

The 17th Resource Committee of Cellular Materials
Evaluation and Suggestions

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Division/Team Name: Cell Engineering Division

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1. Achievements and plans for the Division

(1) Have the current achievements reached the standards of those made by the major international bioresource centers?

- The achievements by the Division are evaluated as high as those by related other international biorepositories.
- The Division has collected the world's largest number of cell lines, which makes it a global leader in bioresources.
- The Division has several unique advantages compared to other centers as described below, and hence should be highly evaluated.
 - The Division has collected and is ready to distribute a large number of Epstein-Barr virus (EBV)-transformed B cell lines developed from healthy Japanese. It is extremely important that human leukocyte antigen (HLA) information is attached to the cell lines. Even if similar collections or even larger collections were established in other countries, it would still be a significant collection as a diverse repertoire of Japanese HLA.
 - Sonoda-Tajima collection, EBV transformed B cell lines collected in various countries from the Pacific Rim, Eurasia, and Africa are expected to have great significance in the future, as the development of evolutionary biology has been remarkable in recent years.
 - The Division has also collected B cell lines derived from patients with cancer and those with rare diseases such as Werner syndrome.
 - The Division is distributing several different preparations of human umbilical cord blood-derived cells, i.e., nuclear cells, mononuclear cells and CD34+ cells.
 - As for pluripotent stem cells, the Division has provided a large number of mouse embryonic stem (ES) cells, which contributes to infrastructure for basic research. Moreover, the Division's contribution by distributing human ES cells and disease-specific induced pluripotent stem (iPS) cells as national bioresources is not limited to basic science, but extends to the development of practical application.

- As a member of the International Cell Line Authentication Committee (ICLAC), the PI is actively warning not to use misidentified cell lines and emphasizing the importance of quality control (QC). The Division is not only world-leading in the numbers of cell collections and varieties, but has also reached the global standards for QC as it has acquired ISO9001 certification. In addition, the Division is contributing to improving the quality of global cell banks and research.
- The research activities unique to the Division have been carried out and improved global recognition of the Division.
- The Division's projects collaborating with other BRC divisions that deal with mice and genes will lead to efficient operation of the center and improved its strength by novel resource development. This is considered unique advantage of BRC. The Division should keep on actively promoting such collaborating projects.
- To demonstrate its presence globally, it might be necessary to promote domestic and international distribution more actively.

(2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?

- The Division is distributing high-quality bioresources to large number of academic institutions and companies within Japan and overseas. Their contribution to domestic community can be evaluated as significant. However, the achievements in the international position are slightly insufficient.
- There are a considerable number of published research papers and patents by using the cell lines supplied by the Division, which indicates that the Division making a sufficient contribution to society, as well as to research community.
- The Division's initiative against misidentified cells can be evaluated as significant in QC.
- Besides handling their deposited cell lines with strict QC, the Division is consistently raising awareness of researchers for microbial and contamination with other cell lines. This makes an extremely large contribution to the improvement of the quality of research in our country. A striking example by the continued supply of properly-quality-controlled cell lines is its contribution to a Nobel prize-winning results.
- The Division's efforts to regularly host technical training courses which are expected to boost the number of users. It is a laborious activity, but it is hoped that the Division to continue the course by all means. Nevertheless, for accurately evaluating the Division's contribution by the technical courses, specific information including the number of participants and their occupation need to be presented.

(3) Are current activities and plans based on the results of the 3rd Mid- to Long-Term Plan or the achievements in the previous position? Are they in line with the BRCs 4th Mid- to Long-Term Plan (7 years from 2018 to 2024)? Are they appropriate and do they contribute to the development of the center?

- Their activities and plans are based on the achievements of the 3rd Mid- to Long-Term Plan and are in line with the 4th Mid- to Long-Term Plan. They are appropriate and expected to contribute to the further development of the center.
- Though flexible responses may be required in the activities in some occasions within this 7-year period, the Division has the capability to actively respond to the new knowledge and development.
- The infrastructure has been established for a stable supply of cell resources such as modified ES cells and disease-specific iPS cells that are expected to be requested more.
- New research teams have been established to investigate the characteristics of iPS cells and to promote their application. The foundation has been established for developing new cell lines through application of genome-editing technology. These are expected to contribute to the further development of the center in response to the increasing diversity and acceleration of stem cell research in the future.
- There is a lack of awareness on the importance of clinical information. The expanded application of genome editing was planned, but it is not necessarily regarded as established technology, and therefore the Division needs to assess to what extent BRC should proceed and whether this is feasible with the current number of staff.

