual Comments

  - Collaboration with other teams and other research organizations, which was pointed out in the previous review committee, is considered to be promoted adequately. The PDCA cycle seems to be functioning well.
  - Although there were certain achievements accomplished, further efforts to initial analysis of phenotype and further characteristic analysis in combination with various KO mice are desired.

B. Strategy and implementation plan in the two remaining years remaining in the current mid-term plan.

- **Conclusion**

  The strategy seems to be identical with that proposed in the previous meeting. Achievement of all 3 missions will be difficult. Some focusing is needed. The current position of the team is desirably re-examined.

  Individual Comments

  - Significant research results are seemingly being obtained recently. Intensified collaboration with other organizations is desired. Efforts should be directed primarily to publication of the findings obtained in the past.
  - Efforts should be made to publish scientifically valuable results as a responsible author.
  - More specific milestones are to be determined.
  - The impression is that the plans are slightly ambiguous.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, if available)

Individual Comments

- The numbers of mice provided both domestically or abroad increased

drastically, indicating promotion of collaboration. In particular, the efforts for expanded use of resources, which resulted in fruitful achievement, are highly evaluated. Collaborative studies within Riken, particularly with the Research Center for Allergy and Immunology, should be promoted in the future.

- NF-KB family KO mice are provided aggressively. The fact can be estimated from the increase in the number of publications made in collaborating with research groups.
- There was no explanation on collaboration with other departments and teams. There were provided only requests to mouse-providing departments.

4. Others

Individual Comments

- Efforts to contribute to maintenance of resources are expected.
- They are very characteristic and interesting as resources.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Subteam for Biosignal Integration will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1 Does the Subteam for BioSignal Integration have achievements of major scientific significance and/or social impact?

- Concerning the indication that if the Subteam for Biosignal Integration places a greater emphasis on research outcomes, it would be desirable to produce superior results, such as high-level research papers, etc.
  - With regard to research outcomes, we will work to express results rapidly in the form of papers. In doing so, we will attempt to submit the highest-level papers we are capable of, and to have these papers accepted.
- Concerning the direction for joint research.
  - Consulting closely with our research partners, we will proceed with cooperation in presently active projects and will work towards rapid publication of research papers.
- How far the mice will be developed as human models remains an unknown. Concerning the failure to obtain clear outcomes in the past two years.

- As indicated, use of the mice as human disease model mice as is difficult at present. However, the mice have proved extremely useful in basic research for the elucidation of the mechanism of bone metabolism, and given this we will make efforts to rapidly publish papers presenting this evidence and engage in publicity activities to promote the widespread use of these resources in the field of bone metabolism research.

2. Does the Subteam for BioSignal Integration have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Concerning the status of responses to items indicated as requiring attention in the previous reviews conducted by the BRAC and the Committee, and the Center internal self-inspection and evaluation.

- Concerning the need to make efforts towards the initial analysis of the phenotype, and to proceed with further analysis of characteristics using combinations of various types of KO mice.
  - We are already crossing KO mice to create mice deficient in multiple genes, and are presently proceeding with analyses.

C. Concerning guidelines and action plans for the remaining two years of the current mid-term plan.

- Concerning the recommendation to work with the publication of papers on the basis of findings obtained up to the present as the main goal.
  - We will attempt to publish results obtained up to the present in the form of papers with staff members as the corresponding author as rapidly as possible.
- Concerning the setting of clear milestones and planning.
  - Because our fields of research cover such a broad range, in addition to conducting detailed reviews with specialists in each field (who are involved in joint research), we will set clear milestones and formulate more effective plans. By this means, we will clarify the positions of our research teams in each field of research.

3. Internal and external collaboration and also international collaboration

- Concerning future cooperative research with other divisions and teams in the BRC, in particular cooperative research with the Research Center for Allergy and Immunology, etc.
  - We are presently conducting cooperative research with the Research Center for Allergy and Immunology. However, in accordance with the Committee's recommendation, in future we will attempt to pursue research involving closer cooperation.

4. **Other**

No specific comments.

RIKEN BioResource Center Review Committee of
Subteam for Manipulation of Cell Fate
Review Sheet
(January 21, 2011)

Committee Members: Drs. Ryo Kominami (Chairperson), Atsushi Aiba, Minoru Kimura, Naohiro Hashimoto, Satoru Takahashi

Summary

1. Does the Subteam for Manipulation of Cell Fate have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The Subteam has been conducting researches at high technical level and has an excellent potential, and also has made many achievements. Altogether the Subteam is highly evaluated.

  Individual Comments

  - The research and development of lentiviral vectors is particularly highly evaluated.
  - Sufficient achievements have also been made on *ex vivo* expansion of hematopoietic stem cells and production of iPS cells.
  - There have been significant achievements despite of the small size of the Subteam.
  - Many achievements have been made by collaborating with research groups. Efforts to produce achievements as a corresponding author are recommended.

2. Does the Subteam for Manipulation of Cell Fate have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Review Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  It was difficult to judge whether or not proper measures have been taken to the issues raised in BRAC, review committee, and self-inspection and evaluation in the RIKEN BRC.

  Individual Comments

  - To respond to raised issues, efforts have been made to accomplish new

objectives.

- Although there are some measures that are not completely appropriate to the issues raised in the previous review committee, excellent results are made. Thus, studies in the direction along the wish of the researcher may be permitted.
- The Subteam has been contributing to establishment of iPS cells. On the other hand, the purpose of iPS cell study was standardization of iPS cells when the study started. There is "difference" between internal and external viewpoints on the position of the iPS study. The measures taken by this team is somewhat "puzzling". More intensive discussion will be needed within the RIKEN BRC.
- Expectation on lentiviral vectors is different from that in the RIKEN BRC.
- There has not been much progress in hematopoietic stem cell study.

B. Strategy and implementation plan in the two remaining years in the current mid-term plan.

- **Conclusion**

An aggressive plan is proposed. Priorities should be given before execution, considering the size of the Subteam.

Individual Comments

- A revision of the research plan will be often needed in the future.
- A study on cell aging by using iPS cells is planned, but it is doubtful whether there is any advantage for Dr. Miyoshi in this study. The study on hematopoietic stem cell, which Dr. Miyoshi has produced many achievements, should be promoted.
- The study on iPS cells conducted until now does not seem to be the main task of Dr. Miyoshi's work. Contribution to iPS cell study should be re-examined within RIKEN. Studies using cord blood should be considered.
- The direction of research is strongly influenced by Dr. Miyoshi's own interests.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

Individual Comments

- The Subteam has been doing well, considering the size of the team.
- Collaboration through supply of lentiviral vectors has resulted in very large achievements, which is highly evaluated.
- Collaboration at least with some of the Divisions and Teams is carried out

smoothly.

- International collaboration should be promoted, if the Subteam has the bandwidth.
- Collaboration work on imaging study has been well conducted within RIKEN. However, more communication is needed in the hematopoietic stem cell research field.

4. Others

Individual Comments

- Reduction of the number of R&D projects is recommended, because the size of this Subteam is small. More strategic research plan is recommended.
- A new horizon may be opened, if lentiviral vectors can be used for production of TG mice or mouse models for human disease.
- Collaboration on development of lentiviral vectors is requested to be continued.

Responses and Actions by the Subteam to the Evaluation and Comments

For issues that received positive evaluations, the Subteam for Manipulation of Cell Fate will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Subteam for Manipulation of Cell Fate have achievements of major scientific significance and/or social impact?

