



The Report

**The Third Advisory Council Meeting
of the RIKEN BioResource Center**

January 19-21, 2009





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Dr. Kuroki Dr. Takahata Dr. Nakahata Dr. Okada Dr. S. Miyazaki**

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Dr. Yoshiki Mr. Shishido Dr. Ogura Dr. Doi
Dr. Wakana Dr. Masuya Dr. Miyoshi Dr. Gondo**

**19-21 January, 2009
Asakusa View Hotel in Tokyo**



List of the RIKEN BioResource Center Advisory Council Members

[Core Members]

Dr. Stephen D.M. Brown --- *Absent*

Director, Mammalian Genetics Unit, Mouse Genome Centre
Medical Research Council, United Kingdom

Dr. Jean-Louis Guenet

Director, Unite de Genetique des Mammiferes
Institut Pasteur, France

Dr. Barbara Knowles

Senior Principal Investigator, Institute of Medical Biology
A*STAR, Singapore

Dr. Maarten Koornneef

Professor, Laboratory of Plant Genetics
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Dr. Toshio Kuroki

Deputy Director, Research Center for Science Systems
Japan Society for the Promotion of Science, Japan

Dr. K. C. Kent Lloyd

Professor and Associate Dean, School of Veterinary Medicine
University of California, United States of America

Dr. Naoyuki Takahata

President
The Graduate University for Advanced Studies, Japan

[Chair of Review Committee for Experimental Animal Division]

Dr. Hiromichi Yonekawa

Vice Director
The Tokyo Metropolitan Institute of Medical Science, Japan

[Chair of Review Committee for Experimental Plant Division]

Dr. Kiyotaka Okada

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The National Institute for Basic Biology, Japan

[Chair of Review Committee for Cell Engineering Division]

Dr. Tatsutoshi Nakahata

Professor, Graduate School of Medicine

Kyoto University, Japan

[Chair of Review Committee for Gene Engineering division]

Dr. Jun-ichi Miyazaki

Professor, Graduate School of Medicine

Osaka University, Japan

[Chair of Review Committee for Microbe Division]

Dr. Makoto Watanabe

Professor, Graduate School of Life and Environmental Sciences

University of Tsukuba, Japan

[Chair of Review Committee for Bioresource Information Division]

Dr. Satoru Miyazaki

Professor, Graduate School of Pharmaceutical Sciences

Tokyo University of Science, Japan

[Chairs of Research Review Committees]

Dr. Ryo Kominami

Professor, Graduate School of Medical and Dental Sciences

Niigata University, Japan

Dr. Toshihiko Shiroishi

Professor, Mammalian Genetics Laboratory

National Institute of Genetics, Japan

バイオリソースセンターアドバイザー・カウンシル報告書 (仮訳) 概要版

理化学研究所バイオリソースセンター(BRC)と各開発室、研究チームの成果と 将来計画に対するコメントと勧告

過去3年間のBRC全般の成果

・ 総論

理研BRCは、前回のレビュー以降の3年間で、高品質のコレクションの収集、保存、保管、提供において顕著な前進をもたらした。理研BRCは日本の科学を支える重要なバイオリソース供給源となるという使命を果たすとともに、アジア各国の研究機関との連携活動を活発に実施し、世界各国へのバイオリソース提供数を大きく伸ばした。理研BRCは国際的な研究コミュニティ、特に、実験動物コミュニティにおいてその存在が良く認知された組織に成育し、またiPS細胞の提供事業で地位を確立することにより目標を達成している。この状況は小幡センター長と彼が率いる組織の不断の努力によって実現したものである。このことは、理研BRCが世界一のリソースセンターとしての地位を確立すべく、その努力を継続かつ加速してきたことを示唆しており、賞賛すべきことである。

世界を先導する理研BRC計画が、毎年定率の予算削減(年約1%)という環境にも関わらず、健全に遂行されたという点は特筆に値する。BRACは理研BRCと同様の視野と品質をもつリソース機関は他には思いつかないということは強調すべきであろう。理研BRCの活動水準は維持されるべきであり、特定の分野におけるスタッフの増員と予算の追加並びにセンターの施設の改善を検討することを強く勧告する。例えば、国際レベルで成功させるため、出張や人事交流、重要な事務・法務活動を支援する予算が必要である。

前回のBRACで勧告に基づく、日本国内レベルの評価システムの設立は理研BRCにとって大きな前進である。日本の権威ある専門家の意見はBRACの海外委員から高く評価された。

小幡センター長の有能なリーダーシップの下で理研BRCは、大変うまく組織されており、各開発室と関連研究グループは全般的に目標を達成している。小幡センター長は、理研BRCの継続的な活動を維持するために必要な適切に調整された運営体制を構築した。

