The Report

The First Advisory Council Meeting of the RIKEN BioResource Center

April 24, 2004

The First Advisory Council Meeting of the RIKEN BioResource Center

March 1-3, 2004
RIKEN Tsukuba Institute

Dr. Ogura Dr. Kobayashi Dr. Abe Dr. Obata Dr. Doi Dr. Nakamura

Dr. Miyoshi Dr. Fukami Dr. Moriwaki Dr. Yokoyama

Dr. Koornneef Dr. Kuroki Dr. Sugano Dr. Nagai Dr. Guenet Dr. Brown Dr. Takahata

Three Council Members, Drs. Eguchi, Old and Paigen, were absent from the picture but participated in the meeting through mail review and discussion.

List of the RIKEN BioResource Center Advisory Council Members

Dr. Stephen D.M. Brown	President Mouse Genome Center, Medical Research Council, U.K.
Dr. Goro Eguchi	President Educational College of Shokei, Japan
Dr. Jean-Louis Guenet**	Director Unite de Genetique des Mammiferes, Institute Pasteur, France
Dr. Maarten Koornneef	Professor Laboratory of Plant Genetics, Wageningen University, Netherlands
Dr. Toshio Kuroki	President Gifu University, Japan
Dr. Yoshitaka Nagai*	President Mitsubishi Kagaku Institute of Life Sciences, Japan
Dr. Lloyd J. Old	Institute Director & CEO Ludwig Institute for Cancer Research, U.S.A
Dr. Kenneth Paigen	Former President The Jackson Laboratory, U.S.A
Dr. Haruo Sugano	Director Emeritus The Cancer Institute of the Japanese Foundation for Cancer Research, Japan
Dr. Naoyuki Takahata	Vice President The Graduate University For Advanced Studies, Japan

* Chairperson
** Vice Chairperson

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Item 1. GENERAL COMMENTS AND RECOMMENDATIONS ON THE OPERATION OF THE BRC

Members of the Advisory Council all agree that the RIKEN BRC is an essential component of both the national and international biomedical research field and allied research enterprises, including bio-industries. The BRC has enjoyed a rapid but healthy growth for the past three years since its establishment in January 2001, and its activities have been highly praised by the recently instituted national bioresource project, NBRP. The BRC is essentially a purpose-oriented service facility and the principle of "service" should be considered a pillar of its operations. A consistently reliable supply of high quality materials, speedy service, an ever-expanding collection of new materials and the development of an information network for bioresource users are essential to the activities of the BRC. As well, fundamental research in support of maintaining the above-mentioned characteristics inherent to bioresource collection constitutes another pillar whose activities should be actively pursued. These two pillars are mutually complementary. Based on such recognition the Advisory Council of the RIKEN BRC advises the following, with reference to policy on the operation of the BRC:

We prefer to comment on the work and achievement of each division, as this is more pertinent; we will include any remaining comments at the end.

1. Establish contact with other similar resource centers worldwide.

2. To ensure adequate expansion of the resources in balance with demand, the BRC will require:
    - 2.1 Good scientific staff well aware of the most recent developments.
    - 2.2 An advisory council covering most aspects of biological research.

2.3 An internal council well aware of scientific developments in Japan and most developed countries.

3. Establish at an early date an intellectual property office with international competence within the BRC, to deal with the complex and unique issues associated with the handling and transaction of bioresources.

4. Secure funding for additional facilities and personnel to ensure sustainable growth as well as efficiently serve the scientific community with high quality bioresources and relevant information while maintaining BRC's three principles that are "Trust", "Sustainability" and "Leadership". We recommend that the BRC moves increasingly toward recovering from the beneficiaries the cost of the services they provide.

5. Expand/strengthen services in the following areas:
   5.1 Informatics of bioresources
   5.2 Public relations and advertising

6. Review strategic case for other bioresources, including tissue and DNA repositories of other species, including integrating informatics to underpin these resources.

7. Make efforts to increase the value of bioresources as models for biological functions and diseases.

8. Encourage the continued development of an active training programmed that enhances the community's ability to utilize and contribute to the resource center.

