

Advisory Council Report in 2019 for RIKEN Center for Biosystems Dynamics Research

August 19-22, 2019

Introduction

The Advisory Council (AC) of the RIKEN Center for Biosystems Dynamics Research (BDR) met in Kobe from 19-22 August 2019 to review the Center's new research directions and achievements. BDR was established in 2018 by reorganizing three centers, Center for Developmental Biology (CDB), Center for Life Science Technology (CLST), and Quantitative Biology Center (QBiC). On day 1 of the AC meeting, the RIKEN Executive Director Dr. Koyasu and the BDR Director Dr. Nishida gave an overview for RIKEN and BDR activities, respectively. On days 2 and 3, all PIs of BDR (divided into three groups) were reviewed by the AC. Progress reports and future plans were provided in the advance documentation, and each PI gave a summary presentation and responded to questions from the AC. On days 3 and 4, the AC had a closed discussion and drafted the report and recommendations. The AC had a further discussion with the Director Dr. Nishida. Finally, the AC chair summarized the AC reports and recommendations to BDR PIs with Dr. Koyasu in attendance. Here the Chair and Vice-chair have summarized their AC panel members' reflections and recommendations.

1. Evaluate (1) whether the center's research meets international standards and is regarded as world-leading, (2) whether its research results have contributed to society, (3) and whether its up-to-date activities and strategies meet the aims of RIKEN's fourth mid- to long-term plan (7-year plan).

BDR aims to establish life science that contributes to the extension of the healthy lifespan, which appropriately covers broad fields of biology. The AC enjoyed the PIs' reports and presentations, which overall are at an international level, with some being world-leading. Many senior PIs are international authorities, while most junior PIs are leading new talents for their fields. Some examples of the strikingly outstanding senior PIs are H. Hamada (Organismal Patterning), M. Ueda (Cell Signaling Dynamics), C. Furusawa (Multiscale Biosystem Dynamics), K. Takahashi (Biologically Inspired Computing), T. Kitajima (Chromosome Segregation), Y. Okada (Cell Polarity Regulation), Y. Watanabe (Pathophysiological & Health Science), T. Tsuji (Organ Regeneration), H. Ueda (Synthetic Biology), S. Hayashi (Morphogenetic Signaling), and F. Matsuzaki (Cell Asymmetry). Examples of the most talented junior PIs that we interviewed include M. Morimoto (Lung Development & Regeneration), I. Hiratani (Developmental Epigenetics), and Y. Wang (Epithelial Morphogenesis).

Furthermore, some of the research results are close to translation for wider impact than in academic science alone. Examples include methods for generation of hair follicles, pituitary, salivary, and skin having hair and sebaceous glands from iPS cells, already supporting advancement to clinical trials (T. Tsuji), promising translational molecular imaging validations in rodent models before applications in human subjects (Y. Watanabe), and rational epigenetic drug design with delivery of candidate molecules targeting LSD-1 (T. Umehara). However, the panel wishes also to emphasise the equally important contributions to society from conceptual advances in basic research provided by RIKEN scientists. Some highlights include structural snapshots of nucleosome transcription by RNA polymerase (S. Sekine), explorations of evolutionary dynamics (C. Furusawa), the structural basis of translation initiation under diverse stresses (T. Ito), AI-integrated automated in-cell single molecular imaging system (M. Ueda), and 3D genome-wide structure (Y. Taniguchi).

All of the projects align well with at least one of the aims of the 7-year plan. More than 300 papers are published annually in international journals, including some in the highest impact journals such as *Nature*, *Science*, and *Cell*. Each of the predecessor centers was already recognized as a world-leading center in their respective fields; the AC is convinced that BDR soon also will be internationally recognized as a world-leading center.

In addition to the above research, BDR delivers wider benefits to society. BDR supports generation of transgenic mice for many laboratories not only in Japan, but also in other countries. This is a valued resource for researchers in many biological fields. BDR also is actively engaged in outreach activities. In 2018, BDR held three Open House activities, and more than 6,000 people visited BDR. Furthermore, BDR organized workshops for high school teachers and students and received 95 visits from school students and delegations. These are important public engagement activities that will educate and encourage the next generation to become involved with and use science responsibly.

To achieve RIKEN's fourth mid- to long-term plan, center-wide projects were launched under the leadership of the BDR Director Dr. Nishida. This is a new funding scheme that should provide incentives for productive collaboration among researchers not only in BDR but also outside BDR. To date, two projects, the Organoid project and the DECODE project, have been launched. These projects have the potential to facilitate productive collaboration among researchers that used to belong to three different centers, but this will need explicit implementation plans and careful monitoring. The Organoid project has fostered development of a new collaboration with Cincinnati Children's Hospital, which promises to make BDR research more visible to biomedical researchers internationally. The AC strongly supports the Director's plan to launch additional BDR Center projects

proposed by BDR PIs, which should promote further collaborations between researchers who work in different locations. The AC strongly supports the Director's plan.