・ 評価

卓越している。

・ 特記事項および勧告

理研 BRC が、最低限、現状の予算規模で活動ができるよう、日本国政府に奨励する。現在の状況においては容易ではないが、理研 BRC の使命を達成するためには、増員が必要である。

情報解析技術室は、体制やマンパワーの制約にも係わらず、研究コミュニティに対する理研 BRC の公的な顔の役目を効果的に果たしている。当室への追加の人員によって、このようなサービス業務に加え、研究活動の可能性も高まるだろう。

リソース事業と研究事業とを調和させている現在の理研 BRC の構造は、その事業の円滑な運用と進展のために、非常に重要である。BRAC はこの構造に賛成する。研究活動なくして、科学コミュニティの要請に応える効果的なリソース整備ということはありませんからである。これは、リソースの多様化が進んでいる現時点において特に重要な点である。開発室の研究者も、関連研究グループの研究者も、ユーザーのニーズを的確に判断し、提供するリソースの世界トップレベル品質についてアドバイスを与える立場にある。この観点から、技術者に対しては、適切な評価に基づき報奨を与え、また特に優秀な技術者に対しては、テニユア・トラックの処遇を与えることを検討することも重要である。

知的基盤の改善のための基礎研究も大学や他の研究機関との連携で実施すべきである。専門知識やマンパワーの制約のため、新しいリソースの開発や既存のリソースの特性解析を理研 BRC 単独で実施することは不可能であろう。このような背景において、理研 BRC の外部に新しいリソース開発のための「サテライト」グループを構築することには意味があろう。

理研 BRC の提供事業に係わる開発室のほとんどは、中核である筑波キャンパスに配置されている。しかし、微生物材料開発室は筑波から約 100km の和光キャンパスに残ったままである。筑波キャンパスの施設の改修もしくは新設によって、微生物材料開発室を収用する適切なスペースの確保することを強く推奨する。

バイオリソースセンターとしての理研 BRC の役割が拡大していることを考慮するに、これまでとは別種の予算やファンディングの方法を文部科学省は考えるべきである。

理研 BRC は国際的な科学コミュニティのために、リソース、情報、プロトコルの標準化を確立する最大の努力をすべきである。理研 BRC がアジア各国すべてのコレクションのリソースの品質を標準化するメカニズムを提案するように、BRAC は示唆する。

理研 BRC 全体の中期計画について

・ 総論

BRAC はセンターの運営、教育・訓練、評価、その他の中期計画について同意する。特に、国際協力と教育に関する計画は特筆に値する。

・ 特記事項および勧告

本中期計画を実施し、運営の質を維持するためには、継続したファンディングが与えられることが必須である。これに加え、理研 BRC は外部資金の獲得増を目指すべきである。

理研 BRC の資源を最大限活用するためには、各々の専門性に従い BRC のリソースの特性解析を実施するサテライトを設置することを推奨する。このようなサテライトには追加のファンディングが必要だろう。

理化学研究所ゲノム科学総合研究センターから移管されたグループは、理研 BRC にとって、非常に有用な強化である。また、BRAC は、これらのグループが理研 BRC へ追加のリソースやリソース特性解析技術を導入しており、これらのグループの質について大変好意的な印象を持った。

iPS 細胞株のコレクションの増加は、ヒト由来細胞株の増加とともに、ここ数年の重要な目標となるだろう。

BRAC はさらに多くの特許を取得するよう勧める。

理研 BRC の国際的役割のさらなる発展については、ヨーロッパや米国の同じ分野の組織との連携と同様に、特にアジアの組織との連携を勧める。加えて、アフリカ、南アメリカ、東ヨーロッパの組織との連携について可能なところから推進すべきである。

海外に対する理研 BRC の広報活動や知名度の向上については、可能な部分から改善すべきである。

研修事業や人材開発について継続した配慮が必要である。

各センターAC への理事長からの諮問事項について

- ・ 科学的に大きな意義のある業績及び社会的に波及効果の大きな業績があったか？
- ・ 科学史に影響を与える業績があったか？

BRAC は理研 BRC が日本のライフサイエンス分野の基礎研究、応用研究の進展に顕著に寄与している、類のない研究資産であるということで全員の意見が一致した。マウス遺伝学、マウスミュタジェネシス、表現型解析、微生物学、リソースの保管や提供等、各分野においての理研 BRC の業績は日本の社会に顕

著なポジティブなインパクトを与えてきた。理研 BRC の科学とリソースの質の高さは、ISO9001/JAB の認証取得に反映されているように、理研 BRC の価値と重要性を証明している。結果として、理研 BRC は国際的な科学コミュニティのなかで賞賛に値する定評と信頼を確保している。理研 BRC は未来においても、より高い成果を挙げることを確実にするために、卓越した活動を追求し続けるべきである。