- On the comment that, while the Subteam for Manipulation of Cell Fate is achieving significant outcomes in collaborative research, it would be desirable for it to make efforts to have team members publish as corresponding author(s).
  - Given the small size of the team, our ratio of publication on the basis of collaborative research is high. However, to date we have always published one or two papers per year with a team member as corresponding author. In future, we will work to reduce our ratio of collaborative research and enhance our own team research, aiming to publish three to four papers per year with team members as corresponding author(s).

2. Does the Subteam for Manipulation of Cell Fate have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Concerning the status of responses to items indicated as requiring attention in the previous reviews conducted by the BRAC and the Committee, and the Center internal self-inspection and evaluation.

- While the Subteam for Manipulation of Cell Fate is contributing to the generation of iPS cells, it was expected that standardization would be achieved in the area of iPS cells; there are differences in perspective on the iPS cell research between the Center and other entities, and the Committee feels that there was some confusion in the Subteam's response. Concerning the need for a deepening of discussion of iPS issues within the BRC.
  - With regard to standardization in the area of iPS cells, studies are necessary at a variety of levels, including methods for generating iPS cells, generation efficiency, safety, stability, and differentiation capacity, and it is still at an early stage globally. Depending on future trends, we will discuss matters with the Cell Engineering Division of the BRC, and if there is any way that the Subteam for Manipulation of Cell Fate can contribute, we will do so.
- On the comment that expectations in relation to lentiviral vectors emerging from the review process differed from those held within the BRC.
  - The previous reviews by the BRAC and the Committee evaluated lentiviral vectors as a highly international and original resource that suited the orientation of the BRC's operations and positioned this area as possessing a high order of priority, and we continued in their development. However, the Center internal self-inspection and evaluation indicated that we should not respond to user demands but rather narrow our scope and contribute to resource activities other than lentiviral vectors. In the future, we will discuss this issue with the BRC Gene Engineering Division, and if we can secure their cooperation, we will try to avoid as much as possible any involvement in new collaborative research or development projects, and will leave development in response to user demands to the Gene Engineering Division.
- On the comment that there has been little progress in hematopoietic stem cell research.
  - We are accumulating basic data towards ex vivo expansion of hematopoietic stem cells and publishing papers on this basis; in Section 1, the Committee evaluated us as having obtained adequate results in this area. In the future, using reprogramming technologies to explicate the mechanism of aging of hematopoietic stem cells, we will work towards the development of technologies for ex vivo expansion of hematopoietic stem cells while controlling their aging, which currently represents a significant challenge.

B. Concerning guidelines and action plans for the remaining two years of the current mid-term plan.

- On the recommendation to correct the orientation of the Subteam for Manipulation of Cell Fate in future.
  - We will correct the orientation of our research and development while constantly incorporating new data and techniques generated by the development of the field of iPS cell research.
- On the comment that cell aging research using generation of iPS cells is planned, but there is some question as to its merit for Dr. Miyoshi. On the recommendation that hematopoietic stem cell research should be advanced, given the progress that has been made in the field.
  - In our cell aging research using senescent fibroblasts that have ceased dividing, we can take advantage of lentiviral vector technology capable of transferring genes into nondividing cells. In addition, the results obtained thus far by the Subteam in research on hematopoietic stem cells indicates that control of cell aging will be important in the development of technologies for ex vivo expansion of hematopoietic stem cells, and as indicated in Section 2.A above, we seek to make progress in clarifying the aging mechanism of hematopoietic stem cells using reprogramming technologies.
- On the comment that the Committee feels that iPS work up to the present has been a sidetrack, and indicates that it will be necessary for the Subteam to further organize its contribution to iPS cells within the BRC and also to consider conducting research using umbilical cord blood.
  - Globally, iPS cell research has only just begun, and there are numerous basic technologies that must be developed. Among these, the development of safe and efficient lentiviral vectors for generating iPS cells represented a basic technology for which there was a significant need. The developed lentiviral vectors have contributed to the generation of human and rabbit iPS cells in the Cell Engineering Division and the Bioresources Engineering Division, and have also been provided to numerous laboratories both within and external to RIKEN. In the future, we will seek to hold discussions within the BRC and conduct projects for the development of technologies essential to iPS cell research. Research using umbilical cord blood is being conducted by the Cell Engineering Division, and we are already collaborating with them in the area of lentiviral vector technologies. Further collaborations would be extremely difficult for us, given the size of the Subteam.
- On the comment that the Subteam has a research project strongly influenced by a

personal interest.

- We believe that interest in and motivation towards individual research is extremely important in all research and development efforts. However, to ensure that we don't become complacent, we will attempt to pursue our research and development initiatives with a focus on trends and the status of progress in the relevant research field, and while accepting opinions from both within and outside the BRC.

3. Internal and external collaboration and also international collaboration

- On the recommendation to promote international cooperation.
  - Given the size of the team, we do not possess any reserve capacity, and it would be difficult for us to extend our scope to international cooperation. However, if the demand exists, we will respond to it within our limits.
- On the recommendation that, while cooperation in imaging of pluripotent stem cells is well provided for within the BRC, more communication is needed in the field of hematopoietic stem cells.
  - We are participating in collaborative research with RIKEN RCAI (research conducted by Dr. Fumihiko Ishikawa) and Chiba University (research conducted by Professor Atsushi Iwama) in the field of hematopoietic stem cells, and in the future we will actively participate in conferences, etc. in order to gather information.

4. Others

- On the comment that, given that the size of the team is small, it would be better to restrict the scope of research and development topics. On the recommendation to formulate more strategic research plans.
  - For the immediate future, we will do the minimum necessary research towards the development of lentiviral vectors, and will focus on research on cell aging using reprogramming technologies and research on hematopoietic stem cells. We have already formulated detailed research plans, but will respond flexibly in light of any findings during their implementation.
- On the comment that new opportunities will open up if lentiviral vectors are able to be used in the production of TG mice and human disease models.
  - As indicated in 2.A above, rather than developing lentiviral vectors to meet user demands, we have been required to restrict our scope and to contribute in the area of resources other than lentiviral vectors, in particular cell resources. We

will focus on the development of iPS cell technologies in collaboration with the Cell Engineering Division.

- On the comment concerning future cooperation in lentiviral developments.
  - As indicated in 2.A above, if we are able to obtain the cooperation of the Gene Engineering Division, we will pursue the absolute minimum necessary development, and will rely on the Gene Engineering Division for development in response to user demands.

RIKEN BioResource Center Review Committee of
Technology and Development Team for Mouse Phenotype Analysis
Review Sheet
(December 16, 2010)

Committee Members: Drs Toshihiko Shiroishi (Chairperson), Toshifumi Ishino, Masaru Okabe, Hiroaki Yamamoto, Keiji Wada.

Summary

1. Does the Technology and Development Team for Mouse Phenotype Analysis have achievements of major scientific significance and/or social impact?

- **Conclusion**
  Achievements contributing to research community have been made.

1) Achievements of major scientific significance.

Individual Comments

- The existence of this Team is very important for the RIKEN BRC, because the next goal of genome science is to understand function of every gene and phenotype analysis of mutant mouse is critical for elucidating gene function. The feedback of information of the phenotype to human diseases is also important contribution to genome science. The Team has performed analysis at high scientific level, and it can be one of the scientific contributions of Japan. Accelerated disclosure of the phenotypes obtained so far will be effective in promoting functional genome science in Japan.
- Excellent achievements were made in establishment of a platform for the mouse clinic phenotype analysis and acquisition of the data of standard strains as well as on-demand mouse clinic data. In addition, the genotyping system to test the genetic background of the mouse strain before the phenotype analysis is highly evaluated.

