

**The 1st Review Committee of iPS Cell
Evaluation and Suggestions**

(February 14, 2019)

Division/Team Name: iPSC-based Drug Discovery and Development Team
(Haruhisa INOUE, Team Leader)

1. Achievements and plans for the Team

- (1) Have the current achievements reached the standards of those made by the major international bioresource centers?
- The Team has established differentiation induction techniques and various cell evaluation techniques necessary for an approach making use of disease-specific iPS cells. The Team has produced most excellent results in this field. The Team's status is assessed to be a top-level laboratory of the world.
 - In addition to banking the world's largest number of disease-specific iPS cells, it is also commendable that the Team has been disseminating methods for the use of the iPS cells. Dissemination of the information on "development of the basic technology for drug discovery, using iPS cells" by publication of many papers is also highly regarded.
 - As a member within the BRC, the Team may be able to execute research and offer contributions with comparatively few problems. Nonetheless, the Team needs a thorough examination of and focus on what should be done as a BRC-related projects.
- (2) Have sufficient achievements been made for contributing to society and to the research community within Japan and overseas?
- Research has already been advanced to the development of disease-specific iPS cells to delineate the causes and processes of diseases. The Team has started to develop fundamental technologies for drug discovery using disease-specific iPS cell. Research has been carried out with a good balance between diseases with many patients worldwide, such as Alzheimer's disease, and rare diseases. It is hoped that this Team will make great contribution to social benefits. Although specific results have yet to be delivered, openness toward seeking collaboration with pharmaceutical companies is commendable.

- The Team has a track record of registering valuable disease-specific iPS cell lines in the global stem cell bank network. This is recognized as an extremely valuable contribution to domestic and international research communities. Activities for promoting use of iPS cells by research communities, such as by giving shared ID numbers are laudable. Regarding iPS cell lines deposited in the bank of overseas, It is hoped that the Team will continue the effort to establish mechanisms enabling Japanese researchers to use them in the same manner as those lines held by RIKEN BRC.

(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 BRC's 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?

- The current plan and achievements are in line with the 4th Mid- to Long-Term Plan. In terms of use and application of the disease-specific iPS cells, its contribution to the BRC's overall plan is high.
- Based on the achievements, R&D have been conducted appropriately, i.e., in accordance with the plan and with the mission of the iPSC-based Drug Discovery and Development Team. High levels of contribution are expected to continue in the future.
- It is hoped that the Team will take the lead in the use and application of the disease-specific iPS cell resources held by the BRC. For this, validating usefulness of disease-specific iPS cells in drug discovery and pathophysiology research is essential. Presenting successful results to researchers in Japan and overseas will further contribute to the center.
- Guiding users who wish to carry out “bridge research using disease-specific iPS cells” is a commendable future goal. Since “URS analysis of companies” and “consideration for reduction of cost, time, and effort reduction targets in technology under development” are as yet insufficient, these efforts must be continued.

(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?

- Even if the Team focuses on disease-specific iPS cells specialized for the nervous system, it is practically impossible to study all of iPS cells. The strategy of the research and development is needed to be well planned. However, in the case of this Team, it may be important to show not only the utility of cell resources, but also to develop and present methods of analysis and evaluation of iPS cells.

- The Team should focus on producing clear results by developing fundamental technologies in order to build a platform that many researchers can utilize. As an example, development of an assay system using multi-electrode arrays is consistent with this objective.
- Collaboration with researchers in the engineering field (particularly in the evaluation of cells) should be prioritized over the targeting of many diseases.
- It is desirable that the Team to sort out many methods for cell differentiation of the various organs developed in Japan and overseas. Moreover, it is necessary to advance the consideration of how various organ cells are “organ-like.” This will allow researchers to begin examining target values for methods of differentiation induction.
- Given the progress in establishing a drug discovery platform using human disease-specific iPS cells, it is also important to develop banking of control iPS cells of healthy donors and of normal organ cells as references.
- While not a biological concern, rare diseases with few patients require special solutions incorporating socio-economic science perspectives. These solutions should be shared among researchers as methods for providing cure to patients.