- ・ 他国の類似研究機関との比較及びそれに基づく改善点は？
- ・ 世界の研究コミュニティにおける理研のランクは？

世界の類似機関との比較において、理研 BRC は類のない重要なライフサイエンスの資産として高く評価されるということで BRAC の意見は一致した。コレクションの多様性と価値、生物資源の提供、そして共同研究と協力活動によって、理研 BRC ブランドは世界的な尊敬と称賛を獲得している。ATCC やジャクソン研究所のような機関と比較して、決して多くはない財政支援、狭いスペース、限られたマンパワーであることを考えれば、この業績は特筆に値する。さらに、遺伝子、細胞、動物、植物、微生物からなる比類なき科学分野の多様性が理研 BRC を世界の他機関から差別化している。このように、理研 BRC は国内から海外に至るまでのライフサイエンス研究をサポートする、価値ある欠くことができない機能を提供している世界レベルのバイオリソースセンターである。将来にわたりこのレベルの成果を挙げ続けるためには、理研 BRC は価値ある類のないコレクションを進めるとともに、便利で有益な技術を開発し、またリソースとサービスの広範な提供と利用を国の内外を問わず推進すべきである。理研 BRC は世界規模のリソースセンター・ネットワークへの融合を追求すべきである。加えて、理研 BRC はより広範な研究コミュニティに対する提供事業へと拡大するため、MTA などの方針においてより柔軟な対応の検討をしても良いかもしれない。

- ・ 理研内外における連携活動の評価及び国際化を含めた連携推進に関すること
- ・ 連携活動がより良い業績や、さらなる連携に結びついているか？

総体として、発表論文の質と量、リソースの保存数、受入数、寄託数及び提供数は、理研 BRC の科学者が理研 BRC 内、日本全国、そして世界の科学者との連携を求め、それに参加して活動していることの証明である。彼等自身の研究活動や、共同研究者やユーザーの研究プログラムを強化することを通して、理研 BRC は日本の社会の前進にポジティブなインパクトを与えている。BRAC は研究連携と協力関係の強化のためのさらなる努力が確実に行われることを提

案する。特に、理研 BRC のリソース活動、活動水準、成果を増強するような研究分野で、理研 BRC と理研の他のセンターの科学者がシナジー効果を生むことは期待できる連携関係を構築する貴重な機会がありそうである。同様に、理研 BRC の卓越した名声とインフラは、日本全国の科学者間、また同様に近隣のアジア諸国との間で連携を推進するために利用可能である。AMMRA (Asian Mouse Mutagenesis and Resource Association)の例に従えば、理研 BRC はマウス、植物、微生物を利用した研究の国際連携を強化することが可能である。さらに、理研 BRC は理研 BRC で働く科学者のリクルートを増強し、そして彼等の研修や教育の強化に努力すべきである。国際連携の展開を進めることは、このリクルートの努力を助けることにもなり得る。



The Report

The Third Meeting The Advisory Council of RIKEN BioResource Center January 19-21, 2009

1. Comments and Recommendations on Achievements and Plans of RIKEN BRC

(1) Achievements of the BRC as a whole during the last three years

General Comments

The BRC has made significant advances in acquisition, preservation, archiving and distribution of their high quality collections in the three years since their last review.

They are on target to achieve their mission of becoming an important bioresource in support of Japanese science, they are actively collaborating with other Asian institutions and their worldwide distribution has increased significantly. The BRC is becoming a well known entity in the international research community, especially in the animal resource community and are on target by taking their place in the distribution of iPS cells. This has come about through constant effort of the part of Dr. Obata and his team. This is to be commended while also suggesting continued and accelerated efforts to ensure that BRC becomes the number one resource center in the world.

It is noted that this world-leading BRC program has been established despite a consistently lower budget each year (ca 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 as comparison because they were for support of whole institutions that also did things other than providing resources. It should be noted that the Advisory Committee could not think of any other Resource Institution with the scope and quality of the BRC. This level of effort should be sustained and consideration of an increase in staff and budget in specific areas and for 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 significant administrative and legal activity is necessary.

Great progress was made by establishing a national evaluation system, a point which had been recommended by the previous Advisory Council. The opinions of the distinguished Japanese colleagues were highly valued by the international members of the Advisory Committee.

The BRC itself, under the very able leadership of Dr. Yuichi Obata, is very well organized and on the whole both the Division and Frontiers programs are achieving their goals. He has provided the well coordinated management so essential for the sustainable activity of BRC. The addition of the Mouse Phenotyping and Gene Ontology efforts are to be commended as is the ongoing and planned blending of the Microbial Division with the Tsukuba distribution efforts.