2. Center director will present a SWOT analysis on the management of the center to their AC. The AC is asked to evaluate whether the SWOT analysis and the director's management proficiency are suitable.

The AC agrees fully with the analysis provided by Dr. Nishida. BDR was established by merging three centers, CDB, QBiC, and CLST, in 2018. BDR has now more than 60 labs scattered across Kobe, Osaka, Yokohama, and Hiroshima. Because of the distributed locations and diverse research fields, it is challenging to integrate the new center in a harmonious way and to realise advantages from this merger. Despite these difficulties, Dr. Nishida already has shown strong leadership in joining strengths of the laboratories to address three strategic aims: 1. Visualization of molecular and cellular states to enable prediction and control, 2. Multi-level analysis of organogenesis and inter-organ relationships, and 3. Regulation of life cycle progression. These will harness strengths in BDR across the broad fields of biology, spanning from structural biology, cell biology, and developmental biology to brain imaging and regenerative medicine.

The panel believes that these aims well capture the diversity and potential of BDR PIs. Further, there was considerable evidence of collaborations within the BDR, with many papers having multiple PIs as authors. This is excellent and will naturally encourage innovation through cross-fertilization. However, a caution that the AC wishes to highlight is that efforts to align science do to risk realizing the outstanding potential of its individual investigators; the AC feels that the research area for each PI should not be defined or constrained too rigidly if creative science is to flourish. These aims will contribute to the efforts in extending healthy lifespan, which is a major concern for Japan's rapidly aging society. The center projects launched by Dr. Nishida also offer a great opportunity for highly committed, excellent scientists with various expertise to collaborate with each other to achieve greater impact. Furthermore, the opportunity that BDR affords for an exclusive focus on research with no distractions (other than contributing to the management of core support structures), complete independence (even for the junior PIs), good resources, and excellent core support in specific areas such as microscopy and mouse unit are strong points for BDR. Additionally, BDR is supporting its early career researchers; both students and postdocs emphasized the excellent training that they received from their mentors. Director Dr. Nishida thus has set appropriate strategies and created an environment in BDR allowing its researchers to work efficiently. Nonetheless, the panel noted areas in which the effort could be improved. To complement the work of individual investigators focused on methods, such as Nikaido, it would be desirable to invest further in core support for genomics, that could deliver cutting edge, advanced

genomic methods unavailable commercially, and with the ability to deliver unique observations for all laboratories. The electron microscopy and sequencing facilities are not at the level that an institute such as BDR deserves and should be strengthened. The AC strongly encourages BDR to develop and implement an actional roadmap and leadership position (can be a part time appointment) to achieve rapid growth and development of robust cryoEM workflow as a core facility.

The institute has a number of unique opportunities to further distinguish itself internationally, e.g., by promoting many more links between the live imaging and organoid/developmental groups. Specifically, the imaging capabilities enable assessment of metabolic function, oxygenation, cell type composition, and linkage of transplanted tissue to the host vascular system in real time. Few or no other stem cell/developmental biology institutes are in the position to perform these assessments.

Initiation of a new programme of “mini-grants” dedicated for collaborative projects, would also open for postdocs and students, could help to encourage such integration further.

An apparent problem for the merger is the dispersed nature of the institute, with its constituent sites being so far apart. This makes it difficult to preserve optimally productive, day-to-day communication. The regional dispersion threatens to undermine the development of BDR into a coherent, leading research institution. The AC feels that the turnover of faculty in the next few years offers an opportunity to begin to consolidate the institute at a single site on the Kobe campus. While appreciating the logistical challenges, the AC views this as an important move for the long term competitiveness of the institute at the international level. The planned new Projects could aid this process.

A guesthouse or overnight accommodation for international visitors, students, and collaborators at each site would contribute to addressing this issue. However, even in the same center, the panel believed that there were insufficient opportunities for people to meet and socialize in ways that would enhance productivity. A central venue where everyone working in a site could interact informally, like a cafeteria or common room, will be desirable. In addition, because of a large number of labs in BDR, the panel were disappointed to learn that the retreat does not accommodate the entire staff. This hampers joint visibility of research and interactions of researchers. All researchers should participate in a centre-wide retreat at least once every two years.

The panel felt that opportunities for students and postdocs to regularly present their research in English, and for mentoring and career training of junior faculty, postdocs, staff scientists, and students, should be increased. An essential additional component of developing early career staff would be strengthening the mechanisms by which senior PIs mentor junior PIs, postdocs, and students. Thus, regular meetings of PIs with their

mentors should be mandatory, even when the perception is that no apparent problems exist. Such meetings should continue throughout the term of appointment of the junior faculty. Seminars and workshops focused on challenges of career development, increasing formal training offerings in how to write and present research proposals also are important, particularly for junior PIs coming from overseas. It also would be important to support all PIs to establish clear identities for themselves by focusing on a limited set of related biological problems rather than studying many topics superficially. Regular joint progress reports to encourage feedback would be helpful for all. We encourage the RIKEN administration to find ways of accessing funds to support the salary and tuition of international students.