Item 2. SPECIFIC COMMENTS AND RECOMMENDATIONS TO DIVISIONS ON POLICY AND PRACTICE ON COLLECTION, MAINTENANCE AND DISTRIBUTION OF BIOLOGICAL RESOURCES

A. Experimental Animal Division

This division builds on Japan's leading international profile in mouse genetics. It has mainly focused on the archiving of mouse embryos. A very significant number of strains and mutants have been archived and the BRC are to be congratulated for this. Significant efforts have been made to ensure high health status of archived and distributed material. In

addition, quality control through genotyping is in place and significant emphasis is being placed on developing phenotyping platforms to validate lines.

A significant number of lines are archived also as sperm. It was encouraging to hear that there is significant use of IVF for archiving and that its use in other areas was being considered.

Given world-wide efforts to establish a genome-wide targeted mouse mutagenesis resource, it would be advantageous for the BRC to establish a parallel ES resource and to be one of the holders of the genome-wide resource when it is created. Already a large number of knock-outs (KOs) have been archived, yet the corresponding ES cell lines are not available. The BRC would be able to provide mice or embryos from any ES cell line, particularly given the support of the bioresource engineering division.

The underlying data structure on archived lines is relatively simple at this point. However, the development of phenotype ontologies will require the BRC to adopt a more sophisticated approach to the data descriptors for each line archived. It would be valuable for the BRC to become more closely involved with the world-wide developments in the informatics of phenotype vocabularies and ontologies, which themselves are tied to the development of standard operating procedures for phenotype testing. These connections and collaborations will be helped by the move to the site of the RIKEN ENU program, which provides a natural focus for the development of phenotype platforms and ontologies.

Key activity (see below) that is required to complement the ongoing program is training, for examples, on:

- Archiving of embryos and sperm
- Recovery of mice from diverse frozen material e.g. embryos and sperm, which is vital for ensuring the easy and wide dissemination of genetic material – including IVF
- ES cell technology

Others activities that are recommended are:

- Backcrossing knockouts on an inbred background (and better on two) is very useful; even clever
- Maintenance of new mutants collected from the Japanese ENU mutagenesis program as live stock, not in frozen form until they have been roughly characterized. Experience indicates that they will never be thawed back unless they have been characterized, at least roughly

B. Experimental Plant Division

The current program deals with the distribution of plant genetic materials with a strong emphasis on *Arabidopsis*. The choice is based on the size of the research community and on the fact that several genomic resources are being developed in Japan.
The seed bank consists of insertion lines and in future will consist of other transgenic stocks developed in Japan. In addition SACC stock center has been incorporated. The latter is composed of a set of widely available mutants and accessions and a unique collection of Japanese accessions. The first part should serve as a general resource for Japanese scientists. To be of optimal use, the BRC should have a critical look at the composition of this rather old collection of standard lines and add new frequently used materials, which can be obtained from the two *Arabidopsis* stock centers. Examples of additions might be some recombinant inbred line populations, important mutants, reporter lines, etc.

We suggest that as a backup or an exchange item, the BRC may consider making the Japanese accession collection, or a core selection from it, available to the other stock centers when no MTAs are involved. However, this may cause a problem with the other resources. A novel seed resource could be a tilling population linked to a tilling facility. When this is an accession other than from the USA, it will complement international initiatives in this direction. The full-length cDNA clones are a success story because they are unique and fulfill a need of the international community as indicated by the many orders from abroad. With respect to the cell cultures, the need of specific cell cultures, especially in *Arabidopsis*, should be carefully thought out, because such cultures are difficult to make and the scientific community makes use of only a limited set. The choice of the plant group as a center for metabolic analysis should be justified by the need of the plant science community and by the capacity of the group. For specialized determinations this might be better done in collaboration with specialized laboratories for which the BRC can act as mediator. Development as a technology platform is an option that was also implemented by the NASC center for microarrays, but a large investment might be wasted on something that is not used.

Because plant seeds and clones can be stored easily there is no problem in keeping materials that are considered now as mainly archival.

Customers should, and are willing to pay a reasonable fee. Keep in touch with the fees of other stock centers. Full cost recovery will be difficult, especially when overhead and

research needs are included.

