Advisory Council Report in 2023
for RIKEN Center for Biosystems Dynamics Research

September 5-8, 2023

Introduction

The Advisory Council (AC) of the RIKEN Center for Biosystems Dynamics Research (BDR) met in Kobe from 5-8 September 2023 to review the Center's research directions and achievements. BDR was established in 2018 by reorganizing three centers, namely the Center for Developmental Biology (CDB), Center for Life Science Technology (CLST), and Quantitative Biology Center (QBiC). Therefore, the last AC meeting, 2019, was conducted shortly after their union, and the current AC meeting is the first opportunity for the AC to give advice based on the activities of the BDR in its current form. We were very pleased to see the progress.

On day 1 of the AC meeting, the RIKEN Executive Director Dr. Miyazono, and the BDR Director Dr. Nishida gave an overview of RIKEN and BDR activities, respectively. On day 2 the AC heard presentations about the six Center Projects and core facilities, followed by a well-organized facility tour. On day 3, six PIs presented their own research activities, followed by short talks and discussions with students and postdocs. In the afternoon, the BDR's plan for its future direction was presented by Director Nishida, Deputy Directors Kitajima, and Taiji, who were accompanied by the BDR Management Committee and Personnel Committee members. During the three days, the AC had several closed discussions, some with the attendance of the Director and Deputy Directors of BDR when necessary, and drafted its report. On the last day, the Chair summarized the AC reports and recommendations to BDR Directors and PIs, with Dr. Miyazono in attendance.

This report was written jointly by all AC panel members according to the Terms of Reference provided by RIKEN and finalized by the chair and vice-chair.

Overall comments

The BDR was created from the consolidation of several distinct RIKEN institutes. The combined institute has a strong tradition in developmental and cell biology as well as excellent imaging (live and fixed, superresolution and confocal) capacities. These are complemented by outstanding CryoEM capacity from Yokohama, a new team using NMR from Yokohama and experts in robotics from within Kobe. The strategy that drove this consolidation was intelligent and well justified, yielding an institute that is diverse and exciting, because both technological and biological know-how are united under one directorate. BDR has the potential now to make major changes to the way biology is perceived and pursued in Japan. This vision was laid out in the future plans presented by the BDR, but is also evident in new initiatives that they have already launched and which were presented to the AC. It fits well and makes excellent use of the TRIP initiative of Riken.

Building on the strengths and the diversity of the combined institutes, BDR now has six Center Projects: Organoids, Decode, Structural Cell Biology, Stage Transitions, Research Automation, and QMIN. The challenge is to marry the diverse modes of functioning (i.e., structure biology with a CryoEM and NMR service vs. basic developmental and stem cell biology research) in a productive and innovative manner. This is especially challenging because of the distance separating the cryoEM and NMR (Yokohama) from the more biological research (Kobe). The move of other imaging and structure groups from Osaka to Kobe will be a step in the right direction. It is encouraging to see that the BDR has held several retreats, aiming to provide an environment for all research staff to actively engage with each other. We emphasize that increasing the regular exchange among postdocs and students across BDR, rather than just among PIs, as creative new collaborations are often driven by exchange among postdocs. Support for intra-BDR collaboration could be embodied in a cross-disciplinary program that advertises internationally to attract top postdocs, which we elaborate in more detail below. Core funding could be dedicated specifically to fund such postdoc projects, much like that which is currently done for the Stage Transition projects. A complementary approach would be to Increase the allocation of Stage Transition projects to be able to hire postdocs specifically for collaborative projects.

The BDR, both at present and in its envisioned future, supports three distinct modes of research. One consists of question-driven basic research projects driven by PIs, and here the strength is clearly developmental biology and organ and organismal function. The AC saw many exciting projects in this arena, including QMIN, the Organoid research, and many of the Stage Transition projects. The second mode is that of Infrastructure-based research projects. This research promotes technologies through optimization and engineering, and pursues the application of cutting-edge methodologies (examples are CryoEM, NMR, robotics, fluorescent imaging and ALPS). These research teams rely largely on collaboration for their biological relevance. Finally, the third mode of research is based on synergies between individual laboratories and technologies, such as the application of robotics to high throughput data analysis, the development of innovative single-cell 'omics,' and in the future, the application of AI to research project design and data analysis. While the combination of the three modes is in many ways the strength of the BDR, it also adds to the complexity of its management. Each of these modes requires somewhat different organization and strategy for investment, and it would help the BDR management to be fully transparent on a) how areas of targeted hiring are decided; b) how permanent (rather than 10-year-limited) positions are assigned, c) how internal funding is allocated and d) how large infrastructural investments are decided upon, and balanced against investment in individual laboratory support. Obviously, bottom-up questions and creative ideas are to be fostered and balanced with high-end technology advancement.