Evaluation

Excellent

Specific Comments and Recommendations

The Japanese government should be encouraged to support the activity of RIKEN BRC at least at the present budget level. Although it is not easy under the present circumstances, increase of manpower is needed to support the mission of BRC.

The Bioresource Information Division has effectively served as the public face of the BRC to the research community, despite restrictions due to infrastructure and manpower. Additional personnel would increase the possibility for research within this division in addition to their service work.

The current structure of BRC, which blends research and resource, is extremely important to its smooth operation and progress. The Advisory Committee approves of this structure because without research, efficient resources, responsive to the scientific community cannot exist. This is particularly important at this time when the variety of resources is expanding. The research/resource scientist is in a position to judge the need and to advise about the quality of the products distributed at the top level world wide. With this in mind it is also important to see to it that the technical personnel are rewarded with a clear evaluation system and a tenure track for outstanding technical staff members.

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 develop new resources outside of the BRC. 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.
- results of their activities are immediately fed back to the BRC so that the resources and information can be made available to the research community.
- these groups should be evaluated regularly to determine whether their activities should be continued as is or integrated into the BRC.

Most of the divisions involved in distribution of the RIKEN-BRC resources are sited at the core Tsukuba Campus, but the Microbe Division remains at the Wako Campus, about 100 km from Tsukuba. Renovation or new construction of proper space to accommodate this Division is highly recommended. Distribution of microorganisms may require special conditions.

Considering the increasing role of the BRC as a bioresource center another type of budget/ funding should be considered by the Ministry of Education, Culture, Sports, Science and Technology.

BRC should make every effort to establish the standards for resources, databases and protocols for the international scientific community. We suggest that the BRC proposes mechanisms to standardize the quality of the collections from and at all Asian countries.

(2) Plans for medium term of the BRC as a whole

General

The AC agrees with the mid term plans for management, training, education, valuation, etc. Especially the plans for international collaborations and education are noteworthy.

Specific Comments and Recommendations

To allow these plans to be executed and to sustain the quality of the operation it will be essential that continuous funding is provided. In addition the BRC should try to increase external funding from grants.

To make optimal use of the resources of BRC the formation of satellites that characterize according to their specialty these BRC resources, is recommended and may need additional funding.

The groups taken over from the RIKEN Genomic Science Center provide a very useful addition to BRC and the Advisory Council has an excellent impression of the quality of these groups, which provide additional resources and technologies to characterize these resources.

Increasing the collection of iPS cell lines may be an important goal for the coming years, as well as increasing the number of human cell lines.

We recommend trying to obtain more patents.

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.

Public relations and visibility of BRC to the outside world should be improved where possible.

Training and human resource development requires continuous attention.

2. Responses by the BioResource Center Advisory Council to the Terms of Reference from President of the RIKEN

(1) Are there achievements with major scientific significance or achievements with significant social impacts?

- Are there achievements which will be notable in the history of science?

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. Their achievements in the fields of mouse genetics and mutagenesis, phenotypic analysis, microbiology, and protection and distribution of resources have had a substantive positive impact on Japanese society. The quality of BRC science and resources, as reflected by ISO9001 accreditation and JAB, is 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.

(2) How does the Center compare with similar research institutions abroad? Make recommendations for possible improvement based on this investigation.

- Where does RIKEN rank in the worldwide research community?

Compared to similar resources worldwide, the Advisory Committee 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 resources, such as ATCC and The Jackson Laboratory. Further, the unique diversity of scientific areas, from genes, cells, animals, plants, and microorganisms, sets 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 throughout 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 MTA, in order to increase

distribution to a broader research community.

(3) Evaluate the Center's collaborations within RIKEN and with outside institutions, and evaluate the Center's effort to promote international collaborations.

- Are the Center's collaborations resulting in better research achievements and more contribution to society?

In general, the quality and quantity of publications, and the number of accessions, depositions into, and distributions, are evidence that BRC scientists actively seek and engage 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 Committee suggests that additional efforts to enhance research collaboration and cooperation are warranted. Specifically, there are likely great opportunities to develop synergistic relationships between BRC and other RIKEN scientists on research areas that will enhance BRC resource activity, performance, and output. Similarly, the outstanding reputation and infrastructure of 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 mouse, plants, and microorganisms. Further, the BRC should work to increase recruitments, and to enhance the training and education of scientists who work at BRC. Developing international collaboration can also help this recruitment effort.

