

**Advisory Council Report**  
**RIKEN Center for Developmental Biology**

**February 2010**

## **Meeting Programme**

The Advisory Council of the RIKEN Center for Developmental Biology met in Kobe from 21-24 February 2010 for the fifth review of the Center's activities. The Director first provided a strategic and financial update and presented the Center response to the previous series of Advisory Council recommendations. Further information was accessible to the Advisory Council through the 2010 white paper that had been prepared by CDB and circulated in advance of the meeting.

Reviews of the seven Group Directors comprised the main business of the first full day. Each Group Director gave a presentation and responded to questions from the Advisory Council. The Advisory Council had previously nominated mail reviewers. The written documentation contained the reviewer evaluations along with Group Directors' progress reports and future plans.

The next day began with presentation and discussion of the Director's Strategic Projects by the Project Leaders. A newly recruited Team Leader then introduced his activities followed by the new imaging facility manager and the leader of the new unit for science policy and ethics studies. Heads of supporting laboratories for genomics and human pluripotent stem cell technology also presented. AC members had lunch with postdocs and students which provided an opportunity for informal discussion. The AC requested a presentation from Dr Takahashi on her translational research, then split into three groups to visit laboratories and hear reports from Team Leaders on their work. Team Leaders had been invited to speak about their most interesting progress rather than attempt to cover all their activities. The AC also discussed future career options with several Team Leaders nearing the end of their 10 year term and preparing to leave CDB. The day ended with an informal buffet for AC members and CDB investigators.

On the final morning the AC retired for closed discussion and to finalize the reviews of the Group Directors. Following a private meeting with the Director, the Chair summarized the Advisory Council findings and recommendations to the CDB staff. The AC subsequently provided the Director with confidential evaluations of the Group Directors and summary assessments of Team Leaders.

## **Overall Evaluation**

The CDB is now firmly established as one of the leading developmental biology institutes in the world. The Center is headed by an exceptional scientist in Dr Takeichi, has several other researchers of high international profile, and contains a good mix of senior, mid-career and junior investigators.

The CDB has three major research themes: Developmental Mechanisms; Organogenesis; Stem Cells and Regeneration. These are interdependent and combine synergistically to create opportunities for biomedical translation. The AC recommend that this inter-relatedness is given a higher profile and made visible in all CDB documentation and activities in order to establish the public “branding” and mission of the Center.

The excellent infrastructure and generous funding available to CDB investigators demand research achievements of high impact and originality. In this respect the output of publications in the major peer-reviewed journals is commendable. CDB researchers had 332 publications in 2008-9, one third in the leading international journals, including several in *Nature*, *Science* and *Cell*. Furthermore, the value of external grant awards to CDB investigators increases year on year. Thus while the AC remains of the opinion that a small number of CDB groups could make better use of the resources available to them by being more focused and pursuing deeper questions, most CDB research teams are performing at a good or very good international standard. Indeed several are making exceptional contributions at the forefront of important and competitive fields. Furthermore, CDB is contributing to the international developmental biology community in a variety of ways, including the provision of transgenic mice, partnering with a range of institutions, and hosting the highly successful annual CDB symposia. Overall therefore CDB is adding significantly to the global visibility and standing of Japanese science.

## **Full-term Reviews of Group Directors**

The AC is pleased to report that all Group Directors have been reviewed positively for renewal by expert mail reviewers and that this opinion is shared by the AC following oral examination. The AC notes, however that, whereas some GDs are consistently making major scientific contributions, there are differences in the achievements of the GDs and that performance does not in all cases appear fully commensurate with the high level of resources. Accordingly the AC recommends some reduction in individual resource allocations. The AC was pleased to note, however, that Group Directors had adopted a realistic perspective on research management and planned to cease expansion or to contract group size.

## **CDB response to previous Advisory Council Recommendations**

The AC commends the CDB leadership for actions to implement recommendations, several of which are challenging. Notably formalization of the 10-year term for Team Leaders is a break from the established career system in Japan. However, by setting this example CDB is likely to influence wider practice as well as secure its future vitality. The AC acknowledges the personal efforts of the Director in supporting departing Team Leaders in their attempts to find suitable positions. CDB has also followed AC recommendations to establish a strategic programme in stem cell biology through the Director's projects and to support translational stem cell research through the work of Dr Takahashi. Team Leader recruitment has been maintained in the face of reducing budget, and new female laboratory heads have been appointed where possible. The AC notes acceptance of the recommendation that Group Director budgets should be adjusted in line with performance as evaluated at full-term reviews and that several Group Directors have planned to contract their group size. Incoming Team Leaders are also offered more modest start-up packages than previously, with scope for increase based on positive mid-term evaluation. Efforts to improve internationalisation, collaboration and mentoring are proceeding, although there remains scope for further progress in these areas. Similarly, rationalization of in-house services is ongoing but not yet complete.