2) Achievements of major social impact.

Individual Comments

- As a global trend in advancement from International Knockout Mouse Consortium (IKMC) to International Mouse Phenotyping Consortium (IMPC), phenotype analysis is becoming more important. The request for participation to IMPC proves successful achievements of this Team.

- It is the only one project of comprehensive mouse phenotyping in Japan, which makes it very important. With the international collaboration in progress, bright future is expected. In particular, IMPC would be important.

2. Does the Technology and Development Team for Mouse Phenotype Analysis have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Review Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  Although measures are steadily taken to the problems, as emerged in operation of mouse clinic, further effort is recommended.

  Individual Comments

  - It is meaningful to carry out the high level analysis of the mouse clinic, so the mouse clinic should be taken in the direction making useful of the results as described above. The service charge should be calculated carefully from the balance between the achievements and results, and discussion only toward reduction in charge is not welcomed.
  - Technologies for operation of mouse clinic, such as speed congenic and other necessary techniques have been established, and progress has been made as planned.
  - As for the operation concerning on-demand request from outside to mouse clinic, the service charge system has not established yet, although it was pointed out in the previous meeting. It is necessary to design the charging system as soon as possible.
  - Consistent efforts should be directed to solve difficult problems, particularly to financial problems.

B. Strategy and implementation plan in the two remaining years in the current mid-term plan.

- **Conclusion**

  As issues that require certain measures, such as participation in IMPC and financial problems including charging system, are obvious and further efforts are recommended.

  Individual Comments

  - Participation in the IMPC and execution of the plan with the initiative of the

Team are appropriate. It is necessary to make the charging system come in effect. The operation is worth receiving support of the government science budget in a sense that it is aimed at establishing scientific infrastructure. Efforts in this direction are also recommended. In addition, it is important to collect financial support from various domestic and foreign organizations.

- As for the necessity of the full-set clinic analysis, it is important to grasp the needs of research community. Conversion to the service charge system is essential.
- Participation in the IMPC is fully approved. For the necessary funding to join IMPC, further discussion is needed including conversion to charging system by on-demand operation of the mouse clinic. Cooperation with Masuya Unit would be a key to manage the obtained phenotype data integration.
- Development of comprehensive analysis considering environmental factors will be expected.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

Individual Comments

- Sufficient international collaboration, including participation in the IMPC as a membership is in progress. Make every effort to contribute to IMPC as a representative of Japan.
- Although there was a doubt whether standardization of phenotype analysis is possible or not, the problem will be overcome if the concept on ontology of the Masuya Unit is applied. Regardless of the number of analysis strains, make the RIKEN RBC more influential in IMPC by unique analysis.
- Description of phenotype is an essential step in biomedical science. Particularly long-term viewpoints are needed, and there are many problems in making the operation profitable. Public relation activities to be gain social recognition are needed more than ever.

4. Others

Individual Comments

- Conversion to service charge system is requisite. It is possible to determine the

date for disclosure of the data in advance. It is also possible to obtain permission to disclose data aggressively from customers who do not want to disclose the data.

- There are numerous problems that cannot be solved only by funding. Please make the best effort with a pride that the RIKEN RBC is a center generating very important intellectual property information.
- Possibility of starting the business may be examined, e.g., testing charging inspection, licensing out and others. Market survey concerning service is absolutely required. In addition, revise the contract-related practice.
- Intensified public relations activities are recommended.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Gene Engineering Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Technology and Development Team for Mouse Phenotype Analysis have achievements of major scientific significance and/or social impact?

- On the comment that the Team's existence is extremely important to the BRC, given that the basic purpose of genome science is to feed results back into the analysis of phenotypes and the study of human diseases.
  - We are very pleased that the Committee has recognized mouse phenotyping analysis as one of the achievements of scientific research on genome function. We will attempt to increase our awareness of the significance of the Team's existence. In future, we will work to conduct detailed phenotype analyses in response to the needs of the research community.
- On the comment for participation of the IMPC.
  - We will create a Mouse Clinic system that enhances international cooperation through our participation in the IMPC.

2. Does the Technology and Development Team for Mouse Phenotype Analysis have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Concerning the status of responses to items indicated as requiring attention in the

previous reviews conducted by the BRAC and the Committee, and Center internal self-inspection and evaluation.

- On the comment that the charging system for mouse phenotyping will be necessary.
  - The Japan Mouse Clinic receives a very large number of requests for on-demand tests from other institutions. Including inquiries, they amount to more than 100 per year. The creation of a charge system for Japan Mouse Clinic test costs was recommended by the Committee in the previous review, but system design has not yet been completed. We are at present calculating the costs of Japan Mouse Clinic tests for individual testing processes, and formulating proposals in relation to how to create a charge system. We are intending to set individual fees very soon for tests including adipocytokine tests, which necessitate the use of Japan Mouse Clinic supporting technologies, including the previously mentioned accelerated construction of congenic strains using reproductive technologies and the genetic background check system, and high-cost reagents. We seek to create a charge system that functions on the basis of individual tests rather than a generally applied system, and to stabilize the operation of the Japan Mouse Clinic.

B. Concerning guidelines and action plans for the remaining two years of the current mid-term plan.

- On the comment that the Committee's indications that as it advances project plans as a participant in the IMPC, and furthermore launches leading initiatives, the Japan Mouse Clinic's work in building scientific foundations merits the allocation of funds from the nation's science budget, and that the JMC should also seek funding from a variety of sources, both in Japan and overseas.
  - We believe that the Japan Mouse Clinic's formal participation in the IMPC is important for the nation's research community. In other words, we feel that the smooth provision of public resources to Japan and collection of phenotype data enabled by close cooperation with the international community will enhance the research foundations of the BRC. Taking that point sufficiently into consideration, and in consultation with BRC Director Yuichi Obata, we will make efforts to receive an allocation of the science budget in accordance with our operation as a participant in the IMPC.
- On the comment to the research program of mouse phenotyping including environmental factors.
  - The clarification of genetic and environmental factors, with a particular focus on the fetal stage, is a research topic that will respond to the bases of the Japan Mouse Clinic, and one which we believe accords with human health and social

issues.

3. Internal and external collaboration and also international collaboration

- On the comment that the Committee's indication that the Team is engaging sufficiently in international cooperation, for example as a formal member of the IMPC, and its recommendation to work without stint to ensure that Japan is able to contribute to the IMPC.
  - Our Team Leader, Shigeharu Wakana, participated in the IMPC/EUMODIC meeting held in Barcelona from February 28 to March 4, and discussed the mouse phenotype analysis platforms to be employed at the IMPC during the IMPC Phenotyping Work Group Meeting held during this meeting. In addition to the already accepted Standard Accepted Tests, Dr. Wakana also exchanged opinions proactively concerning Possible Additional Tests, Potential Tests for Consideration and Challenge and Neche Tests. We plan to implement a smooth response to the final IMPC platform that will be decided in June, rebuilding our phenotyping analysis system to enable us to participate in the international mouse phenotype analysis business. The Japan Mouse Clinic is playing a leading role in the mouse phenotype analysis business in Asia, and we intend to continue in these activities in future.
- On the comment that standardization of mouse phenotyping and the unique analysis.
  - We will enhance our cooperation with Dr. Masuya's unit in order to standardize phenotype data and promote international cooperation using phenotype ontological technology.