(4) What are resources to be developed and research/technological development to be undertaken in addition to those currently planned in the initial 4th Mid- to Long-Term Plan?

- The Division has established significant infrastructure with regards to cancer cell lines. It is recommendable that the Division should make more efforts toward clinically useful materials such as patient-derived xenograft models (PDX).
- Establishment of a system to share clinical information for a wide variety of diseases is extremely difficult. For sharing clinical information, the Division should consider cooperation with existing disease registration systems.
- The enrichment of resource information is very important. In order to add more information, it is essential to handle various data in an integrated manner, including cooperation with existing databases, although it may be difficult to do all by themselves. Information on the relationship between diseases and resources is particularly important. Such information is sensitive personal information, but it is most significant for the research indispensable for promoting public health and medical care, and therefore it is recommendable that the Division to actively address this

issue.

- The integration of clinical information of donors of cell lines with omics data, such as the genome and transcriptome data, should be further promoted. The former information is steadily integrated, and the Division should focus on the latter. For example:
 - Exome sequencing costs less than 100,000 yen even if outsourced. It is recommended to introduce such sequencing, giving priority to the cell lines that are heavily used. This may lead to enhanced QC.
 - Data of single nucleotide polymorphism (SNP) typing should be attached to disease-specific iPS cells. Research using disease-specific iPS cells has been designed with a comparison of a cell line derived from patients with a disease, with that from healthy individuals. While this is useful for pathogenesis is directly associated with genetic factors, this is not necessarily useful for diseases with multiple environmental factors or multifactorial diseases. Therefore, recent approach of research incorporates grouping and comparison of patients based on the presence or absence of disease-susceptible SNP, rather than comparison of patients with healthy persons. Therefore, it would be significantly beneficial to be able to respond to user's order like "I would like to have 3 cell lines with rsXXXXXX C allele homo, T allele homo, and CT hetero." This will also lead to utilization of the results of the many GWAS performed in Japan.
 - Such an approach will promote research and drug discovery for multifactorial diseases. Large population of target patients with multifactorial diseases provides possible large market opportunities that highly motivate companies. A large number of patients will be benefited, and thus, it is expected that the contribution attributed to bioresources will be dramatically enhanced.
 - With regard to transcriptomes, Japan has a world-class cap analysis gene expression (CAGE) technology. By collaborating with the Functional Annotation of the Mouse (FANTOM) team, they will definitely obtain data to be internationally accredited. This will also lead to the creation of a more stringent catalogue of cell phenotypes.
 - Since importance of immunotherapy for cancer patients and transplantation is increasingly emphasized today, enrichment of HLA information has a great significance.
 - The Encyclopedia of DNA Elements (ENCODE) is an international integrated platform for omics data. If these data were linked with bioresources, then a truly unique global platform would be created.

Financial resources for implementing the aforementioned items may include increase of the in-house budget or establishment of projects funded by the Japan Agency for Medical Research and Development (AMED). However, specific proposals should be drafted by BRC.

- It is important to prepare modified ES cells and disease-specific iPS cells with high efficiency for the banking without sacrificing quality. The Division needs to examine the whole process to make it more efficient or to automate the cell preparation. Kawasaki Heavy Industry's equipment might be effective; but if their stable support cannot be obtained, another automation system should be searched.
- It is recommended that the Division should examine the efficient promotion of bioresources utilization by collaborating with companies or corporate groups.

2. SWOT analysis

(1) Are the results of the presented SWOT analysis valid?

- It is considered to be adequate.
- However, it could be analyzed with a larger perspective. The suggestions mentioned above in (4) could also be incorporated into the Opportunities. More items can be listed as Strengths.
- This may be too specific, but for example, the Sonoda-Tajima collection is a great Strength and they could aim at global coverage in the future if they could incorporate cell lines from Europe. If the HLA information and other accompanying information are gradually expanded, this can be included as greater Opportunity.

(2) Are the countermeasures for the results of the SWOT analysis appropriate?