## **Challenges and Opportunities for CDB**

The CDB is approaching a period of change and potential uncertainty. At the same time this is a moment of great opportunity for research at the intersection of developmental and stem cell biology. It is therefore of paramount importance that RIKEN give full support to CDB through transitions in leadership and funding.

### ***Leadership of CDB***

The eventual successor to Dr Takeichi must be a developmental biologist of the highest scientific distinction and a champion of fundamental research. A future Director will face the challenge of consolidating the position of CDB as one of the world's foremost institutes in developmental biology during a period of political and financial uncertainty. International stature and well developed leadership skills are essential for this role. The AC is unanimous that an external appointment is necessary to maintain the vitality of CDB and lead the Center through the next phase of its evolution. The AC is particularly enthusiastic about the potential for attracting a world-leading non-Japanese scientist due to the reputation and resources of CDB. While there may be excellent Japanese candidates to consider, a foreign appointment would instantly enhance the global presence of CDB. This benefit should greatly outweigh any

administrative difficulties. It is also hoped that RIKEN can be responsive to the international salary level expectations of a foreign Director. The AC urges the CDB management to discuss thoroughly with RIKEN the case for considering a possible foreign appointment.

### ***New Group Directors***

Dr Aizawa and Dr Nishikawa have both indicated their intention to retire during the next quinquennium. It is strategically important for CDB to replace both the expertise in mouse transgenesis of Dr Aizawa and the stem cell biology research programme of Dr Nishikawa. The AC also consider that it is important to avoid or minimise any gap in appointment of new Group Directors, which might otherwise weaken the scientific profile and the internal management of CDB. Effort should be made to identify a Director designate before the retirements of Drs Nishikawa and Aizawa in order that he/she could be involved with the timely recruitment of successors. The GD recruitments should be done through an open international search to identify the strongest possible candidates for these posts. As with appointment of a foreign Director, recruitment at GD level of a non-Japanese or a repatriating compatriot with extensive overseas experience, should be considered. This would help attract more of the world's best young scientists to post-doc and Team Leader positions, and would also provide a more international mentorship within CDB.

### ***Turnover of Team Leaders***

The AC gives complete support to the CDB Director for implementing and adhering to the 10 year rule. The AC judges that the majority of TLs should have little difficulty in obtaining good appointments provided they are realistic in their expectations and prepared to consider different institutions. As one AC member noted "they should realise that there are more than three Universities in Japan". AC members from Japanese Universities emphasised that there is no bias against job applicants from CDB, but also noted that legitimate questions will be asked about teaching experience and research funding. TLs should therefore prepare thoroughly for interviews, not just in terms of their research presentation but also by considering how to address issues of teaching, research costs, grant proposals and all round ability to function in the University environment. If some of the funding of TLs was obtained through internal grants (see also comments below on TL reviews) it would give TLs experience of preparing applications and provide them with a form of grant history for a prospective University employer.

The timing of initial recruitments to CDB means that multiple TLs are now nearing the end of their contracts and seeking external positions at the same time. While exceptions should not be made to the 10 year rule, the AC recognise that in the next couple of years, before the expected wave of retirements in the Universities, there may be one or two instances where a deserving individual TL does not secure a suitable appointment at the end of the 10 years. If there is a

genuine prospect of such a TL finding a research position, the AC suggest that a transition grant could be awarded for up to 12 months. The application format for such a grant should be similar to that for an external project grant, which will provide useful experience for the TL. The application should also include information on positions applied for or known to be coming open. The funding should be considerably less than that of a TL in order not to undermine the 10 year rule, and the AC suggest a maximum of 60%. In some cases it may be more appropriate to provide only TL salary to support manuscript writing. Applications may be scientifically evaluated by the GDs plus one or more external assessors, for example from the TL's previous review committee. AC members would also be willing to provide evaluations or advice if requested by the Director.

More generally it may be appropriate to consider whether the current number of team leaders is in line with the capacity of the Japanese University system to both provide high quality new independent investigators and to absorb departing TLs. Appointment of more foreign TLs would alter this national dependence. Nonetheless it may be worth considering adjusting the balance of junior and senior appointments in CDB by, for example, creating an additional GD post at the expense of two TLs. Such a decision may be best left for the next Director, however.