4. Others

- On the comment to the fee-based operation: The Team faces issues to which it will be difficult to respond within the budget. Operation as a business, including charging fees for tests and licensing out, should be considered. And the necessity for market surveys, advertising, etc. in line with this.
  - We will take initiatives in relation to the for-profit operation of the Japan Mouse Clinic as a top-priority issue in accord with our basic principles stated above. In addition, we would like to actively push ahead with the publication of data in consultation with the Experimental Animal Division, and create a base of high value-added open resources. We intend to proceed with effective publicity activities to ensure greater understanding of and support for the Japan Mouse Clinic.

RIKEN BioResource Center Review Committee of
Team for Advanced Development and Evaluation of Human Disease Models
Review Sheet
(January 21, 2011)

Committee Members: Drs. Ryo Kominami (Chairperson), Atsushi Aiba, Minoru Kimura, Naohiro Hashimoto, Satoru Takahashi

Summary

1. Does the Team for Advanced Development and Evaluation of Human Disease Models have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The achievements are highly evaluated.

  Many new human model mice such as hearing deficiency model mice, lifestyle related disease model mice and human carcinogenesis model mice were established, indicating the Team's high research activity in quantity and quality. On the other hand, there is no published paper. Thus the results above should be published as soon as possible. Presentation as published paper will accelerate collaborative studies effectively.

Individual Comments

- Research themes were focused well and the progress was significant. However, the achievements are less visible to the society. Early publication of the results is required.

2. Does the Team for Advanced Development and Evaluation of Human Disease Models have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Review Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  Measures to the issues raised in BRAC, review committee, self-inspection and evaluation in the RIKN BRC have been taken properly.

Individual Comments

- According to the suggestion, the numbers of the Team staffs and the research subjects are reduced to those suitable for the fund available.
- Effective use of past research results is recommended.
- Coordination within RIKEN seems to be rather insufficient.

B. Strategy and implementation plan in the two remaining years in the current mid-term plan.

- **Conclusion**

The proposed plans are appropriate. However, plans that can be accomplished within the period are preferable.

Individual Comments

- The priority should be given to publication of the past research results. After publication, it is important to make the relevant mice available to the community.
- The most important objective is to increase the value of human carcinogenesis models. This can be achieved easily to the certain extent, considering the capability of the leader.
- It is shown that the number of research subjects is significantly reduced.
- Although the circumstance may be very difficult, it is desirable that wider range studies are conducted by the support provided internally from RIKEN BRC.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

Individual Comments

- There is strong collaboration with certain Teams.
- The Team cooperates with the Mouse Clinic. However, this is some burden to the Team. The adjustment would be necessary within RIKEN BRC.
- There is strong collaboration with the Japanese Foundation for Cancer Research. However, there is an impression that it is not an effective collaboration because there are much unpublished data.

4. Others

Individual Comments

- Publication of research results is needed!
- Earlier disclosure is recommended.
- Human carcinogenesis model mice are promising.
- Establishment of human experimental systems by using mouse models would be important for analyses of human diseases.
- Adjustment with the Mouse Clinic is needed.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Gene Engineering Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. Does the Team for Advanced Development and Evaluation of Human Disease Models have achievements of major scientific significance and/or social impact?

- Concerning the Committee's indication that joint researches will be significantly advanced through the publication of papers, and that the rapid publication of papers is essential, given that achievements have not been communicated to society in general.
  - We are commencing preparations for the publication of 15 papers, comprising 13 papers describing the analyses of mouse mutant strains established in the ENU-mutagenesis project, and two papers discussing about methodologies in metabolome analyses. We plan to successively write up manuscripts for submission, and to complete submissions within fiscal 2011.

2. Does the Team for Advanced Development and Evaluation of Human Disease Models have a functioning Plan-Do-Check-Action (PDCA) cycle?

- Concerning the Committee's impression that the coordination within the BRC is somewhat inadequate.
  - In order to facilitate sufficiently smooth coordination within the BRC, we will ensure that researchers and technicians working in RIKEN and in the Cancer Institute (JFCR) can communicate more closely with relevant Team Leaders and

with me concerning the information and the intentions. We will make efforts to comprehend the details of the important meetings including the BRC Operating Committee and to implement the necessary responses. Furthermore, we will consider a major reconstruction of the system for cooperation with the Japan Mouse Clinic.

- Concerning the Committee's indication requiring the plans to be completed within the given time and their scopes.
  - Based on the recommendations of the 1st review conducted by the Review Committee, we restricted the scope of our plans to those able to be implemented in the following two years. In addition to rapidly compiling and publishing our research outcomes to date, and disclosing details of the mice, we will use these mice as human disease model for experiments currently being planned, results from which will be further outcomes of the next two years research.
- Concerning reporting of results and disclosing details of mice.
  - As described above, we will focus on the publication of papers, and will disclose details of the mice following publication.
- Concerning adding values to human carcinogenesis models.
  - We will implement our research plans in close cooperation with the Cancer Institute (JFCR).
- Concerning enhancing supports within the BRC.
  - In the process of using the disease model mice in experiments of metabolomics analyses and for adding values to these human carcinogenesis models as well as publishing our results, we would like to engage in broader cooperation with other teams in the BRC in the areas of mouse production management, data analysis, establishment of a database for the provision of the information on the mice. We will seek to use shared devices more effectively in order to actively utilize unique Cancer Institute devices and unique BRC devices. Since it is expected that much more human disease model mice will be used in future for metabolomics studies, we will therefore work cooperatively with the BRC Experimental Animal Division in this area. In addition, because metabolomics research is being conducted on plants in advance of animals, we will engage in discussions with researchers in the Experimental Plant Division with experience of metabolomic analysis and other available means with support from the divisions of BRC beyond the boundary of research areas. We will also give consideration to collaborations within the BRC and with other entities in fields of theoretical and structural biology.

3. Internal and external collaboration and also international collaboration

- Concerning the burden of collaboration with the Japan Mouse Clinic, and the necessity for coordination within the Center.
  - With regarding the Team's intended mission to be implemented as the highest priority, we will ensure the Team's capability and survey the status of our system of cooperation with the Japan Mouse Clinic for its overall restructuring.
- Concerning the Committee's indication that although the collaboration with the Cancer Institute (JFCR) has proceeded well, its performance does not show itself effective enough-because significant amounts of data remain unpublished.
  - We have made progress in our joint research with the Cancer Institute (JFCR), and we intend to publish two papers concerning carcinogenesis model within fiscal 2011. We believe that the content of these papers will clearly demonstrate the effectiveness of our collaboration.

4. Others

- Concerning the publication of papers.
  - We intend to submit 15 papers within fiscal 2011.
- Concerning the promotion of rapid disclosure of the details of model mice.
  - We intend to disclose the details successively following acceptance of the papers.
- Concerning the Committee's expectation for human carcinogenesis model mice.
  - We shall proceed with cooperative research with the Cancer Institute (JFCR).
- Concerning the Committee's belief that the establishment of a human experimental model system using mice is important for human disease analysis.
  - We intend to set up the model system, making use of the model mice we have developed up to the present.
- Concerning the Committee's belief that the rectification of the coordination with the Japan Mouse Clinic is necessary.
  - We intend to restructure the whole configuration of our cooperative relationship.