Seeds and DNA stocks can easily be stored elsewhere and having a backup will not be a large investment.

C. Cell Engineering Division

The BRC management of established cell lines, most of which are human cancer cell lines, is very efficient. Hopefully they will collect more human and cancer cell lines, because there are many useful cell-lines, already or yet to be established.

The stem cell project should receive more emphasis. Regarding stem cell, please refer to Item 3 C.

There are natural synergies between this division and the Experimental Animals Division in terms of the logistics of archiving large genome-wide sets of mutant ES cell lines. There are 866 interesting human cell lines from the viewpoint of genetic diversity in the human population. However, it is important to know the ethic origins of these cell lines. More detailed information should be supplied in this regard.

D. Gene Engineering Division

Examining the published results by customers can best assess evaluation of the activity. The division tries to do it, showing a list of publications. Although this appears very tedious, we would like to suggest that the BRC as a whole utilizes this kind of objective evaluation system, rather than simply listing the number of distributions. In any case, this should be greatly encouraged and officially supported if possible.

However, it is necessary to review regularly the value of the resources in the repository. For example, if BAC is more reliable than YAC, any project for YAC may be abandoned.

Regarding promoter banks both from mouse and human DNAs: The division might contemplate beginning to develop a mouse promoter resource. In particular, such a resource of, for example, tissue or stage specific promoters would be valuable for the creation of new cre stocks of mice. Such validated stocks could also be a focus of the creation of a "cre-zoo" by the Experimental Animals division and would be an extremely valuable

resource for the mouse genetics community.
- Development of technology for mutation detection
There should be a point for reflection explain in Gene Engineering Division to make sure that the potential pool of 'clients' is not decreasing or that interest in the resource is not diminishing.
- High molecular weight DNA samples of several perfectly characterized species might be an interesting addition to the resource given that these are frequently requested by members of the community.
- Regularly checking requests posted by members of the community (for example the mouse community on the mgi-list) might be a good way to be in phase with the needs of the community. This suggestion is not only for this Division but for most of the project managers as well.

E. Bioresource Information Division

Although this division was recently established strong support is urgently needed for further healthy steady development because it will become very important in the near future.

This division is important particularly when the entire collection in the BRC is to be incomplete in terms of needs of customers. Nevertheless, if the division will develop a service system from which customers can know where the materials they want, the division will play a central role in the BRC activity. It is therefore important to develop such a system not only for the BRC resources but also for resources maintained in any other established resource centers in the world.

It would be valuable for the data of the BRC to be integrated with efforts to provide one-stop shops to search globally for biological resources, e.g. mouse mutants. For example, it would be useful for the BRC to join the International Mutant Strain Resource (IMSR) web site which is hoped will provide easy access to identify the location and availability of any mouse mutant around the world.

Item 3. POLICY AND PRACTICE ON RESEARCH AND DEVELOPMENT: DEVELOPMENT OF NOVEL BIOLOGICAL RESOURCES, DEVELOPMENT OF TECHNOLOGIES FOR EFFICIENT COLLECTION, MAINTENANCE AND DISTRIBUTION OF BIOLOGICAL RESOURCES AND RESEARCH ON BASIC CHARACTERISTICS OF BIOLOGICAL RESOURCES

A. Experimental Animal Division

The division appears to be making useful connections with other divisions that sustain its research and development. In particular, good progress has been made in the development of phenotyping/testing technologies and this will be further sustained through increasing interactions with the RIKEN ENU program. As discussed above, one area that the division could place more emphasis is in the development of ontologies – and here, working with the ENU team, the division could make a significant contribution to the world-wide effort in ontology development.

It is hoped that more rodents related to genus *Mus*, e.g. rats, are collected, preserved and distributed. In doing that, basic research for taxonomic classification must be simultaneously carried out.
Mice have been extensively checked on a DNA level together with behavioral testings. Very recently importance of proteomic analysis was recognized with a particular reference to evaluation of phenotypic changes, brain shows characteristic alteration of proteins expressed for example, in between human and chimpanzee. In this connection with behavioral alteration proteomics analysis may provide important information.