3. Specific Comments and Recommendations to Divisions and Teams on Policy and Practice

A. Experimental Animal Division

Description

The Experimental Animal Division of the BRC is a valuable asset in support of biomedical research in Japan and the world. Important mouse collections have been solicited and accepted into the Division, such as the collection from the Mitsubishi Institute, and the collection of wild-derived mice from the National Institute of Genetics, Mishima. A variety of other mouse models is very important and useful for research into human clinical regenerative medicine, as they provide a means to study the biology of various stem cells, such as somatic stem cells, ES cells and iPS cells. The scientific and societal value and importance of the mouse collections is supported by the number of published papers in prestigious journals, such as Nature and Science.

Achievements

The Division is to be commended for its impressive list of achievements and successes. It has responded efficiently and effectively to the advice of the 2006 BRAC. The Division has made excellent to outstanding progress in archiving and distributing valuable mutant mouse strains, preserving and maintaining mutant germplasm and gene trap embryonic stem (ES) cells, providing useful data and information (e.g., genetic differences in C57BL/6 strains) to the research community, and expanding their capacity and capability to manage an increasing number of mutant mouse strains under development. The growth in diversity and number of mouse strains in the Division is particularly impressive, and the trajectory for continued growth appears appropriate. The effectiveness of efforts to enhance their visibility is reflected by the number of successful collaborations with Japanese scientists and international researchers and organizations, such as FIMRe. In addition, the Division appears to be successfully interacting and collaborating with other BRC Divisions, notably the Bioengineering Division. The Division should also be commended for applying risk management practices to protect their valuable collections, by duplicating the archive at a distant site. Overall, the BRAC unanimously agrees that the Division has demonstrated an outstanding level of accomplishment during the last 3 years, and their achievements have exceeded all expectations. In addition, the BRAC would like to point out that the Division is one of most successful and well-managed within the BRC, operating with very high quality and standards under the capable leadership of Dr. Yoshiki. The

leadership of the Division can serve as a model of excellence for other Divisions within the BRC.

Recommendations

The BRAC agrees with the recommendations of the Resource Committee, from late 2008. In particular, the BRAC recommends that the Division seek an even more active role in serving the international community, especially in Australasia and America. In addition, considering recent successes in developing rat ES cells, the Division should consider cooperating or collaborating with Dr. Serikawa in Kyoto. Further, although there appears to be adequate space and security, the BRAC recommends modernization of the facilities to preserve and protect their valuable collections. The Division should also establish specific criteria for evaluation and acceptance of mouse strains, and seek user feedback , such as through electronic surveys. The Division should reconsider the necessity to maintain so many hundreds of mouse strains as live mice, and instead consider maintaining all but those with special genetic backgrounds and those in greatest demand as frozen stocks. Also, if there is any question as to the demand for DNA and tissue resources, the Division should conduct a cost/benefit analysis to determine whether to continue to archive frozen tissues and DNA for distribution. Further, now that the Division has successfully responded to the recommendations to increase their operational capacity, more efforts should now be expended in the area of quality control and standardization as soon as possible. Finally, the solicitation and development of other mouse models, such as CRE transgenic mice, NOD/SCID mice, and conditional knockout mice, should be pursued, but in context and in cooperation with similar efforts around the world.

B. Experimental Plant Division

Achievements

The BRC plant division is well established as one of the three main Arabidopsis resource centers which distributes Japanese resources that are complementary to the other available resources.

The improvement of the databases has been very useful and needs to be continued. The establishment of the new SABRE and ABRANA is an important achievement.

Progression and Recommendations

It is important that these updated data sets are well connected to the Arabidopsis

Information Resource (TAIR) database.

The addition of the FOX (full-length over expressed) lines and making homozygous transposon tagged lines is very useful. A newly started collection of cultured cell lines of Arabidopsis would be useful, too.

The genotyping of the wild accessions from the present SASSC (Sendai Arabidopsis Seed Stock Center) collection has been useful. However it is suggested to contact the group of Dr Borevitz who is genotyping all available wild accessions with a standard set of 149 SNP markers at low cost.

This will allow the comparison of the genotypes that might be present in the Japanese and the collections present in the other stock centers.

It might be of interest to increase the wild accession collection, especially of those native to Japan.

The group started to expand their effort to the Brassica rapa (Chinese cabbage) by comparing the gene expression of similar mRNAs in both Arabidopsis and Brassica as an example of comparative genomics. It may be useful to expand the resources for Brassica rapa corresponding to the growing interests for agricultural research. To make a Brassica rapa stock center requires consideration of which genotypes will be collected (only Japanese or more widely) and will require embedding in a Brassica research committee and integration with the efforts elsewhere (Korea, China and the UK).

A main focus of the international collaboration will be organization of the international Arabidopsis conference in 2010.

Establishing interaction with other Asian stock centers and collections is a very useful goal but may be complicated by the lack of structure in the most relevant countries (Korea, China and Taiwan).