RIKEN BioResource Center Review Committee of
Mutagenesis and Genomics Team
Review Sheet
(January 21, 2011)

Committee Members: Drs. Ryo Kominami (Chairperson), Atsushi Aiba, Minoru Kimura, Naohiro Hashimoto, Satoru Takahashi

Summary

1. Does the Mutagenesis and Genomics Team have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The Team has succeeded in identifying a large number of mutations by analysis of whole genome exome with an ultra-throughput sequencer and thus made a significant achievement that has a large impact to the research community. It is highly evaluated.

  Individual Comments

  - Two hundreds and forty seven mutations identified with an ultra-throughput sequencer must be open to public soon.
  - A proposal that allows direct analysis without backcross is highly evaluated.
  - It is also highly evaluated that the Team has established a realistic system enable to identify genetic modifiers.

2. Does the Mutagenesis and Genomics Team have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the issues raised by the previous BRAC and Review Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  Measures to the issues raised by BRAC, the review committee and the internal self-inspection and evaluation are taken properly, and the PDCA cycle seems to be functioning well.

  Individual Comments

  - The measures were taken sufficiently enough, based on the fact that the Team has made the original efforts of the ENU mutagenesis project in Japan fruitful.

- The fact that the Team has made a considered-to-be unrealistic objective realistic is favorably evaluated.

B. Strategy and implementation plan in the two remaining years in the current mid-term plan.

- **Conclusion**

Adequate. Further progress is desired with particular attention paid to the following issues:

Individual Comments

- It is important to demonstrate the effectiveness of the mutant mouse identification system. Publication of the outcomes is needed for this.
- It is important to identify mutant mice corresponding to particular phenotypes, and the evaluation depend on the results. Screening of mutation should be continued and phenotype analysis for the remaining period should be considered.
- Acquisition of users and public relations are the most important issues.
- The research subjects are promising and the progress has been steadily made. In addition, the Team should appeal to the research community for importance of basic science.

3. Internal and external collaboration and also international collaboration (activities and achievements that are worth to be specially mentioned, only if available)

Individual Comments

- The efforts toward stronger collaboration with other Divisions and Teams in the BRC are favorably evaluated. In addition, the collaborative studies with the Kawaoka ERATO Project and Agilent are favorably evaluated.
- The proposal to use the system with ultra-throughput sequencer to the current users would be a good idea.
- Establishment of the system is a valuable achievement, and the value of its application should be proven by collaboration with outside the Center.

4. Others

- It is a strong system, thus it is recommended that the priority should be given. By proving the effectiveness of the system by analyzing a model case first, collaborative studies will be greatly promoted. It is a wonderful system and its effective use is recommended.

- This subject can contribute greatly to the mission of BRC.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Gene Engineering Division will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. **Does the Mutagenesis and Genomics Team have achievements of major scientific significance and/or social impact?**

- Concerning releasing of the list of discovered mutations.
  - Mutations originally discovered by RIKEN using a Next-generation Sequencer (NGS) are, as indicated, released immediately.
  - New issues in relation to releasing mutations: More off-target mutations, namely non-coding mutations, have been discovered than was expected, and there is not yet an international nomenclature for mutant alleles in non-coding sequences.
  - Response: At the present, we will temporally assign names and release details of mutant alleles using position data for the DNA sequence in the mm9 database for the C57BL/6J genome. As resequencing proceeds, the international consensus will be essential to resolve the issue, and we will seek to establish a nomenclature at the international Mouse Genetics Meeting to be held in June in Washington D.C., U.S.A.

2. **Does the Mutagenesis and Genomics Team have a functioning Plan-Do-Check-Action (PDCA) cycle?**

- Concerning the fact that providing indications of the system's effectiveness is important, and that the publication of papers is essential in this respect.
  - The Team is keenly preparing for the original papers. We have also published the following review papers, which have a high citation rate. Furthermore, we will put efforts on the publication of review papers as well:

    Y. Gondo (2008), Nature Reviews Genetics (Roles in relation to large-scale projects)

    Y. Gondo et al. (2009), BMB Report (Review of the development of the next-generation gene targeting system)

Y. Gondo et al. (2009), Progress in Brain Research (Review of model mice related to psychyatric disorders and mouse mutagenesis)

Y. Gondo (2010), Journal of Genetics and Genomics (Introduction of the roles by reviewing Human Genome Project and mouse models)

Y. Gondo et al. (2010), Experimental Animals (How to utilize RIKEN's mutant mouse library)

R. Fukumura and Y. Gondo (2010), Biological Functional Models and New Resources/Research Tools (Review of ENU mutagenesis and examples of its use)

These review articles have already been published.

- Papers published by external users who have utilized our systems demonstrate their efficacy to an even greater extent. We have proposed a new system incorporating our Next-generation Sequencer (which reduces the time period necessary for phenotype analysis about three years and at the same time detects gene-to-gene interactions), and five users have so far been using the system as a trial base.

- Identification of mice with mutations correlating with the phenotype is important, and the Committee believes that it could change the evaluation of the team's outcomes. Concerning the Committee's recommendation to use the time remaining under the present plan to conduct phenotype analysis in addition to extending mutation screening.
  - The phenotype analyses conducted by the Team already exceed our space and personnel capacities, and in fact we supplement our shortfalls using external facilities. In order to be more active in phenotype analysis, as per the Committee's recommendation, it would first be necessary to increase the space available for breeding mice where Team members are able to analyze the phenotype by our own hands day by day.
  - Expansion and speeding-up of phenotype analysis by users is proceeding smoothly. We have introduced a beneficiary-pays system to ensure that the Team will not bear any budgetary burden even with an increase in the number of users. In addition, in order to speed up our detection of mutations in target genes with limited Team's space and manpower, we have introduced a robot able to automatically load multiple plates. The combination of our Next-generation Sequencer and a phenotype analysis method that makes backcrossing unnecessary has reduced the time to start the analysis about three years, and can therefore be expected to reduce the time required for publication of papers.

- Concerning the Committee's indication that attracting users and engaging in publicity activities are important issues.
  - The present rate of increase in user numbers puts the Team at its very limit in terms of our laboratory space and personnel capacities; any further increase would destroy the balance and should actually have an adverse effect, by making users have to wait several years to obtain mutant mice. Better yet and more importantly, we already have requests from external users for more than 300 genes, and we have been providing about 100 strains of mutant mice; the promotion of the achievement of further outcomes and publications from these resources would have a greater effect of the publicity. It was for this purpose that we urgently developed and launched a new foundation for resource use that reduces the period to completion of phenotype analysis about three years and even makes it possible to identify factors producing gene-to-gene interaction.
  - While we have not demonstrated it to the Committee, we have also commenced development of a transcriptome analysis system using Next-generation Sequencer that makes it possible to conduct rapid phenotype analyses for multiple samples at one time. We also intend to call for users to use this system at the trial stage.
- Based on the facts that Team research topics offer hope and that progress is concrete, Concerning the Committee's recommendation to appeal to the importance of the basic science to society.
  - The publication of outcomes in academic papers, review articles and books, and the presentations at international conferences represent major personal goals for the Team Leader as well as each research scientist in the Team every fiscal year. As a demonstration that our outcomes are widely recognized, in the fiscal year of 2010, we were invited to give a presentation by three domestic and three international conferences. Our efforts have also borne fruit, and in the past two years three of our conference presentations have received awards (two internationally and one domestically).
  - We are also actively participating in the publicity to promote awareness among the general public concerning the importance of basic science. For example, we have actively participated in other BRC schemes when we have had the opportunity, such as the BRC's open campus events and visits by high school and university students, and also the BRC Summer School (for graduate students and young researchers), which is a new initiative from fiscal 2010. We have also set up more than ten "A0-size poster display boards" in areas such as hallways and corridors, enabling visitors to see the status of the Team's

activities including details of the latest research at any time.