2. SWOT analysis

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

- They are reasonable.
- Next time, it will be needed to analyze this Team from the perspective of whether the projects contribute to the BRC.
- In relation to O, the Team must describe more specifically the needs of the iPS model in the drug discovery field, for example, appropriate selection of target organs/disease/market size etc. Also in relation to O, the PI should analyze what S and W are for the Teams. In section T, it is necessary to record analysis of external factors that may reduce the Team’s originality. It is likewise important to record any social circumstances/behaviors that may hinder the Team's mission within RIKEN BRC.

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

- It is an appropriate.
- Based on the analysis of results, the necessity of further reinforcing S should be recorded. If strengthening is necessary, then the policy should go along with it. Alternatively, continuation of the current state may be desirable.
- In relation to W, more specific targets to be improved should be recorded. Whether the above policies for S and W are also appropriate for the self-analysis of O and T should be considered and

recorded.

3. International collaboration

- (1) Is the international collaboration being actively addressed, and is the Team functioning as a hub of international scientific technology?
 - There are many international joint studies, and international exchange is being addressed actively. Thus, the Team is functioning as an international hub for science and technology.
 - The Team already has a high international profile in the form of numerous paper citations, requests for cell lines, etc. The Team plays a major role as a hub for BRC's international collaboration.
 - The PI has a track record of organizing international symposia. These events are expected to produce synergistic effects which facilitate the fulfillment of the Teams' missions.
 - In the future, more strategic implementation of international collaboration will be desirable. Such plans coincide with the Team's goal of contributing as a BRC member, and increasing efforts to heighten international presence.
 - From next year onwards, it is hoped that the Team will manifest more specific examples of hub functions.

4. PI assessment

- (1) Is the PI fulfilling the role in line with the BRC mission?
 - The PI is formulating and carrying out research and development strategies leading to the use of disease-specific iPS cells held by RIKEN BRC in the drug discovery field. Thus, the PI is playing an important role in accordance with the mission.
 - It is desirable that the PI should contribute to the management and operation of the Team as a leading researcher. It is also recommended that the PI should analyze societal needs. These actions will lead to increasing development of the BRC.
- (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

- The PI is acting to satisfy international standards for all items.

Regarding (i):

- Publication of original articles in high-impact IF journals is proceeding steadily for each individual topic. The PI is promoting research at a high international standard.
- Since the potential for societal implementation is also high, these actions have a great impact.

Regarding (ii):

- The PI is fulfilling his own mission to promote the utilization of disease-specific iPS cells in Keihanna laboratory as a BRC satellite.
- The PI is carrying out his mission at a high level by providing methodologies such as methods of analysis for disease models and drug discovery screening, as well as development of iPS cell lines of rare chronic diseases.

Regarding (iii):

- In addition to leading the “drug discovery/incurable diseases pathophysiological study” which has garnered worldwide attention, publication of research results is producing informed awareness in society, and thus a return on results.
- By hosting symposia, the PI has aimed to promote collaboration and social contributions both in Japan and overseas.
- It is desirable that the PI should present a model of commercialization by providing treatment opportunities for rare diseases.

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

- Being mission-driven, the PI has been progressing development and adoption of necessary technologies. The PI is working to manage and operate the Teams appropriately.
- If the experimental systems such as RNA seq/single cell analysis etc. that are planned to be incorporated within this Team are half-finished, it may also be desirable to consider other options. Possibilities include utilizing world-leading research technology through collaboration with the RIKEN FANTOM Team, or outsourcing to reduce routine costs.
- In order to enhance application of disease-specific iPS cell resources at the BRC, a new laboratory was established in the Keihanna area. It is hoped that operation of the laboratory will be soon on track with the support of researchers and technical staff.
- Development of young talent is a pending issue. In the future, plans should be made to take into consideration not only recruitment of young talent, but also their future career paths.

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