C. Cell Engineering Division

Description

The Cell Engineering Division has a very large collection of cells that they distribute nationally and internationally. In addition to human cancer cell lines, immortalized B cell lines and human primary fibroblasts, there are special collections that are notable. Examples are:

- The Sonoda-Tajima collection, of interest to understand genomic changes during the migration of early man .
- Human and mouse iPS cells.
- Umbilical cord blood and mesenchymal stem cells, also for basic research

- Mouse ES cells from many different strains.
- Macaque ES cell lines.

Achievements

An excellent combination of research and resource work that is both elegant and diverse.

This group, under the able leadership of Dr. Nakamura, is to be commended for their work distributing these cells nationally and internationally. Most notable are:

- Development of a quality control system consisting of STR and SSLP analysis to prevent distribution of cross contaminated cell lines
- Mycoplasma testing to ensure the distribution of uninfected cell lines
- Rich collections now available for researchers, a great resource for Japan and a great stimulus for Japanese and international research.
- Their swift action in making human and mouse ES cells, and now human and mouse normal iPS cell lines, available to all researchers highlights the efforts of the BRC in significant and diverse areas of research.
- Distribution to the international community of researchers, the result of their number of publications in high quality journals and oral presentations at important international meetings
- Recommendations by the internal evaluation committee have already been taken into account
- Conversion to ISO 9001 went smoothly
- The distribution of iPS cells to basic researchers will have a long term social impact as they develop the possibility of cell-based therapies based on ethically acceptable human iPS cell lines

Recommendations

This group should continue on the trajectory they have established but also encourage researchers to use their current and planned collections

- This is the right time to enable research on stem cells. The preparation and collection of iPS from diseased patients may be very useful and should be encouraged and this division should lead the standardization and characterization on human iPS cells for Japan.
- The Sonoda-Tajima collection will be useful in the genomic studies being undertaken by the RIKEN sequencing facility in Yokohama.
- Keep up the efforts on publicizing the resource to the international community and make these results available.

- Continue enriching the cell collections.
- Continue collaborative work with scientists to characterize unique cells, especially iPS and adult stem cell types.

D. Gene Engineering Division

This division appeared very active, and the DNA resources provided are unique (and accordingly invaluable!). It is also developing a series of important technologies for further use that may have an important impact both inside the BRC and outside of it. It also deals with many essential aspects of functional genomics.

Two of the three team leaders will resign in the forthcoming months and this situation appeared as a very serious concern for the advisory committee. The Director informed the Committee of his intention to prepare plans to insure continuity in the activities of this division in spite of this abrupt transition. The Advisory Committee will comment on these plans when they are ready.

Members of the AC suggested that DNAs from characterized species be accompanied by sequence information by taking advantage of the new-generation sequencing now available in RIKEN Yokohama

E. Microbe Division / Japan Collection of Microorganisms

Achievements

The division has made good progress in collecting, preserving and distributing the microbial strains including type strains. The division should be highly commended for playing a leading role in JSCC (Japan Society for Culture Collections of Microorganisms), Asian Network of Microbial Researches and WFCC (World Federation for Culture Collections of Microorganisms) since its establishment in 1978.

Recommendations

The AC recommends that this division:

- Consider the promotion of its development in the fields of human-health and environmental microbiology. It is necessary to establish a cooperative relationship with relevant scientific societies and researchers, while taking into account microbiological trends in the next five to ten years in the fields of environment and human-health sciences.

- Continue to play a leading role in international and national networks of microbial resources.
- Establish a human resource development system to solve the shortage of young scientists in this division. The ongoing mentorship of new curators and investigators is important and commendable.
- Transfer the division from Wako campus to Tsukuba campus for efficient operation of the BRC and build a new facility without any deterioration of infrastructure.

F. Bioresource Information Division

Achievements

The success of this division is extremely important to the success of the BRC in its entirety and there is an increasing amount of new work as well as maintenance of the already established databases. It is difficult for the current team to maintain their level of activity and accomplish the vast amount of work to be done. There are too few people available and these people must be able to interact with the national and international life science community. Even with these difficulties this team is accomplishing their tasks very well, with insight and good sense. It is noteworthy that the web catalogs of the various resources as well as a one-stop shop system etc. have been developed in a short period of time with limited manpower. This is excellent work.