We note that for open-ended curiosity-driven research, postdocs are the key driver, while for the second research mode, high-end engineers with long years of experience are essential. A multi-year strategy from the BDR leadership is important to maintain the financial and personnel balance among these three types of research. We recognize this challenge and believe that the Director and his deputy directors have done an excellent job to date. However, the future promises to be even more complex, and it will be wise to set up strategic committees that involve PIs representing all three interests, to help design the future and direct internal funding in an optimal way. Transparency and communication are key to good management in complex situations like this. A general review of the aims, scope and size of core facilities would be useful.

The AC embraces the vision for the future presented by the BDR directorate, in which large data sets (often from model organisms) will be analyzed by AI to generate hypotheses that will be tested and later incorporated into new ways to control or create improved life cycles. However, we note that the institute at present has only limited strength in AI and in synthetic biology. The organoid work has the potential to contribute to regenerative medicine (and some currently do), but if the ultimate goal is clinical application, then human genetics needs to play a more major role in guiding the model organism studies. In conclusion, there are several areas of "construction" needed to fulfill this new vision.

Finally, the AC applauds the steps already taken to integrate the diversity of scientists brought together by the merger of institutes and recognizes the efforts taken to break down "silos" and barriers between the more technology- and engineering-oriented scientists and those who conduct open-ended, curiosity-driven research. Systems of reward and recognition need to be adapted to align with the distinct types of activities pursued within BDR. The efforts made to include younger members of staff in leadership roles are exemplary. Attention should be given to fostering independent PhD student and postdoc events, and to organizing career development seminars and activities that help guide junior researchers towards their future. Teaming up with Women-in-Science Japan to organize events that promote female scientists may be a good idea.

1. Evaluate the responses to the 2019 AC recommendations.

1-1. BDR Center Project

The 2019 AC expressed strong expectations and suggestions for the BDR Center Projects, two of which had been launched by Director Nishida at that time. Since 2019, the BDR has launched four new Center Projects, bringing the number up to six current projects. The AC heard presentations about their aim, scope, organization, and results from the six project leaders.

The AC strongly supports the BDR's policy to enhance the personal and professional interactions between labs through the Center Projects, in particular those that were previously separated in independent institutes or represent different scientific disciplines. The AC expects that the Center Projects will further incubate intra-institutional networking, overcoming the difficulties caused by geographical distance. Below, we summarize our views on each project.

Organoid

The Organoid project builds on the traditional strengths of the Kobe Research Institute in the field of organoid and developmental biology. Initiated by central discoveries in the field of kidney organoids, the project has assembled excellent research groups that are focused on improving organoid systems for the kidney and the lung. The AC commended the project team for their deep, rigorous mechanistic approach to understanding self-organization in organoid biogenesis. Over the review period, the team has developed new collaborations within the BDR and also with the Cincinnati Children's Hospital. The latter strategic alliance builds on complementary strengths of the two institutions, to encompass foregut organoids.

The AC supports the Organoid Project's commitment to fundamental mechanistic discovery. We believe that it gives the project a research momentum that now opens opportunities to further strengthen the research and its impact:

1. Further collaborations could be reinforced within the BDR. The Organoid project could take even further advantage of the outstanding imaging, 'Omic, and EM capacity of the BDR. Closer links with the Transitions and Decode projects could be synergistic. 3D and 4D spatial transcriptomics should be developed alongside the ALPS technology and applied to organoids. This is an obvious area for collaboration with the DECODE project.

2. The collaboration with the Cincinnati Children's Hospital has proven essential for the success of the unit, ensuring international exposure, benchmarking, and exchange. It will be crucial to ensure continuation of this collaboration, including the provision of adequate funding. However, the team should not rely on this single collaboration. Instead, its success provides a model for them to look for other complementary collaborations domestically and internationally.