B. Experimental Plant Division

A good description of the materials such as with newly collected accessions should be made. These should be genotyped with a set of standard markers – try to decide on these markers internationally.

For plant resources, it should be carefully evaluated whether new technologies in the materials are required since the Japanese research community is generating these. The development of genomic tools (insertion lines, tilling populations) for other plant species might be an interesting goal for the BRC but any project of this type is large and probably will need considerable extra resources and needs discussion case by case by the plant

science community. The example of *Arabidopsis* might work for other plant species also and therefore the BRC has a role to play in initiating such projects.

It is questionable how much the BRC should invest in new phenotyping technology including metabolomics and expression analysis except for the characterization of their own materials in view of the capacities elsewhere in Japan. However, if the community feels the need this type of research can be initiated.

Adopting other plant species is an option but especially for species which require more space an agricultural institute might be more appropriate.

C. Cell Engineering Division

Stem cell is an important and hot area and should be focused as the Cell Division, including hematopoietic stem cells. The project proposed at the meeting is exciting and it contains both biological and practical significance. We have high hopes for this project. The division should think about the opportunities to develop new mouse ES stem cell lines that could be made widely available to the rest of the community.

D. Gene Engineering Division

See above Item 2 D.

E. Bioresource Information Division

Highly original studies on animal behavior. The use of ontologies to define mutant phenotype will be increasingly important and this division will need to be alert to the development of phenotype ontologies. We suggest that the division is introduced to and plays a role in the world-wide effort to develop phenotype ontologies for the mouse.

F. Bioresource Engineering Division

It is encouraging to see active development in the areas of embryo cryopreservation, sperm freezing and nuclear transfer. The developments in the use of frozen sperm and microinsemination are particularly interesting and exciting.
Excellent including somatic cell cloning.

G. Technology and Development Team for Mammalian Cellular Dynamics

Very nice; mutation assays and promoter-banking are exciting and very promising. It is certainly useful to have a team that can make a contribution to the development and application of genetic and genomics resources, such as new EST sets and BAC libraries.

This Team achieved important contributions to developmental biology and mouse genetics. In developmental biology they have used GFP-labeling for cell lineage study and found that estrogen-related receptor β (ERP β) plays an important role in PGC function, though its natural ligand has not been identified. Their approach to mouse genetic is unique in that Asian wild-derived mice, collected by Dr. Moriwaki, Director of the BRC, have been used. These studies may contribute to our understanding of laboratory mice as well as the evolution of rodents.
ES cell project is exciting.

The MSM/MS library is very interesting in mouse genetics and oncology.

H. Subteam for BioSignal Integration

This Subteam demonstrated their results on genetically manipulated mice of NF-κB, TNF, RELA and C-REL. Because signal transduction is most important in understanding cellular functions, and thereby most competitive, this group should be advised and evaluated by experts for future programs.

The goals of this Subteam seem very ambitious, and perhaps a bit too much. There are clearly potentially interesting projects developing using both RNAi and KO approaches in gene function. However, it was not clear from the presentation how the balance has been made between technical development and the work on NF-κB and RelA. In addition, it should have been more clearly demonstrated what specific biological questions are being asked. Given the size of the Subteam, it is recommended that a clear plan and focus should be developed for the future.

I. Subteam for Manipulation of Cell Fate

This Subteam is doing three different studies, telomere, stem cell plasticity and HIV vector. The presentation was rather superficial. The program should have its main focus and depth.

This Subteam focused on the cell fate of stem cells when returned to an in-vivo situation. The data on telomere, mesenchymal differentiation and lentivirus vectors are generally well conducted. All may contribute to future clinical applications. Collaboration with other RIKEN institutes, in particular RIKEN Institute of Developmental Biology in Kobe, would be important for future studies.