### ***Animal Resources and Genetic Engineering Support Laboratories***

The efficient generation of sophisticated mouse transgenic models is extremely important for many research projects within CDB and is also highly valued by University based researchers and international collaborators. This is a prized asset of CDB and it is therefore necessary that an appropriate individual is identified to provide leadership for these facilities upon Dr Aizawa's retirement. It is possible that this position may be separated from the GD appointment.

### ***Management of Budget Cuts***

The AC strongly recommends that CDB maintains its full research complement by continuing to recruit TLs at the present time. Accordingly the AC suggests that the present budget cut should be spread evenly across all current CDB expenditure categories rather than cease recruitment. Full funding could be maintained for selected TLs at the Director's discretion, based on the indicative grades provided by the AC.

Budget cuts could be ongoing, however. The CDB should prepare for this possibility by identifying opportunities to rationalise administrative support and core services. In this light the AC recommends completing the amalgamation of Genomics Support laboratories.

There is scope to improve the targeting of research funding to investigators who are most productive and to reduce funding to individuals who lack focus or depth in their studies. The

AC recommends that future renewal reviews of GDs and TLs should include a proper evaluation of the level of funding according to scientific quality and needs. Review documentation should follow the format of a grant application, including full justification of requested salaries and research costs.

### ***Patents and Licensing***

CDB has filed several patent applications, but information is lacking on commercial licenses and revenues. It is valuable for the long-term sustenance of the CDB to create an entrepreneurial culture that synergizes with the scientific endeavour. An important issue to resolve is how revenues are shared between RIKEN, CDB and individual inventors which may impact on the incentive for translating the scientific knowledge gleaned from laboratory discoveries.

### ***Project Prioritisation/External Funding***

Excepting the special case of iPS cells, the AC had some concerns that the research balance of CDB might be distorted by the targeted availability of government funds in specific translational fields. It is not clear to the AC to what extent CDB may be expected to undertake certain projects by national or local government, or may be pursuing external funds opportunistically without full consideration for the strategic implications. Forceful articulation of the research mission of CDB, as discussed above, could help clarify this situation. It is also necessary that RIKEN maintain funding to CDB to prevent diversion away from the core mission of generating new knowledge in basic mechanisms of developmental and regenerative biology.

## **Recent Developments in CDB**

### ***Strategic Project Initiative***

The AC congratulates the CDB Director for initiating Strategic Projects in the high priority areas of Systems Biology and Pluripotent Stem Cell Biology and for identifying two outstanding scientists to lead them. These projects can build on the strengths of CDB and advance into new areas. The multi-disciplinary approaches of Dr Ueda, from atom to organism, are very innovative, while Dr Niwa brings deep expertise in the molecular regulation of pluripotent stem cell biology. The AC is enthusiastic about the prospects of collaboration between these two investigators. This interaction should begin to address the next level of questions in pluripotent stem cell research and bring new biological insights. As such, this fundamental science should also be of high relevance to iPS cell research and applications.

The Stem Cell Project will benefit from appointment of additional team(s) to complement Dr Niwa, possibly through studies of tissue stem cells. This issue will become pressing as the retirement of Dr Nishikawa draws near and requires attention if CDB is to maintain critical mass and international profile in stem cell biology.

The AC are pleased to note that not only are Dr Ueda and Dr Niwa highly productive, but they also have excellent track records of collaborations within and beyond CDB and of securing external grant funding. They contribute significantly to the wider recognition of CDB in Japan and provide an example for other CDB investigators. The AC also commends the CDB management for inviting Drs Ueda and Niwa to GD meetings and engaging their participation in certain aspects of recruitment and strategic decision making.

### ***Imaging Facility***

The AC was pleased to see that high specification imaging equipment will now be organised as a centralised facility supervised by a highly skilled specialist. The AC note that Dr Mimori-Kiyosue's personal research interests are concerned with methods and technology developments that align well with interests of several research groups in CDB. Therefore, once the imaging facility is consolidated in one place and operating efficiently, the AC support the suggestion that she could apply for modest internal grant funding. We recommend that such a grant application should specify likely users/collaborators within CDB of the methods she intends to develop.