3. The advances in mechanistic discovery in this project provide a foundation for further

translational applications. Potential opportunities lie in disease modeling, regenerative medicine or drug screening. For the first, it would be important to integrate human genetic information (GWAS and rare disease mutations) with the model organoid studies. We suggest that these could be explored with clinical teams in Japan and internationally. Strategically, this could be pursued by projects that are closest to clinical or biomedical translation; it does not need to be pursued by all the teams in Organoid.

DECODE

The DECODE project has made impressive technological progress in recent years to integrate omics with dynamic gene expression at the single-cell level. The patented ALPS (automated live imaging and cell picking system), the development of Raman imaging and the activities within the national (Systems Science of Biological Dynamics database; SSBD) and international (Global Bioimaging, GBI) bioimage database networks put this core project into the international limelight. DECODE's technological achievements are impressive and its future plans are fascinating.

The team uses ALPS to obtain microscopic images on individual cell morphology over time and correlates this with single-cell transcriptomes. A deep learning model was trained on these data to predict transcriptomes from the cellular morphology. So far DECODE has focussed on the analysis of single-cell suspension systems. However, since cellular dynamics are mainly context-dependent, the DECODE consortium is strongly encouraged to prioritize their future plans to analyze tissue sections and organoids. Thus, it will be interesting to see if this approach scales to cover a broader range of cell types and whether it will be able to consider cell and tissue context-dependent phenomena. Developing approaches that allow the collection of data not only in 2D but also in 3D within the context of an organoid would greatly extend the value of this technique and would create synergies with the organoid core project. With a major focus on technology development so far, the time has now come to translate this expertise to clinical applications and establish further insight into tissue development in close collaboration with the ORGANOID core project.

DECODE's activity in the bioimage database networks is highly commended, and it increases BDR's international visibility. To unleash the full potential within BDR, DECODE may want to consider establishing the imaging database across BDR, in particular in collaboration with the Organoid project. In further developing their image database activities within BDR and internationally, DECODE may also take a lead in establishing and promoting a convincing AI strategy within BDR.

Structural Cell Biology

The Structural Cell Biology project includes structural biology and adjacent fields such as imaging, automation, and computation. The main foci so far are structural biology of Pol II transcription and signal transduction, with a strong emphasis on the use of X-ray and cryoEM. Some outstanding results were presented, including elucidation of Pol II transcription going through the nucleosome. This relies on long-standing collaboration with external groups such as that of Kurumizaka in Tokyo. The Cryo-EM program has been successfully established by the structural biology groups in BDR Yokohama. Understanding structure in the context of the cell is an area of great scientific opportunity for BDR. Approaches such as Cryo-ET coupled with correlative light microscopy and cryo-FIB sectioning will be essential for this. The AC recommends that the BDR management consider how to invest in these technologies and consider ways in which the technology development can be integrated with the research investigating a broad range of biological phenomena conducted at BDR. There should be particularly strong synergy effects based on the techniques and the equipment BDR has recently acquired, such as high-resolution atomic/molecular level structure determination with cryo-ET and CLEM, nanoscopy, and various UV and IR imaging methods. The AC would also recommend a closer integration of computational methods, including general molecular modeling and simulation, structure prediction techniques such as AlphaFold, and new AI/ML-based methods, in particular, to integrate data from different experiments and length/timescales. Finally, the AC encourages BDR to revisit the role of NMR within RIKEN.

Bridging CryoEM to cell biology will probably be achieved through Cryo EM Tomography, and CLEM (correlative Light and EM) which allows atomic resolution analysis of macromolecular complexes in their cellular context. Promoting projects in this area may help bridge the Yokohama teams to the Kobe expertise.