Item 4. POLICY AND PRACTICE ON TECHNOLOGY TRANSFER AND EDUCATION

It is important that major international resource centers have a very active program of disseminating expertise that enhances the community's ability to both utilize and contribute to the archives. It will be important to provide courses on:

- archiving of embryos and sperm
- recovery of mice from diverse frozen material, e.g., embryos and sperm, which is vital for ensuring the easy and wide dissemination of genetic material – including IVF ES cell technology

Education provides an excellent link with the customers and will help the proper use of the materials distributed by the BRC. In general, advance training courses are important and useful because they will help especially young researchers to get an overview of the field, they will meet colleagues and scientists from other labs etc. Although training courses may be time consuming, they could be beneficial not only for Japanese, but for foreign researchers, especially those from East Asian nations.

In addition the concept of open laboratories should be considered, where researchers from different research fields work together under continuing collaboration and information exchange. This would also be helpful for efficient education. Of course this should be done by other scientists and the training should pay a cost-covering fee if possible when no central organization pays for it.

Item 5. INTERNATIONAL COLLABORATION

It is clear that if the BRC is to be successful that it must engage with the international community and integrates its effort not only with that of other resource centers but also

with the key scientific development that are emerging in the field. In this regard, it is important that the BRC:

- engage in dialogue with other resources centers over the integration of dissemination of data, ensuring that the wider community has easy access to the availability of resources worldwide
- focus on key scientific developments that may impinge upon its resourcing strategy e.g. take account of international developments in large-scale targeted mouse mutagenesis that will transform the nature of mouse genetic resources and that will require new thinking on the nature of resource collections in mouse genetics, for instance, the archiving of large sets of ES cell lines
- consider the bioinformatics issues that will emerge from the demand for better descriptors of archived material e.g. improved and more robust descriptions of phenotypes through the emerging ontologies that will improve the richness and searchability of the resources offered

In addition, close international contacts provide an important variety of other advantages including:

- a timely appreciation of developments in archiving technologies
- benchmarks for assessing practice at the BRC
- identification of opportunities to fill niches not occupied by other resource centers

The BRC should position itself as one of the world's principal repositories of biological resources. It should have strong interactions with equivalent institutions around the world and consider mirroring collections, sharing know how and seeking to complement expertise on an international scale. In addition, the BRC might seek to foster the creation of one or more mirror sites within its sphere of international influence with a view to helping make biological resources more available in developing countries. Such a mission could also be a joint venture with one or more resource centers.

The AC strongly recommends that the BRC coordinates its collection building and what it distributes with the two other *Arabidopsis* stock centers. For bioinformatics coordination should be done with TAIR as much as possible. This will make the position of the BRC as one of the three leading *Arabidopsis* stock centers clearer.

Item 6. RECOGNITION AND SUPPORT FROM THE SCIENTIFIC COMMUNITY

The most important means of interacting with the scientific community is through a highly informative and regularly maintained web site where the catalogue should be easily available. By backing this up with prompt and reliable service, the BRC can be confident of general support and recognition.

Additional steps to consider are (a) expanding web-site activities with multiple external links, (b) providing a system to answer email queries, and (c) a phone center staffed to answer technical questions regarding use and availability of resources.

In order to promote recognition and support it should be important to let scientific community know by uniqueness of BRC in its activities including development of new methodology. BRC also should endeavor to gain socially prestigious reputation. For this purpose, we recommend opening an office for public relations and exchange of information with not only scientists but citizens. In addition to opening of office and periodic publication, periodic opening of facilities which can be opened and open lecture meeting are thought to be efficient and meaningful to keep good and healthy public relations.

Recognition and support will come from an efficient service that provides high quality reagents that are in demand from the community. This will partly come through excellent promotional material including an attractive and information-rich web site as well as through more traditional routes. The value of a glossy brochure that can be distributed at meetings and conferences should not be underestimated.

Item 7. EVALUATION SYSTEM OF BRC AND ITS STAFF

The BRC should organize and establish a strong evaluation committee consisting of BRC members and outside members with wide-scope and high discernment. The committee should be organized by an independent chairman appointed by RIKEN.

Evaluation through this regular external review should assess the productivity of the service by and large and not, for example, publication output. Productivity should be measured by a number of criteria including:

1. Uptake of resources by the community
2. Some assessment from the user community of the value, quality and efficiency of

the services provided

3. The quality of strategic insight into resource provision including the tuning of the resource portfolio and the timely development of new resources

Some component of this review should include how well the BRC has adopted or developed new techniques or procedures that have had a significant impact upon the operation of the BRC and possibly other resource centers.