### ***Science Policy and Ethics Studies Unit***

The AC strongly endorses the setting up of this Unit. Science Policy and Ethics is a growing topic of international research and collaboration. Doug Sipp is a talented and committed individual and it is hoped that Japanese funding agencies will recognise the value of supporting his research which is an important and timely innovation in Japan

## **CDB Contribution to iPS Cell Research and Biomedical Application**

The AC requested a presentation by Dr Takahashi and members were impressed to hear the considered approaches she is taking to exploitation of iPS cells and hES cells for study and treatment of retinal diseases. Her goal of progressing to clinical trials in Kobe within 5 years appears soundly based and achievable. Dr Takahashi is clearly an able and committed clinician scientist. She is making full use of the resources and expertise available in CDB, and is well supported by Dr Sasai. The AC are also impressed that she maintains good links with Dr Yamanaka and colleagues in Kyoto. This project has the potential to be a major success for Japanese biomedical science and to bring great credit to CDB.



Nonetheless, the AC note strong statements in the MEXT evaluation and the Science and Technology review concerning the priority for Japan of advancing and translating iPS cell research. It is evident that CDB is expected to make a major contribution in this area and indeed has already been allocated significant funds for this purpose, including construction of a new Stem Cell Research building. However, it is not clear how this building will be occupied and how funding will be obtained for long-term sustainability. An obligation to advance iPS cell research is reasonable for CDB, though this should be through synergy with, and not at the expense of, fundamental studies in developmental and regeneration biology. CDB engagement in the iPS cell field should be organised to benefit from investigator-driven discovery research and thereby complement the translational focus at CiRA.

The AC reiterates our previous recommendation that CDB articulate a clear and coherent strategy for iPS cell research that will bring significant added value to the national effort. The CDB approach must be founded in basic research and should not duplicate studies in CiRA and other Japanese centres. The work of Drs Niwa, Sasai and Takahashi provides pillars for such a strategy, and should be promoted as part of the national campaign in stem cell research and regenerative medicine. It is understood that individual competition in specific areas is unavoidable and often productive, but in general opportunities should be explored for fruitful engagement and cooperation with CiRA in key areas.

## **CDB Contribution to Training the Next Generation**

The quality of scientists trained and their future success are key measures of the impact and standing of a research institute over the long term. The AC considers that highly trained scientific personnel should be evaluated as a major output of CDB. CDB trained PhD graduates and post-doctoral fellows should depart CDB to populate leading laboratories in Japan and around the world, and a proportion should progress to become principal investigators. The AC feels that this expectation and sense of ambition should be more evident in the philosophy and day to day practice of CDB.

### ***PhD Students***

The current number of PhD students (30) is low for an institute the size of CDB. While research should be the main focus of CDB principal investigators, it is also important that they contribute to training the next generation. The AC considers that there should be at least 50 PhD students in CDB. The AC also recommends that CDB GDs and TLs should engage fully with graduate programmes in the Universities. This provides an important opportunity for TLs to demonstrate their competence and value in the University setting. If they are involved in teaching, they may

also attract good students and post-docs and generally encourage a more dynamic exchange between the University sector and research institutes. It may be appropriate for CDB senior management to have discussions with the Universities in order to clarify opportunities for mutual benefit rather than competition.

A vibrant PhD student group can contribute greatly to the energy and vitality of a research institute. The short courses for external students on human ES cells and iPS cells are commended. However, the AC has little information on training and networking opportunities offered to CDB PhD students to provide them with an enriching PhD programme. In order to recruit very good trainees it is important that CDB takes measures to be attractive to graduate students, particularly at a time when fewer students are inclined to enter graduate training. Training and interaction should not be exclusively limited to the host laboratory. Students should be encouraged to organise their own activities by forming a cross-CDB PhD club. The activities could take various forms; invited speakers on a range of topics, presentations to each other of their research work, literature reviews. Providing refreshments can encourage participation. The AC suggests that all activities should be in English, but otherwise impose no strict rules.

### ***Post-doctoral Research Staff***

The AC also noted an apparent lack of organised mentoring and career development guidance for post-doctoral researchers. The AC formed the impression that mentoring is mainly in the hands of the TL or GD and varies greatly. There is some central careers guidance provision by RIKEN through the General Affairs Section. Based on conversations with the post-docs, however, this does not seem to be considered overly valuable, possibly because it is too formalised and/or not suited to the particular needs of life scientists.

An important issue to consider is the reality that some post-docs will have to find positions outside of academic research. Advice should be available on alternative career paths and how to pursue them. This should be provided in a confidential manner that avoids any sense of stigma. For those who are best equipped to continue with academic research, advice should be provided on how to advance to a second post-doc or a junior PI position, as appropriate.