Stage Transition

Stage Transitions is one of the most recently launched Center Projects (initiated in 2020). The overall goal is to identify and understand mechanisms underlying transitions between stages in living systems. These transitions can represent temporal separations between stages of an organism's life cycle, or discrete transitions in measurable behavior such as transformations in cellular or functional behavior. Five core projects and seven exploratory projects have been selected in the initial phase of this Center Project. These cover a range of interdisciplinary approaches and a diverse set of biological questions. The logic and originality of the individual projects supported in this theme are clear and progress on these has been very good. It is clear that this Center Project has rapidly achieved excellent momentum. Although connections between the individual projects that comprise this scheme are not always immediately obvious, it was pleasing to see the exciting science that has arisen from the institute-wide call for collaborative ideas. The Center Project stands out in the way it stimulates scientific dialogue and interactions between the groups involved and by launching further internal calls for funding it represents a paradigm for encouraging collaboration and innovation across BDR. It could be a good time to consider whether deeper conceptual development is now warranted by starting a discussion about whether there are common features and principles that define life cycle transitions and how stability is broken in the short term to allow transitions to occur.

Research Automation

The research automation project has an engineering and technology focus with a goal of integrating recent technological advances to benefit scientific progress, as well as developing next-generation technologies for high-throughput data collection and analysis. The robotics and automation work is internationally leading, in line with strong Japanese traditions in the area, and with clear ties to pure robotics research work at other sites, which is a strength. It is also encouraging to see the increasing use of AI to e.g. plan experiments, rather than merely analyze data. Advances in lab automation have potentially large societal and commercial impact, and, in particular as part of a center-wide push towards collection and analysis of massive datasets, state-of-the-art automation could play an important role if fully integrated into domain-focused scientific projects. The setup of allocating resources by allowing research labs to compete for “open projects”, with a committee of senior scientists at the institute selecting them is a factor that appears to promote this integration in the more applied projects. It remains to be seen how much cooperation BDR will be able to obtain from the manufacturers in modifying and improving the robots to meet BDR’s future needs in efficiently operating the robots. These engineering aspects are important.

The major function of Research Automation is to provide key infrastructure, and it can therefore not easily be evaluated in the same manner as a scientific research project. In terms of traditional assessment criteria such as independent scientific publications and citations, the impact is limited, but the work can nevertheless be a critical component for several of the BDR domain science projects. This impact could potentially be made more visible through the "open science" projects, but to achieve that, we feel that both the application and reporting of the open science projects would benefit from focusing more on clear scientific questions, and goals that will be achieved. It would help to analyze what scientific publications came out of each project, and what the role of research automation was in them. It would also be beneficial to be able to show in what way investments in new techniques or core lab equipment are prioritized based on project areas that are able to show the largest biological impact from using this automation.
In particular with BDR's future vision on larger datasets and AI, we recommend BDR take a broad view and consider Research Automation opportunities already at the planning stage of projects, including both technology development and how it will support the scientific goals.

QMIN

The QMIN project pursues an original approach that was presented with an ambitious, long-term science-fiction goal, i.e., to manipulate human life span under the condition of torpor. The idea is to exploit knowledge gained in this project on the ability of certain animals to reduce their metabolism and body temperature upon reduction of external temperature, or food, or other stresses. Hamsters and certain other animals hibernate in a torpid condition, while mice exhibit torpor daily, depending upon the periodicity with which they feed. Neural circuits regulating this behavior have been identified, where mice undergo Q-neuron activation that can be mimicked experimentally to elicit a torpor state called QIH. The QMIN experiments are designed to understand the signaling and metabolic changes that elicit and maintain torpor. The eleven labs contribute to the project with diverse approaches.

The work is built around novel model systems - and brings multiple labs with different expertise to explore the problem, such that the presented subprojects have clear contributions towards this overall goal. The work, or at least the focus, appears to be unique worldwide. Given that the program is more focus-driven than the other BDR programs, it may come at the cost of less freedom for younger researchers. However, the hibernation/torpor goal is also broad enough that there are numerous related subprojects (such as the mouse QIH and its relation to PDH) that provide a diversity of topics for younger researchers who want to set up independent labs. The team may want to consider if torpor has an impact on ageing, rather than lifespan alone. In collaboration with cell imaging groups and MRI groups, mouse QIH model brains under hibernation can be analyzed. While inducing whole-body torpor in humans, whether for medical purposes or long-distance space travel is well beyond the realistic aims of this project, the goals are nevertheless visionary, and used on isolated organs, for example in transplantation medicine, or in other medical treatments might not be out of reach. Given the extensive work done to date, it will be good for the group to focus on publications in the near future.

1-2. Strategic aims

The current BDR's scope aims to "understand the lifecycle and extend healthy life expectancy." To this end, the following three strategic aims were set.