- The countermeasures are appropriate.
- The countermeasures could be analyzed with a larger perspective.
- To maintain a system for preserving and distributing iPS cells is a national project for the development of science and technology in Japan, and hence we would like the Division to ensure constant funding.
- The AMED disease-specific iPS cell bank project is scheduled to be terminated in 2019. Continued support is required. The Division should keenly ask for understanding the necessity.
- Regarding the project that follows the ongoing one, partner should not only be limited to AMED but various opportunities need to be sought urgently, for example, with other agencies or as other projects and joint research with companies.

3. International collaboration

- ### (1) Is the international collaboration being actively addressed, and is the Division functioning as a hub of international scientific technology?

- The Division is actively working on and acting as an international hub for science and technology.
- As an ICLAC member, the PI is globally contributing to the improvement of research resources by enlightening the importance of improving the quality of cell lines as well as importance of the QC within each biorepository.
- Information concerning international collaboration is slightly scarce. We would like the Division to broaden the scope of international collaboration by actively sharing technology and information. With the presence of many similar international organizations, the Division should consider how to demonstrate the uniqueness of RIKEN BRC.
- As some international frameworks are needed for enhancing collaboration on resource information in the future, it is recommended that the Cell Engineering Division should ensure that it can lead global research community as it holds a world-class large number of disease-specific iPS cells.

4. PI assessment

(1) Is the PI fulfilling the role in line with the BRC mission?

- It is evaluated that Dr. Nakamura is fulfilling the PI's role in line with the BRC mission.
- The PI is not only committed to the operation with the cell line collection, but he has also rapidly incorporated disease-specific iPS cell lines into their collection, based on the trend that indicates increasing necessity and potential demand in the future. The number of publications by the users exceeds 1000/year and that of patents exceeds 100/year, which demonstrates the Division's constant contributions to all study fields from basic science to applied research. The PI is continuously raising the awareness of the importance of preventing microbial contamination and cell misidentification in appropriate handling of cells. As an ICLAC member, the PI is also contributing to the spread of proper research environments through international cooperation. Thus, Dr. Nakamura is fulfilling the PI's role at high level in accordance with the BRC mission, and these activities are serving the national interests.

(2) Do the PI's achievements in research and development (R&D) satisfy international standards in light of the following three aspects? (i) Results output and impact, (ii) Contribution to specific missions of each laboratory regarding research support and collaborative exchange programs within RIKEN, (iii) Pioneering new fields of research, acquisition, and commercialization of intellectual property rights, social education for science, the fusion of different fields, and social contribution

- In each item, the PI's achievement has sufficiently met international standard.

- The PI's noteworthy achievements and the items to be conducted for future improvement are as follows.
 - (i) It is necessary to take some measures to increase the number of distribution in the future and to improve the efficiency of operation by promoting active use of preserved bioresources.
 - (ii) The PI is hosting regular training courses on human ES/iPS cells to support domestic research foundation.
 - (iii) The PI's contribution to society is regarded as significant as he serves as a member of the Expert Committee of Specified Embryonic Research, a subcommittee of Bioethics and Biosafety organized by the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) and he is committed to making national guideline policies and deciding future directions as an expert in the management and operation of bioresources.
 - (iv) It is necessary to improve the efficiency of operation by actively obtaining and commercializing intellectual property right and promoting fusion of different fields.

(3) Is the PI appropriately tackling the management and operation of the Division? In addition, does the PI make efforts for training and development of young talent?

- The PI is appropriately committed to management and operation of the Division as well as the training and development of young talent.
- The training and development of young talent is considered to be a particularly difficult issue; however, it is recognized that considerable efforts have been made and rewarded by achievements.
- We consider that human resource can be developed by making the best of special characteristics of the operation performed by the Division. We expect young talents not to stay in BRC but to take an active role in the world.
- It is desirable to examine how to develop the potential of mid- to senior-level staff, more specifically, how to develop human resources who can succeed current PI or act as his substitute in certain situations and how long it takes.
- The PI is striving to improve the careers of senior staff and to secure human resources. The International Air Transport Association (IATA) courses and training on ISO9001 are also regularly performed, which serves as a basis for maintaining the integrated world-class biobank. We expect the PI to actively promote further improvement and reform of the project operations with an awareness of the Plan-Do-Check-Adjust (PDCA) cycle and to give us a report about his highly-motivated staff members actively participating in the project.

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