The AC understands that a standard post-doctoral contract at CDB is for 5 years. This is rather long by Western standards and, although in some cases a 5 year term may be necessary and valuable for pursuit of substantial projects, many post-docs' interests would be better served by encouraging them to achieve a publication within 3-4 years and then move on. The AC recommends that an internal review mechanism should be put in place for post-docs. This should not be overly bureaucratic, but should ensure that for each post-doc there is a one to one discussion with their laboratory head of progress and career plans before the end of year 3 and

annually thereafter. Metrics on post-doc authorship on publications should be collated centrally and monitored to identify cases that may need attention.

Post-doc mobility can present a conflict for GDs and TLs anxious to maintain continuity of their research. However, principal investigators should appreciate their obligations to their staff and recognise that their own standing will be judged in large part by the quality of their trainees. They should actively encourage their most promising post-docs to head to leading international laboratories. The AC recommends that this complex issue should form part of the planned mentoring programmes for TLs and should be taken into account by GDs during their research planning.

As suggested above for the PhD students, it would be appropriate to give the post-docs some capacity to organise collective activities themselves. The Luncheon Forum is clearly viewed positively by the post-docs, and perhaps this can be built on to promote wider networking and interaction. Possibly the time could be shifted to the end of the afternoon to be followed by a social hour.

Finally, in future reports it would be helpful for the AC to see metrics on the post-doctoral scientists at CDB regarding the gender distribution and nationality, research output per post-doc for each research team, and destinations of departed post-docs.

## **Collaborations within CDB**

While there are a few shining examples, overall relatively few collaborations are evident between laboratories in CDB. The traditional Japanese Koza philosophy appears dominant in the minds of many PIs and post-docs. It is of course essential that each TL and GD produces recognisable contributions in their own right. However, a central justification for a research institute is “added value” compared with a conventional University structure. While there are several factors to added value, in-house collaborations and interactions are an important measure. The AC recommends that the CDB consider how to promote and facilitate internal collaborations. One option might be to offer a scheme of internal competitive grants to fund worthy collaborative research, possibly open to post-docs as well as PIs. Such collaborative grants might also extend to interactions with other RIKEN institutes.

## **Future Group Director Reviews**

The AC requests that the scope and contents of the GD reports and plans should be standardized in future. Without becoming overly long or detailed, future plans should summarize the

background and significance of each project, the specific hypotheses being tested, the proposed experiments, and alternative approaches. In addition, a budget justification should be provided, including the roles of the laboratory personnel and the distribution of the resources to accomplish the specific projects. Information should also be tabulated on PhD students and post-docs trained, with their next destinations.

The valuable contribution of GDs to supervision of the core facilities in CDB is appreciated and should be documented as should mentoring responsibilities. This important aspect of their role is not well described. The AC has the impression that some TLs might have benefitted from engaging more with mentors. The Director is applauded for meeting each TL individually. The AC understands that each TL also has a GD mentor, but it is not apparent how this relationship works in practice

### **Content of next AC meeting**

The AC has appreciated the opportunity to meet with post-docs over lunch but would also like to hear some examples of their research work. A suggestion is that for the next meeting the GD mid-term presentations might be compressed into one morning or afternoon, comprising summary presentations from each GD followed by Q&A session (perhaps 20mins each). This would allow time for a session in which one post-doc from each GD group could present their own research project. The AC would also like to engage with some of the PhD students, perhaps at a poster session.

## **Summary of Recommendations**

All Group Directors are recommended for renewal with funding allocations adjusted in line with the outcome of performance evaluations.

Raise the profile of CDB by articulating the core mission and publicizing accomplishments within Japan through public relationship instruments.

The next Director of CDB should be an external appointment and the opportunity to attract a leading foreign investigator should be considered and pursued.

Seek timely replacements for Deputy Directors/GDs Aizawa and Nishikawa.

Search for a suitable successor to Dr Aizawa as Head of the Animal Resources and Genetic Engineering Support Laboratories.

Make new appointment(s) in stem cell biology.

Allocate research funding according to evaluations of performance and potential.

Continue to rationalize Genomics Support laboratories and monitor cost-effectiveness of other support units.

Engage positively with CiRA and other iPS cell centres in Japan and abroad.

Increase the number of PhD students and establish PhD student discussion forum.

Establish review process and mentoring system for post-docs.

Promote internal collaborations.