1) Visualization of molecular and cellular states to enable prediction and control
2) Multilevel analysis of organogenesis and inter-organ relationships
3) Regulation of life cycle progression

During the review period, the BDR has been conducting “Lifecycle Science”, with an ambitiously broad scope covering the lifespan from birth to death. At the last meeting in 2019, the AC realized that Director Nishida had already shown strong leadership in joining the strengths of the laboratories to tackle these three strategic aims. The key endeavor, which Dr. Nishida has been strongly promoting, lies in the Center Projects. The AC acknowledges that this program has been working successfully and has led to novel and fruitful interactions between the labs, including between those based in distant locations and those that used to be separated in different institutions.

Symbolized by the achievements in the Center Projects, the high level of international reputation of the science at the BDR demonstrates that the institute is on the right track. Based on these foundations, the BDR is raising a new perspective “to control and create improved lifecycles” for the 5th Mid- to Long-Term Plan period. As we come back in the later part of this report, the AC acknowledges and supports this perspective (with the proviso that the nomenclature may deserve re-thinking), with an expectation that further intra-institutional synergies will accelerate BDR’s scientific success in line with RIKEN’s TRIP perspective.

AI is a central plank of the new strategy. To realize its ambition, BDR must develop, resource and implement a comprehensive and inclusive plan. This should include data management plans, infrastructure investment, as well as strategies to attract, retain and train researchers with appropriate skills. There is also an opportunity for collaboration with neighboring institutes and the possibility of dual appointments with RIKEN computation centers.

1-3 Laboratory dispersion

The 2019 AC had concerns about the difficulty in preserving optimally productive, day-to-day communication with sites being so dispersed. During the review period, the Osaka campus was scheduled to be closed at the end of March 2025, with the remaining labs and administrative functions in Osaka to be moved to the Kobe campus. Concentrated into two locations, the AC expects much better collaborations and other interactions among laboratories. The benefits of this step are already visible. Nonetheless, the distance between Kobe and Yokohama remains a constraint, and warrants future creative solutions.

To reduce the inherent communication barrier between their distant laboratories, the BDR has organized retreats for all BDR members. While conducted virtually during the pandemic, they have been resumed in person, as productive and positive events gathering in one location. The AC acknowledges that such opportunities benefit further intercalation between people based on different scientific backgrounds and locations.

1-4 Laboratory closure

During the reviewing period, 32 labs were closed, while 15 new labs were launched, resulting in a total reduction of labs from 71 to 54. The AC acknowledges that this is a consequence of employment terms inherited from the founder institutions and the coincident retirement of labs led by senior PIs. The 2019 AC suggested that this should be clearly communicated to all lab members, and that the affected researchers be encouraged to apply to other positions as well.

We were glad to see that the Director conducted mentoring interviews with all PIs of closing laboratories to inform them of the closure schedule and support their transfer to other institutions. In addition, mentor PIs were assigned to members of closing laboratories, so that their transfers to new positions were supported, and they could receive open communication and support, as needed. The 2023 AC acknowledges that the BDR took significant care of the persons concerned, a very important action in this situation. Further, we also acknowledge and support that BDR encouraged a significant number of people to move into newly created positions, in a competitive manner.

1-5. Facilities

The 2019 AC suggested that it would be desirable to invest further in core support for genomics that could deliver cutting-edge, advanced, yet commercially unavailable genomic methods. In response to this, BDR recruited team leader Takefumi Kondo and launched a new genomics laboratory in April 2023. Kondo's team is currently developing spatial transcriptomics. The 2019 AC also strongly encouraged BDR to achieve rapid growth and development of robust cryo-EM workflow as a core facility. In response, in 2021, BDR established the Cryo-EM Operation Team headed by TL Shun-ichi Sekine. Under his leadership, BDR's Cryo-EM facility was upgraded, with the installation of a top-of-the-line 300 kV Krios G4, which is made available both within and outside RIKEN. The 2023 AC acknowledges that these improvements are substantial, both in terms of equipment and personnel.