- To date, the Team has provided research guidance to five undergraduate and graduate students, and in each case the student has received the degree based on the research conducted at the Team. One of our graduate students presented his research outcomes at an international conference. Outside the BRC, we also have been conducting visiting classes for junior and senior high school students, and we participate in seminars for the general public. Public lectures are also placed on RIKEN's YouTube channel, and can be viewed on the Internet anywhere in the world.
- We have offered public lectures for junior and senior high school biology teachers, and we have given lectures to specialists in fields directly related to ethical issues in the biological sciences e.g., a bar association and the Legal Training and Research Institute of Japan.
- We also actively issue press releases. In fiscal 2010, Team Leader and the three researchers in the Team oversaw eight contributions to a series of articles introducing the BRC published by a newspaper. We intend to continue to engage in these types of activities.

3. Internal and external collaboration and also international collaboration

- Concerning the Committee's recommendation to engage in more collaboration outside the BRC in order to demonstrate the merit in using the Team's systems.
  - In addition to mouse-related conferences, we are actively participating in and presenting papers at human- and bioinformatics-related conferences.
  - In fiscal 2011, the International Mammalian Genome Conference, a major international conference, will expand in scale and be held as the Mouse Genetics Meeting, sponsored by the Genetics Society of America, in Washington D.C. in June. In collaboration with researchers from the Jackson Laboratory who are utilizing the Next-generation Sequencer, we were successful in lobbying the organizers of the Mouse Genetics Meeting to arrange a special session. Yoichi Gondo is tentatively scheduled to discuss "ENU Mutagenesis and the Next-generation Sequencer" in the session.
  - Based on an introduction from a UK user, we are planning to make a presentation at a neuropsychiatric disorder-related conference to be held in the UK in July. In addition, the Conference of International Society of Human Genetics will be held in Canada in fiscal 2011, and we are seeking to participate in order to introduce our development of disease models. We have also been invited to provide lectures at other conferences, including the 2011 International

Conference on Environment Omics in Guangzhou, China, and a meeting of the Japanese Environmental Mutagen Society.

- From January 2011, Team Leader will service as a secretariat for two years for the Genetics Society of Japan, enabling us to further expand our network of domestic and overseas specialist organizations.

RIKEN BioResource Center Review Committee of
Technology and Development Unit for Knowledge Base of Mouse Phenotype
Review Sheet
(December 16, 2010)

Committee Members: Drs. Toshihiko Shiroishi (Chairperson), Fumitoshi Ishino, Masaru Okabe, Hiroaki Yamamoto, Keiji Wada

Summary

1. Does the Technology and Development Unit for Knowledge Base of Mouse Phenotype have achievements of major scientific significance and/or social impact?

- **Conclusion**

  The Technology and Development Unit for Knowledge Base of Mouse Phenotype has made steady progress in establishment of information analysis infrastructure. The fact that the Unit has been recognized internationally was also highly evaluated.

1) Achievements of major scientific significance.

Individual Comments

- The core technology is being constructed by an innovative way in the Unit. Efforts are made to construct a database system by which researchers can retrieve desired information. The proposed information system integrating wide-variety of information such as genes, mouse phenotypes and human diseases, has a potential to change the medical science in the 21st century significantly.
- Integration of databases is a very big subject, although it is still in the early stage. We did understand that integration of databases by a program such as SciNetS or YAMATO will possibly break a new ground for information technology beyond that in existing databases. Accomplishment of the picture will require a certain period of time because the targeted field is very wide and large. But it seems to be still possible.
- The Unit is regarded as an important research program in the RIKEN BRC's IT strategy. The Unit has already made certain achievements and developed a database system with wide application. It is supposed that the Unit will contribute to researcher community significantly.

2) Achievements of major social impact.

Individual Comments

- It is highly evaluated that the Unit is internationally recognized through collaboration. Its uniqueness and technological advantages may come from studies of the upper ontology. Making fully use of this advantage, further international contribution is recommended. It is an important activity that may be one of the triggers to increase the use of the mouse resources. Therefore continued efforts are expected.
- Design of a system with wide social application is recommended.
- Public relation activities seem to be still insufficient.

2. Does the Technology and Development Unit for Knowledge Base of Mouse Phenotype have a functioning Plan-Do-Check-Action (PDCA) cycle?

A. Measures taken to the comments in the previous BRAC and Review Committee and also by internal self-inspection and evaluation.

- **Conclusion**

  The Technology and Development Unit for Knowledge Base of Mouse Phenotype has been implemented as a highly unique research program, and its PDCA cycle is functioning well.

  Individual Comments

  - Proper measures have been taken to the issue that the Unit should actively collaborate with an international consortium to take initiatives, for example, by holding an International Meeting on Mouse Phenotype Information in Japan (Kyoto). The Unit also participates in projects concerning human disease information, such as the Disease Ontology Project by Ministry of Health, Labor and Welfare in which number of universities participate.
  - Proper measures also have been taken sufficiently to the other issues made by committees and individual projects were improved. The progress in the last two years is highly evaluated.

B. Strategy and implementation plan in the two remaining years in the current mid-term plan.

- **Conclusion**

  Steady progress on the practical use of the SciNetS that is currently under

development should be made.

Individual Comments

- A strategy of expansion from IT to ICT may be desirable. Make the target clearer.
- Although there was some ambiguity in explanation of research project, the progress that is aimed from the researchers' viewpoint is anticipated.
- The essential research subjects for an initial step of BRC's IT strategy are chosen. Creating an environment allowing some acceleration of projects is desirable.
- In general, appropriate plans were made, such as expansion and verification of the usefulness of the resource database by using SciNetS, and development of automatic annotation and retrieval systems. Collaboration with the Technology and Development Team for Mouse Phenotype Analysis is recommended to participate in IMPC.

C. Internal and external collaboration and also international collaboration (activities and achievements of special mention, if available)

Individual Comments

- The integration of databases in many research areas and the collaborative activity has made steady progress. It is also highly evaluated that the Unit is consistently conscious of the uniqueness of the research program in such collaborative activities.
- It is expected that operation of information will be achieved successfully even in the future, in which the amount of information will be increased by collaborations with IMPC and IKMC, because it is planed to take the efficient methodology such as automatic annotation.
- Currently, the Unit is collaborating sufficiently with domestic and foreign organizations. Continuous efforts taking initiatives are recommended.
- The superiority of the Unit should be publicized. Further effort is recommended to engage in international cooperation.

D. Others

Individual Comments

- It is probable that copy right issue as an intellectual property, may emerge. Development of a mouse management system may be of interest.
- Construction of unique and innovative database with some sense of adventure is recommended. Future progress can be expected.

- The effort to grasp the needs of research community should be made, for example, by a database access analysis.
- The Unit is essential for resource infrastructure. Further effort is recommended. It is recommended to implement public relations activities that are easily comprehensible to the general public.

Responses and Actions by the Division to the Evaluation and Comments

For issues that received positive evaluations, the Technology and Development Unit for Knowledge Base of Mouse Phenotype will maintain its activities to ensure positive evaluations in future.