Item 8. BIOLOGICAL RESOURCES WITH PATENT, INTELLECTUAL PROPERTY RIGHTS, REACH-THROUGH RIGHT AND OTHER PROPRIETARY RIGHTS

It is essential to set up a small office for handling IP issues. The aim must be to keep procedures as simple as possible while safeguarding individual interests. In general, such procedures are well worked out around the world and a standardized approach to this with equivalent institutions and centers is desirable.

Appendix 1

The First Advisory Council Meeting
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March 1-3, 2004

AGENDA

RIKEN TSUKUBA INSTITUTE & OKURA FRONTIER HOTEL TSUKUBA

Monday, March 1 — 1st day —

9：30 *Leave Hotel by Microbus to RIKEN*

RIKEN TSUKUBA INSTITUTE

10:00～10:15 *Greetings*
Director of RIKEN Tsukuba Institute: Dr. Kazuo MORIWAKI

10:15～10:25 *Opening remarks*
Executive Director of RIKEN: Dr. Tomoya OGAWA

10:25～10:30 *Nomination of chairperson*
Adoption of the Draft Agenda

10:30～11:00 *Logistics of the meeting*
Dr. Yoshitaka NAGAI

11:00～12:30 *Overview of BRC*
Director of RIKEN BioResource Center: Dr. Kazuo MORIWAKI
Overall activities of BRC
Head of Department of Biological Systems: Dr. Yuichi OBATA

12:30～13:30 *Lunch at BioResource Center 1F 103,105*

13:30～16:30 *Activities of each Division*

13:30～14:00 *Experimental Animal Division*
Dr. Yuichi OBATA

14:00～14:30 *Experimental Plant Division*
Dr. Masatomo KOBAYASHI

14:30～15:00 *Cell Engineering Division*
Dr. Yukio NAKAMURA

15:00～15:30 *Coffee break*

15:30～16:00 *Gene Engineering Division*
Dr. Kazunari K.YOKOYAMA

16:00～16:30 *Bioresource Information Division*
Dr. Kaoru FUKAMI
16:30～17:00 *General discussion*

17:00 *Leave RIKEN by Microbus to Hotel*

Room "YUBAE" (HOTEL Annex 2nd Floor)
20:00～24：00 *P.C. equipment & coffee available*

Tuesday, March 2 — 2nd day —

9：30 *Leave Hotel by Microbus to RIKEN*
RIKEN TSUKUBA INSTITUTE
10:00～12:00 *Activities of Division and Teams*
10:00～10:30 *Bioresource Engineering Division*
Dr. Atsuo OGURA
10:30～11:00 *Technology and Development Team*
for Mammalian Cellular Dynamics
Dr. Kuniya ABE
11:00～11:30 *Technology and Development Team for BioSignal Program*
Subteam for BioSignal Intergration
Dr. Takahiro DOI
11:30～12:00 *Technology and Development Team for BioSignal Program*
Subteam for Manipulation of Cell Fate
Dr. Hiroyuki MIYOSHI
12:00～12:30 *General discussion*

12:30～13:30 *Lunch at BioResource Center 1F 103,105*

13:30～15:15 *Laboratory Visit*
Facilities of the RIKEN BRC

15:15 *Leave RIKEN by Microbus to Hotel*

Room "YUBAE" (HOTEL Annex 2nd Floor)
16:00～18:00 *Preparation of Council Report :* ***Advisory Council Members only***

Room "YUBAE" (HOTEL Annex 2nd Floor)
20:00～24：00 *P.C. equipment & coffee available*
22:00 *Submit comments and recommendations to Mr. Yamada*

Wednesday, March 3 ― 3rd day ―

Room "YUBAE" (HOTEL Annex 2nd Floor)

10:00～11:30 *Preparation of Council Report :* ***Advisory Council Members only***

11:30～12:30 ***Summary of Council Report from the RIKEN BRC Advisory Council***

12:30～12:40 *Closing remarks* ***by Dr. Yoshitaka NAGAI***