The 2023 AC also acknowledges that BDR will expand its activities for a more data-driven and AI-powered approach. It is critical that these activities be driven by biological problems, and assessed on their scientific impact, rather than merely being a focus on technology. As identified by the BDR leadership, the AC agrees this is a priority area for future recruitments. For such a strategy to be successful, the AC recommends that BDR secure substantial data storage, computing power, and means to generate large-scale high-quality data. The AC recommends BDR investigate whether it is possible to achieve synergies with the nearby RIKEN Center for Computational Science in Kobe, and establish cross-disciplinary collaborations between fundamental AI/ML research and its applications in life sciences.

The AC is concerned about the aging of some of the buildings and key facilities. As an example, the large warehouse management system software, installed 20 years ago to store mouse cages, is at risk. If it breaks down, with no backup measures in place, this will have a severe effect on animal experiments and risk the loss of animals. This is an urgent issue, given the importance of keeping experimental animals in a secure and clean environment, which has been vital for many of the achievements in the history of the BDR.

1-6. Human Resource Development

In 2019, the AC made recommendations about early career researchers and students. These included providing opportunities for them to present their research regularly in English, to attend seminars and workshops focused on career development, and to arrange mentoring of young PIs by senior PIs.

In response, the BDR initiated the "Young Researchers Forum" in 2020, as well as "Technical Introduction Seminars" and other in-house seminars on the use of core research equipment and technologies as training opportunities for young researchers and technical staff. The BDR also launched the "Student Symposium" in 2021, in which student researchers at BDR can present their research, and be involved in chairing or organizing the symposium.

Talking with the students and postdocs, the AC members found that these opportunities are well appreciated, and several international PhD students felt very well supported both by their advisors and the general BDR environment. They feel that they receive a high-quality education. This is a significant achievement by the BDR leadership, and it is likely to improve visibility and future international recruitment.

However, there are also some challenges, in particular for postdoctoral scholars. The salaries in the Japanese system appear to be lower than in many other international environments. This challenge extends undoubtedly beyond BDR, but the AC wants to stress that it is critical for RIKEN and Japan to be able to compete for international talent, and to make sure that Japanese researchers find the academic career path attractive - in particular when focusing on new research topics where large investments are being made in other parts of the world.

We heard a need for improvements on the side of social-personal interactions, in particular between labs, which in part might be related to the physically distributed setup of BDR, and perhaps an after-effect of Covid-19. While this is not strictly a scientific matter it is clear that a warm and interactive social environment and team members' happiness in the workplace support productive research and in particular the exchange of ideas and knowledge. To address these concerns the AC has a couple of suggestions. To improve social interactions between students and PDs, in particular those from foreign countries, BDR should dedicate a small budget to the Student and the Postdoc networks to organize events such as "coffee mornings, pizza nights" etc. It might also be possible to use the "Student Symposium" more effectively to encourage networking.

The postdocs and students also indicated that they would appreciate more career development mentoring and support. Currently, the individual team leaders appear to be responsible for mentorship, and some trainees expressed a desire to hear different opinions from other team leaders. Such career development would include skills training for activities such as grant writing, academic job applications/interviews, running/managing a lab, and effective networking. Establishing such a program would be a long-term goal but could be initiated by offering career mentorship from PIs outside of the student's or postdoc's host lab. Since good mentoring is a skill that can be learned, it would be useful to also provide training in lab leadership to the PIs, through such as the EMBO Lab Leadership courses.

The BDR has already made it mandatory for senior PIs to mentor junior PIs to ensure continuous communication and support. Discussion with individual young PIs suggests that this is appreciated by the junior PIs. Formal mentorship will be very important when the BDR recruits international PIs, to provide support to adjust to a new national environment.

1-7. Diversity

The 2019 AC raised a concern that the diversity of personnel is limited in BDR and should be improved, and pointed out that diversity and internationality could be improved in graduate training. In response, BDR established the "Diversity Working Group" in 2020 and launched the "Women and Future in Science" seminar series, featuring outstanding women scientists to inspire younger women researchers at BDR. In fact, BDR conducted two PI recruitment calls open specifically to women researchers in the fields of lifecycle science and structural life science. The two PIs hired through those calls will join BDR in 2024. For graduate student training, BDR established an "Education Working Group," for planning and implementing educational programs for students. The AC supports these actions of BDR, whose continuity will be quite important.