For any issues evaluated as requiring improvement or reform, the following measures will be taken:

1. **Does the Technology and Development Unit for Knowledge Base of Mouse Phenotype have achievements of major scientific significance and/or social impact?**

- On the comments that a system design with wide social application is recommended, and that public relation activities seem to be insufficient:
  - We will proceed with the development of integrated databases, giving consideration to social utility and public relations. We will link information of the biological characteristics of the bioresources with information of their utilities (e.g. contribution to health and the environment). We will attempt to create a more socially meaningful database.

2. **Does the Technology and Development Unit for Knowledge Base of Mouse Phenotype have a functioning Plan-Do-Check-Action (PDCA) cycle?**

- On recommendations of a strategy for expansion from IT to ICT, and collaboration with the Technology and Development Team for Mouse Phenotype Analysis to participate in IMPC.
  - Aiming ICT, we will attempt to introduce Internet communications tools to our databases. We will collaborate with the Experimental Animal Division and the Technology and Development Team for Mouse Phenotype Analysis in preparing information infrastructures (e.g. data conversion, security, backup), looking towards participation in the IMPC. We will attempt to apply external

funding in order to achieve the expansion of research resources necessary for participation in the IMPC.

3. Internal and external collaboration and also international collaboration

- On recommendations that continued efforts to take initiatives, publicizing of the superiority of the Unit, and further efforts to engage in international cooperation.
  - To take the international initiatives, we will collaborate deeper with the IMPC-IT Committee with contribution in IT development for data integration. We will attempt to publicize our superiority in data integration technology with concrete biological discoveries using informatics and development of useful database functions.

4. Others

- On the recommendation to implement public relations activities that are easily comprehensible to the general public.
  - We will attempt to survey researcher needs by means of analyses of access statistics for our website. We will examine user interfaces and content design with consideration of ease of understanding for the general public.

11 August, 2011

The Ministry of Education, Culture, Sports, Science and Technology
The National BioResource Project (NBRP) Evaluation Committee

The Evaluation Report

CORE FACILITY UPGRADING PROGRAM

Mouse
Core Facility: Experimental Animal Division, RIKEN BioResource Center
Principle Investigator: Atsushi Yoshiki

Arabidopsis thaliana
Core Facility: Experimental Plant Division, RIKEN BioResource Center
Principle Investigator: Masatomo Kobayashi

Human and animal cells
Core Facility: Cell Engineering Division, RIKEN BioResource Center
Principle Investigator: Yukio Nakamura

Genetic materials
Core Facility: Gene Engineering Division, RIKEN BioResource Center
Principle Investigator: Yuichi Obata

General Microbes
Core Facility: Microbe Division (Japan Collection of Microorganisms: JCM), RIKEN BioResource Center
Principle Investigator: Moriya Ohkuma

Resource: Mouse
Core Facility: Experimental Animal Division, RIKEN BioResource Center
Principle Investigator: Atsushi Yoshiki

(1) Summary

From the perspective of both quality and quantity, the Experimental Animal Division has become a core facility of the highest global standard in the collection, preservation, and distribution of mouse resources. In addition to conducting genetic analyses and technological development for the improvement of quality, the Division can also be highly evaluated for its efforts in disseminating information and surveying the status of its operations by actively seeking user feedback and tracking research results from users. The Division's achievement of BAC end-sequencing as part of the NBRP Genome Information Upgrading Program is evaluated highly as having further enhanced the value of relevant bioresources. Efforts towards the establishment of a backup storage can also be praised.

It is time for the Division to consider to become a global core facility of mouse resources and to be always able to respond future needs of biomedical sciences. For this goal, the Division is expected to pursue further the quality improvement of resources and dispatch the data for the microbiological quality and for the recovery rate of the frozen strains.

(2) Status of progress

The Division is making steady progress towards the achievement of its targets, and has held the second largest number of mouse strains in the world from the perspective of both quality and quantity of collection, preservation, and distribution. The Division is to be highly evaluated for its active and strict implementation of genetic and microbiological quality controls of genetically engineered mice deposited by other institutions. It is also making excellent efforts towards the establishment of a backup storage system.

(3) Operating system

While there are no domestic sub-facilities, the Division has responded adequately to increasing numbers of genetically engineered mice by receiving depositions, for example, from NBRP Phase I developer laboratories. The Division also has established a system for the maintenance of quality. In addition, the Division promotes mutual use of overseas bioresources through the international collaboration. In future, the Division is expected to enhance its backup system and establish a system to provide users more

useful information and a higher level of service.

(4) Future prospect

The Experimental Animal Division is already at the highest international level in terms of services, including sophisticated quality management, although the number of preserved mouse strains is the world second largest. The Division is recommended to consistently pursue quality improvement rather than aiming to increase strain numbers endlessly. For example, the provision of the recovery rate of frozen strains should prove and guarantee high-quality service. Since outstanding papers by users have been published in high-impact journals, the research community has a high level of needs and a high degree of trust for the Division. Therefore, sufficient potential exists for the Division to achieve the world's top level by further understanding and responding to those research needs.

(5) Other particular comments

Initiatives in the area of quality management and a high level of the achievement are strong points of the NBRP. The Division is recommended to continue its efforts in this area in future.

Because only a limited number of published papers have been provided by users, the Division has made considerable efforts to collect the information. It may be necessary to take measures to enforce the obligation of users to report their publications. The Division should make efforts to supply scientists requested mice as quickly as possible.

Resource: Arabidopsis thaliana
Core Facility: Experimental Plant Division, RIKEN BioResource Center
Principle Investigator: Masatomo Kobayashi

(1) Summary

The Experimental Plant Division can be evaluated highly for its efforts in building a firm foundation as a center for *Arabidopsis thaliana* resources aiming towards the world's highest level, by working to establish and maintain high quality in unique Japanese bioresources, managing bioresource quality, and fostering specialists through international cooperation. The strong motivation of the Division to establish resources of the world's highest level is obvious from the following points: collecting new resources including wild-derived Arabidopsis, distributing new genome resources including gene-disrupted lines and FOX (over-expressed) lines, and improving the quality of materials provided to the research community. The quality of the papers published by the domestic research community is, however, relatively low. Further improvement on this issue is necessary.
Judged comprehensively, the Division's project has reached excellent level.

(2) Status of progress

The Division has achieved the aims of its project by focusing on collection, preservation and distribution of resources established in Japan, and by improving the quality and value of preserved resources. Additionally, the number of user's manuscripts is increasing. Thus it is judged that the level of recognition and evaluation of the resources in the Division has been improved both domestically and internationally.

(3) Operating system

The Division operates its project without any sub facility. It has much better operation system than other institutions in NBRP, in terms of researchers (permanent staff and postdocs) and technical staff engaged in the project. The Division can also be evaluated highly for the promotion of international and regional cooperation including the establishment of Japan-U.S.-Europe network on Arabidopsis resources as well as establishing its position as a core center in Asia.

(4) Future prospect

Because of the variety of resources and their excellent quality, NBRP resources of Arabidopsis are regarded as world's highest class in basic research area of plant science. In order to ensure that the Arabidopsis resources will continuously open the way for unique and innovative researches in plant science as fundamental tools, the Division

should pay attention to catch the research outcomes. We also ask the Division to foster young scientists and improve the operation by promoting collaborative researches with Japanese and non-Japanese researchers.

(5) Other particular comments

We believe that the RIKEN BRC is considering establishing a backup system of bioresources. It would be desirable for the Division to examine this issue and make progress as rapidly as possible.