Progression and Recommendations

The last BRAC recommended promotion of their own research activities, because it was thought better to develop new technologies based on the results from innovative research. However, it is apparent that service-oriented research is not realistic in this division and that the required service component leaves little time for staff members to do their own research. However, it is important to try to make this division attractive for young people who are interested in bioinformatics. A balance between “service” and “research” should be considered. Routine work should be separated from the main division work and may be outsourced if an appropriate vendor can be found. It is an appropriate time to rethink what to do and what not to do. Therefore the present AC recommends the following infrastructure and important services that should be continued:

1. Intramural bioinformatics education so that other teams can share the simple duties
2. Advertisement of BRC

G. Bioresource Engineering Division

Achievements

It is extremely important to develop the technologies of germ-line and stem cell engineering. This division has made enormous achievements in development of technologies, such as cryopreservation and intra cytoplasmic sperm injection (ICSI). Through these achievements this division has contributed to the core operation of banking activity in the BRC. They have also made remarkable accomplishments in basic science, including reproductive biology and stem cell biology. Overall, their achievements in the last three years are outstanding, and we judge that this division is a world-leading group in this field. We also highly commend the following achievements:

- Technology of nuclear transfer
- Organized technical training course

Recommendations

It is a good idea to classify the plans into three categories, depending upon its difficulty to achieve. It would help to make it clear how their efforts should be allocated to each plan. As a whole, they have enough experience to pursue their plans. There are many good opportunities for this division to work on, so one of our concerns is that limited budget and manpower will require prioritization of the plans in the future. One possible project that may be pursued only if time permits is preparation and preservation of rabbit ES cell lines in the BRC. However, if there are specific subjects to be addressed with the rabbit ES cell line, their plan will be supported by the community. In the same sense, more consideration may be needed of the plan to produce ES cell lines from C57BL/6 (B6) sublines, because B6/N-derived ES cell line is already available in the community.

H. Technology and Development Team for Mammalian Cellular Dynamics

Description

Dr. Kuniya Abe's work is a nice mix of research and resource development consisting of techniques for analyzing genomic diversity and cell dynamics in vivo. This group has investigated using the genomic diversity between the wild mouse, *M. m. molossinus*, and the standard laboratory inbred strains to explore control of complex traits. They have also devised an intravital laser scanning microscope with Olympus devising a

stabilizing stage for fluorescence in vivo phenotype analysis and they have prepared tagged constructs to explore epigenetic changes in living cells undergoing differentiation.

Achievements

- Excellent publication record
- Great diversity of approaches
- Distribution of M. m. molossinus BACs which have been used to detail the mosaic nature of the B6 genome.
- Impressive imaging technology, development of intravital laser scanning microscopy, and a stabilization device to capture clear pictures in living animals
- Excellent collaboration with commercial companies

Recommendations

Good future plans

- If Dr. Abe's team can obtain results on either genomic imprinting, or X-inactivation and reactivation, or finding new monoallelically expressed genes, they will be highly recognized, bringing credit to the BRC.
- The proposed high density SNP chips and BACs will be useful to many who are analyzing complex traits in mice
- Noninvasive FMT should prove valuable to many research collaborators

I. Technology and Development Unit for Mouse Phenotype Analysis: Japan Mouse Clinic

Description

The Mouse Phenotype Analysis team, also known as the Japan Mouse Clinic, will provide high-throughput and comprehensive screening of mutant mouse models. Test animals will come from the mouse ENU mutagenesis program, formerly at RIKEN-GSC. In addition, test animals will also be accepted upon request from researchers outside the BRC on a fee-for-service basis. Further, considering the great increase in numbers of mutant mouse lines, the Clinic will be especially relevant and useful. In this way, the Clinic will prove to be a very valuable service and likely contribute significantly to the Japanese biomedical research community.

Achievements

The Clinic has made excellent progress and appears to be developing quite well. There has been substantial coordination with similar international efforts. Offering on-demand services to researchers outside of RIKEN adds substantial value to the BRC, but could also prove overwhelming. Further, while the goal of this team is obviously interesting and the performance to date excellent, it is still too early to fully evaluate the success of the Clinic.

Recommendations

The BRAC agrees with the recommendations of the Resource Committee, from late 2008. In particular, plans to manage the demand for analytical services should be developed as soon as possible. Also, criteria should be established to prioritize strains to be analyzed in the Clinic. In addition, imposition of user fees should be considered to help defray and recover operational costs. This team should engage in greater cooperation with the BioResource Information Division to implement and maintain the “phenotype database”. It is important to link the description of mutants with research prompts that will follow up the study of specific mutants. It is also necessary to coordinate genotyping platforms. It will be important for Dr. Wakana to work thoughtfully while engaging in cooperative efforts with other international Mouse Clinics. For example, the careful selection of mouse strains for analysis will be very important to demonstrate the usefulness of the Clinic to all, including international partners. Further, the approach should be regularly re-examined with relation to the research environment to ensure optimal operation.

J. Technology and Development Unit for Knowledge Base of Mouse Phenotype

This small team is undertaking the important although ambitious project of developing a new database connecting human diseases information and mouse phenotyping data with the ultimate aim of relating pathology in both species with gene ontology. The Advisory Committee trust, that one can seriously expect interesting achievements in the future. The Advisory Committee also considered important that contacts were already established with other groups working on similar subjects in Europe and the USA. The Committee also recommends that advice be requested from potential users of this database with the aim to make it rich, useful and user friendly at the same time.