The institute should be commended for the efforts made to increase the international diversity of its staff and to promote the career progression of women, and it is satisfying to see the increase in the proportion of women at all career stages within BDR, with examples of creative and impactful research by newly recruited PIs. However, it should be noted that these proportions are still well below international standards. Continued focus on this goal will be essential to ensure that the initial gains are realized and continue. It is important to advertise the positive aspects of the BDR campus in Kobe including very reasonable and convenient childcare facilities. This will help attract and keep scientists of both genders.

As well as continuing to encourage the application and appointment of women at all career stages, particularly as PIs, mechanisms to support the career progression of women in the institute should be considered. The Women and Future of Science seminar series could be coupled with “meet the speaker” sessions for female postdocs and students. Additionally, establishing a women-in-science network, or linking up more closely with the Women-in-Science Japan network, would be a means to provide peer-to-peer support. A small budget to support social activities and training is needed.

More efforts are also needed to attract foreign researchers in order to increase the international diversity of the institute. The progress that BDR has made in the last few years places it in a good position to play a leading role in this nationally. One mechanism to attract international talent would be a high-prestige fellowship scheme to support post-docs pursuing ‘interdisciplinary’ projects involving two or more labs, a proposal we describe in more detail below.

1-8. Bridging basic to clinical

The 2019 AC BDR recommended aggressively seeking opportunities to bridge BDR’s excellent basic science with clinical research in neighboring hospitals and universities. In response, two initiatives have been initiated to facilitate transition of the excellent research done at RIKEN into the clinics. First, a partnership with the Center for Stem Cell and Organoid Medicine (CuSTOM) at Cincinnati Children’s Hospital has been initiated to explore the clinical use of organoid technology. In addition, the institute works with Hyogo Prefectural Kobe Children’s Hospital as a domestic partner to translate BDR research into practical applications. The AC commends the BDR for their efforts to establish these collaborations. They provide a foundation that the institute can use to extend new initiatives.

Currently, the organoid projects are diverse and advanced and are primarily focused on developing structures for further research and pharma/drug screening. Apart from the retinal project, however, the organoid studies could use more opportunities to collaborate with medical centers in Japan for possible tissue therapeutics. Having working relationships with clinicians and transplant surgeons can help guide how organoids may need to be built, function most appropriately for tissue physiology, and expand the scale for eventual clinical applications. Towards this goal and to incorporate human genetics into the research program, we recommend expanding into that area by hiring one or two research groups in this area.

We see some other areas for potential clinical translation and integration. The QMIN project has the potential to inform understanding of aging (especially healthy vs unhealthy aging). It is early days, but the project could be encouraged to consider these possibilities as they proceed in their phenotypic analyses. Obata’s work on nutritional impact on lifespan is another line of work with potential impact on aging, beyond its current focus on lifespan. Many of the projects would benefit from enhanced integration of the vast amount of human genetic and genomic data emerging from around the world. This could be achieved by further engagement with such investigators at Yokohama and, importantly, by considering one or two faculty hires of scientists focusing on human genetics and genomic data.

Overall, BDR should even more actively seek opportunities to bridge its excellent basic science with clinical research in neighboring hospitals and universities.

1-9. International visibility

The 2019 AC praised the BDR's series of high-level international symposia and their launch of the joint lab with CuSTOM at the Cincinnati Children's Hospital. The AC also strongly suggested to attract further foreigners strategically. During the review period, in spite of the pandemic, BDR annually organized BDR symposia; their collaboration with CuSTOM has been fruitful, leading to, for example, a co-authored high-quality study of lung organoids conducted by the Morimoto Lab based on exchange of staff.

In the 2023 meeting, the AC acknowledges that the BDR has a number of outstanding PIs with international visibility. The AC sees areas where the BDR could improve international visibility further by implementing strategic efforts such as more international collaborations, exchange, mobility, and continued efforts in hiring international PIs, younger staff, and postdocs. Another possibility is to offer grants/fellowships to international collaboration projects or visitors (several weeks to months). One mechanism that would contribute to this aim would be the elite postdoctoral program we propose below.