As Director Dr. Nishida noted, the diversity of personnel is limited in BDR and should be improved. For recruitment of more women, provision of extensive daycare for children would make the institute attractive, and this would need to be made widely known if women are to be recruited successfully.

Another area in which diversity and internationality could be improved is graduate training. With its excellent resources and international outlook, BDR could run a “flagship” international PhD program in partnership with universities (IPA), which could attract and develop talented young scientists from overseas (an initiative that should not conflict with the independent missions of Japanese universities). A current IPA program offers only 3-year fellowship but should cover 5 years for students from outside Japan. This program also needs to be made widely known, which may eventually improve the diversity of BDR researchers and help BDR be recognized as an international PhD training center.

The panel appreciated that one of the greatest impending problems for BDR is that many labs will be closed in 2023. This should be clearly notified to all these lab members, and the relevant researchers should be encouraged to apply to positions well before 2023. To move to next positions in universities, external funding and education experiences are important, and BDR should support the affected researchers. Maximal transparency and timelines in communicating decisions from the Senior Management Committee regarding tenure and new recruitments is highly desirable.

The BDR could benefit from more autonomy from the central RIKEN administration in the ability to determine its tenured faculty decisions.

Finally, the panel wishes to highlight what a big loss Dr. Masayo Takahashi’s recent departure from BDR was. Her work is exemplary in demonstrating a path from basic science to regenerative medicine. The panel believes that the work was very important for BDR as an example of world-class translational research. To this end, BDR should even more aggressively seek opportunities to bridge its excellent basic science with

clinical research in neighboring hospitals and universities.

3. Evaluate whether the center's initiatives on the items given below have resulted in improvements and recommend further measures to be implemented by the centers.

- **RIKEN is conducting a program to enhance its function as the core organization for research partnerships, which we refer to as the "Science and Technology Hub." The AC is asked to evaluate the center's achievements in collaborative activities, including those belonging to the Science and Technology Hub.**
- **Initiatives on the internationalization of the center**

BDR currently has 150 domestic and 12 overseas collaborations. In addition, BDR has close collaborations with several universities, institutes, hospitals, and companies. By promoting the Organoid project, BDR launched a joint lab in Cincinnati, which will help BDR research to be more visible internationally. BDR also organized highly successful annual symposia, joint meetings, and many seminars. Furthermore, BDR supports many labs in Japan and other countries to generate transgenic mice, and this is a valued activity for many biology fields. BDR therefore makes an enormous contribution to the global visibility and reputation of RIKEN and is widely recognized as a "Science and Technology Hub."

In BDR, foreign researchers are well supported. However, communication being mainly in Japanese remains a barrier to their full integration. It also hinders the Japanese students from learning English to present their results and function in an international environment. Strong efforts must be made for the institute to become more attractive for foreigners. This could include, for example, generous funding for short-term visits of international experts, funds for visiting students and postdocs etc. All of these would require aggressive promotion of such opportunities.

4. Evaluate (1) whether each of the PIs fulfill their duties in accordance with the mission of the center, taking into consideration the 7-year plan; (2) whether their research meets international standards; (3) and whether they have suitable capability on the laboratory management, including their efforts to support early-career researchers.

Note: For item (2), please refer to the Addendum for the suggested points to be evaluated.

The evaluation of each PI is presented separately, but the AC was impressed by the high-quality research conducted at BDR. All PIs are making their research meet the

Center's mission, but it is important that their research should not be re-directed too rigidly. Most of their research meets international standards, and most PIs seem to have suitable capability on the laboratory management. However, as noted above, formal support mechanisms for early career researchers at the senior postdoc and research scientist level currently are weaker than at many other institutions, (e.g., lack of specific training opportunities for soft skills such as grant writing, etc.). The strongly positive sentiments that the panel heard from early career researchers, postdocs and students provides a strong substrate for improving this.

Members of the BDR Advisory Council

Ryoichiro Kageyama, Kyoto University (Chair)

Maria Leptin, European Molecular Biology Laboratory/University of Cologne (Vice-Chair)

Martin Fussenegger, ETZ Zürich and University of Basel

Christer Halldin, Karolinska Institutet

Makoto Higuchi, National Institute of Radiological Sciences

Midori Kamimura, Teijin Institute for Biomedical Research

Paul M. Matthews, Imperial College London

Hiromitsu Nakauchi, Stanford University/The University of Tokyo

Masaki Sasai, Nagoya University

Michael Sheetz, National University of Singapore

Cliff J. Tabin, Harvard Medical School

Soichi Wakatsuki, Stanford University

Yoshihiro Yoneda, National Institutes of Biomedical Innovation, Health and Nutrition

Kenneth S. Zaret, University of Pennsylvania