Resource: Human and animal cells
Core Facility: Cell Engineering Division, RIKEN BioResource Center
Principle Investigator: Yukio Nakamura

(1) Summary

The Division has carried out strategic operation with advices both from within the RIKEN BRC and outside the organization, in addition to steadily increasing the number of cell lines it holds. This has been particularly conspicuous with activities such as the upgrading of its quality management system by ISO 9001 accreditation and clarification of the associated procedures and processes in NBRP Phase II. These activities will serve to strong appeal points for long-term confidence and also for its sustainable operations, as there are have the significant merits such as improvements in processes visible to staff members. The fact that the number of papers published based on use of the Division's bioresources remains consistently high indicates that its bioresources have attained a firm position as research materials, and this can also be highly evaluated.
The Division can also be praised for actively positioning itself as a bioresources core facility in Asia. Based on the above, the Division can be judged as having achieved an excellent level in terms of the outcomes of its operations.

(2) Status of progress

The Division has achieved well its goals of collection, preservation and provision of bioresources and their use in research. In addition, obtaining and maintaining ISO accreditation of its quality management system has been an important step. In future, it is to be hoped that the Division will further enhance its baking activities of human ES and iPS cells.

(3) Operating system

The Division is going to move to the newly completed building is in June 2011 and is staffed by around 35 personnel. Further advancement of this Division is to be hoped. The future expansion of banking activities as a human ES and iPS cells is expected and cooperation with large-scale projects supported by the Ministry of Education, Culture, Sports, Science and Technology can be exploited. In addition, the Division is playing a central role for international cooperation, for example with other bioresource centers in Asian nations.

(4) Future prospect

The recent earthquake disaster focused attention on the protection of bioresources against disaster. The fact that the Division has already acted to secure resources in the Harima Institute can be evaluated highly. However, while the Division may focus exclusively on storage facilities, the presence of researchers who possess knowledge concerning the resources is the key to risk management in this area. It is to be hoped that future consideration will be given to the question as to what type of research functions Harima will carry out.

(5) Other particular comments

It is to be hoped that the Division will start discussion with other similar operations in Japan in order to define collaboration and share of the work.

Resource: Genetic materials
Core Facility: Gene Engineering Division, RIKEN BioResource Center
Principle Investigator: Yuichi Obata

(1) Summary

National BioResource Project Phase II, the Gene Engineering Division collected new bioresources in collaboration with a variety of national projects, and worked continuously to increase its quality as a bioresources core facility. As a result, it has already succeeded in exceeding its targets of the NBRP Phase II in terms of numbers of genetic materials collected, preserved and provided. As a ratio of overseas provision was more than 30%, the Division has established its position as an international bioresources institution in Asia. Its success in developing strategy of operation is particularly important in a fluctuating trend of research needs for genetic materials. In future, it is to be hoped that the Gene Engineering Division will progress with the establishment of a foundation for the life sciences of the world's highest standard through the expansion of its operations under the strategic guidelines. The outcomes achieved by the Division can be evaluated as being of an outstanding standard.

(2) Status of progress

The Gene Engineering Division has already achieved third place in the world in terms of scale, holding 3.51 million preserved strains. In Phase II, it ha further increased accessibility for users by preparing BAC clones of B6/N global standard mouse strain, bioresources related to the Japanese genetic trait, viruses and vectors as tools for genetic analysis, and DNA bioresources created in Japanese national projects. It is also contributing to the promotion of the use of its resources by providing information concerning bioresources, information on published papers and a search system for bioresources on its homepage. As a result, it has already succeeded in exceeding its targets of the NBRP Phase II in terms of numbers of genetic materials collected, preserved and provided. A ratio of overseas provision is more than 30%. In addition, it has worked continuously as a bioresources core facility to increase its quality, and it has established its position as an international bioresources institution in Asia. One problem forced to be pointed out, if any, is the extreme low numbers of papers published by users on the basis of use of its resources. Efforts in future to study this issue would be recommended.

(3) Operating system

The Gene Engineering Division proceeds with its operations based on strategic

guidelines that consider the fluctuating trend of research needs for genetic materials under a system exactly suited to its status as a specialized bioresources institution. It is also actively pursuing collaboration with national projects, other projects of the NBRP, and the NBRP Information Center. It is also working to establish an environment promoting the use of biological resources by establishing licensing contracts for resources produced by using research tools owned by commercial entities.

(4) Future prospect

The Gene Engineering Division has already been a position as an Asian base of international bioresources institutions, and it is to be hoped that in future it will progress with the establishment of a foundation for the life sciences of the world's highest standard through the expansion of its operations under the strategic guidelines.

(5) Other particular comments

The fact that it has only one permanent employee generates strong concern that may cause problems in the continuity of operations from the aspects of technology, procedures, and etc. Reform in this area would be desirable. It is also to be hoped that the Gene Engineering Division will attain ISO 9001 certification, like the JCM and the Cell Engineering Division.

Resource: General Microbes
Core Facility: Microbe Division (Japan Collection of Microorganisms: JCM), RIKEN BioResource Center
Principle Investigator: Moriya Ohkuma

(1) Summary

In addition to exceeding its targets for collection as a bioresource core facility for general microbes and maintaining a position at the world's top level in its field, the Japan Collection of Microorganisms (JCM) has obtained ISO 9001 certification in the area of quality control system, and is working to cooperate with overseas institutions and disseminate its resources to overseas. Considering the scale of other international microbial resource centers of a similar top level quality, the JCM can be rated highly. The numbers of publication of papers using JCM resources are also sufficient, and its performance is appropriate for a microbial resource center functioning at the very top level in the international scientific community.

(2) Status of progress

The confidence of users, based on factors such as superior technologies for the handling of microbes that are difficult to culture, forms the foundation for the JCM's collection of taxonomic type strains of bacteria and archaea. These collection activities are a major factor in the JCM's having exceeded its targets. With the acquisition and maintenance of ISO 9001 certification, the JCM strengthens its systems for preservation, provision, and quality management, and this contributes to the operation of the Division. The JCM has greatly exceeded its targets for the collection of strains, including those for which it has received deposits from 153 institutions in 34 countries, and it is meeting its targets for preservation and provision. In addition, one-quarter of the JCM's provided microbial resources are sent overseas, and this fact is reflected in the overwhelming number of research papers published based on their use.

(3) Operating system

The taxonomic data concerning the microbes held by the JCM presently published in its database displays a high degree of originality, and is of the highest level of quality, even considered globally. In the area of quality management, the JCM is also working at preparations to progress to the next level, for example by newly appointing staff for gene analyses. The JCM is cooperating with microbial resource centers in Europe and the U.S. through the exchange of taxonomic type strains.

(4) Future prospect

The status of operation of the JCM is presently extremely high, and maintaining the confidence of users represents an important issue. New forms of provision of bioresources, such as in the provision of genome DNA from the JCM's microbial strains in collaboration with the RIKEN BioResource Center Gene Engineering Division, and dissemination of information concerning these activities, have the potential to make the JCM a bioresource center meeting or exceeding the world's highest standards.

(5) Other particular comments

It would be desirable for the JCM to move systematically towards the formation of a network for the transfer of bioresources that takes responses to the Convention on Biological Diversity through cooperation with institutions in Southeast Asia. The JCM should also consider systemic enhancement, including an increase in personnel numbers, in order to expand its collections of microbial resources other than type strains and promote their use in a wide variety of fields.