2. Based on the results of the Center's self-analysis, evaluate operations and R&D activities for the 4th Mid- to Long-Term Plan period (FY2018-2024)

As detailed in other sections of this report, the AC fully acknowledges that BDR has objectively, and correctly, recognized its own strengths and weaknesses, and has appropriately utilized self-evaluations to build up actions for the 4th Mid- to Long-Term Plan period. Our specific comments are in the individual sections above.

3. Evaluate the policies of the 5th Mid- to Long-Term Plan period (FY2025-2031) and recommend new directions for operations and R&D that should be implemented and promoted.

3-1. Evaluation of the policies of the next policy

BDR set "Create lifecycle" as the next strategic goal, including "understand", "predict" and "create" the life.

To **create** life cycles, BDR will use both in vitro and in vivo strategies, by means of synthetic biology and through artificial modification of particular life stages.

To **understand** life cycles, taking advantage of their state-of-the-art techniques, e.g., imaging and sequencing, BDR will analyze organisms across scales and across species.

To **predict** life cycles, BDR will take advantage of the AI and foundation models, underpinned by acquiring quantitative data with a high order of complexity.

While 'create' is visionary, it may evoke false expectations or even concerns, and it might be worth thinking of other terms, such as synthesize, redesign, manipulate, modulate, control, manage, or innovate.

Nevertheless, the proposed vision provides an excellent framework that unites efforts of the majority of the research teams of the BDR towards a common goal.

3-2. Recommendation of the new direction

The vision of the BDR is very much orientated towards human health. At the same time, the institute has a rich diversity of successful teams conducting interesting research on a range of model systems. Many of these are driven by a motive to understand the principles and mechanisms of biological systems' transitions, both in time and space. Such a motive is crucial for a leading research institute to embrace. While a conceptual focus is necessary, it is vital that this diversity is maintained, with team leaders having the freedom to follow their curiosity. This forms the substrate for unexpected discoveries, as the basis for future new research directions.

Our recommendations for the individual Center Projects, research areas, and research policies are included in the paragraphs above, but here we also want to make a particular suggestion for establishing a new high-level, internationally visible interdisciplinary post-doctoral program that would benefit many aspects of the BDR. In this program, pairs of internal PIs with distinct expertise or residing at different sites would propose a joint project that requires a postdoc. The postdoc would have both PIs as advisors. Proposals would be selected for funding through an internal competition and advertised internationally to attract highly competitive postdocs.

Significant core funding would need to be put aside to fund such interdisciplinary projects by this program, for which internationally competitive salaries should be offered. This would give the positions the necessary attractivity, and make the program prestigious. The labs who have successfully competed for such a postdoc should also be given additional consumable funding to support their work.

There are a number of reasons for this: collaborations across fields are often driven by postdocs; the best postdocs are in general a creative driving force of research projects; attracting top-level talent is crucial for BDR to be more international. Such a program would accelerate the mingling of researchers across the BDR and it would create a pool of candidates for the next generation of independent PIs exploring new research fields. If such a program could be established with sufficiently excellent postdocs, this could become a prestigious activity within the BDR, with high visibility, and give the institute an edge in recruiting the best postdocs nationally and internationally.

Shosei Yoshida (Chair; National Institute for Basic Biology, Japan)
Maria Leptin (Vice-Chair; European Research Council, Brussels, Belgium)
James Briscoe (The Francis Crick Institute, UK)
Martin Fussenegger (ETH Zurich, Switzerland)
Susan Gasser (University of Lausanne and ISREC Foundation, Switzerland)
Midori Kamimura (CBI Research Institute, Quantum-Structural Life Science Laboratories, Japan)
Hiroaki Kitano (Okinawa Institute of Science and Technology Graduate School, Japan)
Jürgen Knoblich (Institute of Molecular Biotechnology, OeAW, Vienna, Austria)
Erik Lindahl (Science for Life Laboratory, Stockholm University & KTH, Stockholm, Sweden)
Masaki Sasai (Fukui Institute for Fundamental Chemistry, Kyoto University, Japan)
Yoshiko Takahashi (Graduate School of Science, Kyoto University, Japan)

Soichi Wakatsuki (School of Medicine, Stanford University, US)
Alpha S. Yap (The University of Queensland, Australia)
Yoshihiro Yoneda (The Research Foundation for Microbial Diseases of Osaka University, Japan)
Ken Zaret (Institute for Regenerative Medicine, University of Pennsylvania, US)