K. Subteam for Biosignal Integration

Achievements

The group of Dr Doi is focusing on the study of the NF-kB signaling pathway and has collected and developed a unique set of KO lines that his group is using to describe the role of this pathway in various processes.

Recommendations

The review committee raised a number of issues including focus and collaborations outside the BRC. These issues have been addressed by the decision of Dr Doi to focus on inflammatory diseases. Together with the currently developed conditional KO lines the group has available excellent materials that can be a basis for collaborations and these materials add to the unique resources of BRC.

L. Subteam for Manipulation of Cell Fate.

Description

Dr. Miyoshi is the subteam leader of a group that investigates: genes of importance to human hematopoietic stem cell self renewal; lentiviruses for gene delivery; iPS characterization. They are focusing on identifying signaling pathways controlling stem cell fate and will use this knowledge to develop tissue specific cell therapies.

Achievements

- Excellent publication record
- Excellent distribution record
- One gene, Tmem140, of the 133 they identified to be involved in either differentiation or maintenance of human hematopoietic stem cells has been identified to induce proliferation of hematopoietic stem cells in vitro. This gene has been patented and more are in the pipeline. This is an important finding.
- Great progress on development and distribution of lentivirus vectors for safe use in P2 facilities
- Good work with several other groups such as the Cell Bank and the DNA bank, an excellent marriage of Research and Resource Center work
- Good collaborations outside of BRC have been established

Recommendations

- Continue screening the candidate genes that influence hematopoietic stem cell differentiation or self-renewal in both human and mouse. This is important work.
- Develop a quality controlled technology using both chemical treatment and vector-delivered genes to efficiently reprogram specific cell types or lines to iPS cells at higher average frequency than can currently be achieved.
- Transfer the Fucci gene into a human ES cell for distribution to the scientific community.
- Provide human cells or the vectors for preparing iPS cells with genes suitably marked to understand the differentiation state – Gene Engineering Bank.
- The committee agrees with the decision to abandon somatic cell nuclear transfer as a technique for use at this time.

M. Advanced Development and Evaluation of Human Disease Models

Description

The Advanced Development and Evaluation of Human Disease Models project will enable elucidation of the genetic mechanisms of many diseases in mutant mouse models. This project will seek to enhance the value of the mutant mouse models for the research community. The goals for establishing methods for presymptomatic phenotyping, and modern mouse models for human cancers are fully appropriate for the BRC. Thus, it is hoped that these methods and models will enhance the value of research and contribute to the advancement of translational research. Metabolomic analysis is novel and promises to enhance the development of mouse models for human diseases.

Achievements

The project team has made outstanding progress and appears to be developing quite well. The project is very ambitious and elegant, and one of the leading projects at the BRC. Excellent results have been achieved thus far. Development of technology for NMR-assisted metabolite and multiplex-cytokines measurement system appears to be of great value.

Recommendations

The BRAC agrees with the recommendations of the Resource Committee, from late 2008. In addition, the plans seem to exceed the budget supplied. Therefore, the team should work to ensure continued financial support for this project for the planned period.

More and closer collaborations will be needed with other groups at the BRC and with other research institutions in order to achieve their goals. To verify the effectiveness of their pre-symptomatic phenotyping approach, the team should compare their findings in the same mouse line once it develops overt symptoms.

N. Mutagenesis and Genomics Team

Description

This division has generated a very large collection of mouse mutations by gene driven ENU mutagenesis. These mutations are stored at (virtually) no cost in liquid nitrogen tanks and can be retrieved when desired by thawing up the semen samples. The collection is steadily increasing and it can be predicted that in a very near future almost all mouse genes will be potentially affected by one or more mutations of this kind. Annotation of the mouse genome will then benefit greatly of the strategy that must be considered complementary to the generation of mutation in ES cells by genetic engineering rather than alternative.

Achievements

The Advisory Committee considers that this team is a major addition to the already existing RIKEN bioresources. The strategy developed by the team leader will be of large benefit to the mouse community since a collection of 10,000 samples of G1 sperm cells and associated DNAs makes potentially available mutations of all kinds (and not only knockouts). It also makes visible BRC as an even more important research center for mouse genetics world wide.

Recommendations

Collaborations with other centers, both inside and outside RIKEN, are encouraged at several levels and particularly to enhance further the efficient detection of mutation at the DNA level. Since the division settled in Tsukuba only recently the Advisory Committee strongly recommends more important funding to allow a quick development of the 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 frame of a cooperative project.