

# **6<sup>th</sup> ADVISORY COUNCIL**

## **RIKEN Brain Science Institute**

**April 12-14, 2004**

### **INTRODUCTION**

The 6<sup>th</sup> review meeting of the Advisory Council of the RIKEN Brain Science Institute (BSI) comes at a time when the Institute has begun to realize the promise with which it was founded. It is now well-established as a major neuroscience research institute in Japan, with world-wide stature and visibility. It is well-housed on the Wako campus in four modern research buildings, one recently completed; the laboratories are well-equipped and well-supported; the research facilities are excellent; and most importantly, the overall quality of the faculty is high. RIKEN BSI is a magnet for young Japanese and foreign scientists who come to train here, and through the RIKEN BSI Summer Program, it offers laboratory and classroom instruction on modern neurobiology to students from all over the world. It also sponsors a variety of international symposia and workshops and has cooperative agreements and research collaborations with institutions and companies from around the globe. After a six year period of growth and development, RIKEN BSI may be said to have arrived. Its stature is a tribute to the vision of its founding Director, Dr. Masao Ito, and to the Japanese government which has supported this ambitious and remarkably successful initiative.

Under a new and distinguished Director, Dr. Shun-ichi Amari, RIKEN now enters into a new phase of development. RIKEN has been reorganized as an independent administrative institution, which offers new opportunities and challenges for RIKEN BSI. Concomitantly, the budget and projected size of RIKEN BSI have begun to level off. RIKEN BSI has responded to the new administrative and fiscal environment by reexamination of its management systems and by developing a new budgetary plan. The new environment also carries scientific challenges. As its growth slows, and new resources become more scarce, the ability of the Institute to recruit new scientists and to take advantage of new scientific opportunities will critically depend upon its continuing commitment to the highest scientific standards in evaluating all of its activities and allocating all of its resources.

## **BACKGROUND**

The Advisory Council made a three day visit to the Institute, where Dr. Amari reviewed the current status of RIKEN BSI and the changes that had occurred since the last Advisory Council meeting. We were particularly saddened by the loss of Dr. Gen Matsumoto, the Group Director of the Brainway Group, who passed away in March, 2003. During the first day and a half, each of the groups made presentations, outlining the ongoing work in their laboratories. Members of the Advisory Council then visited scientists in their laboratories to learn more about their activities. These reports and visits form the basis of our report.

## **GENERAL OBSERVATIONS:**

The Advisory Council was pleased by the continued overall high quality of the scientific presentations, which were in most cases, clear, well-illustrated and informative. Several of the talks presented work of unusual scientific quality and excitement.

The quality of the new appointments, particularly the new Laboratory Heads, appeared to be generally high. We applaud the ability of the RIKEN BSI to attract such outstanding young scientists.

We were delighted to see the confidence placed in outstanding young scientists who have recently been appointed as Group Directors. Two of these groups gave presentations that were outstanding.

The Council applauds the establishment of unit leader positions at BSI, which helps to foster independent research career of young investigators. The Council encourages the BSI administration and Group Directors to pay special attention to ensure that these research units function independently and are evaluated in the same way as laboratories.

The Council applauds the recent excellent appointments of several female laboratory heads and unit leaders. We note that there is a large contingent of female graduate students and postdoctoral fellows of high quality and commitment in Japan and BSI provides an excellent environment and infrastructure for the development of independent research career for female neuroscientists. The council recommends that continuing efforts be made in

future recruitment and consideration of female candidates for appointments as unit leaders, laboratory heads, and group directors.

We support the formation of the new section on Nurturing the Brain which addresses a timely and important issue. We note the strong thematic connections between this group and the Recovery Mechanisms group and hope that strong interactions between the two groups will be encouraged.

The separation of areas of responsibility for the ATDG and RRC is a logical step that should further improve the important functions of these groups.

The steps that RIKEN BSI have taken to assist foreign scientists are very positive, but they need to be continued and expanded in order to attract a larger number of foreign scientists, an explicit goal of the RIKEN BSI.

## **RECOMMENDATIONS AND CONCERNS**

1. Overall vision for the future. As growth of the BSI levels off, establishment of priorities for future development become extremely important. We urge Dr. Amari as BSI Director to work with BSI investigators to develop a coordinated plan for the future of the BSI. Such a vision is needed to provide focus and direction for future programs and recruitment, to increase the coherence and integration of work in diverse laboratories. This vision is especially important as a prelude to the September effort to re-imagine the Creating the Brain section.

2. Systems neuroscience. RIKEN BSI boasts extensive expertise in genetic manipulation of rodent neural systems, and this expertise is currently exploited primarily in the arena of neural development and disease mechanisms. Considerable synergism between molecular biologists and systems neurophysiologists could occur, however, if a systems neurophysiologist were recruited to assess the behavioral and electrophysiological consequences of specific genetic manipulations. With such a program in place, RIKEN BSI scientists could truly study the nervous system seamlessly from molecules to behavior in a single organism. Other promising targets of opportunity for the 'understanding the brain' program would include use of multiple patch electrodes in slice preparations to delineate the computational circuitry of the cerebral cortex. These

opportunities must be considered in the context of the overall needs of RIKEN BSI and of those of other thematic areas.

3. Group Directors. We note with concern the delays in hiring Group directors. Drs Ito and Amari together have responsibility for a large number of staff (35% of Japanese and 55% of external people in 5 Groups). This would seem to put a heavy burden on them and would point to a need for significant recruitment at the Group Director level in the future.

4. Promoting Communication and Collaboration between Laboratories.

One of the hallmarks of contemporary brain research is the multidisciplinary and collaborative approach that is often necessary to do cutting edge research. In this context, one of RIKEN's strengths is the breadth and variety of the approaches to brain research that it takes. The Advisory Council believes that some of the scientists at the RIKEN BSI are not able to take full advantage of these resources because of the low level of interaction between some of the laboratories within the Institute. It also limits the experience of post-doctoral fellows at RIKEN BSI, as discussed further below.

The Institute needs to take steps to address this problem. The current evaluation and funding system appears to offer little incentive for collaboration. We suggest several possibilities for improving the contact between scientists.

- a. We urge the Director to set aside funds that would be awarded on a competitive basis for collaborative projects across laboratories and groups within RIKEN BSI.
- b. We suggest that RIKEN BSI incorporate collaboration across laboratories and groups into its evaluation of individual scientists. Any impediment to collaboration (e.g. who gets credit for publication) should be identified and removed.
- c. We encourage the formation of journal clubs within and across groups. A journal club on the cerebellum, for example, would attract scientists from across the Institute. Other examples might be neurodegenerative disease or developmental neurobiology.

5. Post-doctoral fellows. As RIKEN BSI becomes a major training institution for young Japanese and foreign scientists at the post-doctoral level, it is appropriate that more attention be paid at the Institute level to improving their experience at RIKEN. Developing this area could increase the attractiveness of RIKEN BSI for post-doctoral scholars, particularly those

from abroad, and aid in their retention. The Advisory Council was particularly concerned about the relative high proportion of fellows who stay for less than two years. Training of such short duration is not an optimal investment of RIKEN resources and is a potential loss of valuable research time for fellows. We offer the following suggestions to enrich the scientific environment for post-doctoral fellows.

- a. Isolation. One impression of the Advisory Council is that postdoctoral fellows are often isolated, with little contact outside their immediate laboratories. Some of the suggestions offered in the previous recommendation on promoting collaboration may improve this situation. We also urge that Group Directors try to address this issue within their groups.
- b. Courses. The availability of short introductory courses in several specialized areas of neurobiology (e.g. Computational Neurobiology; Molecular Neurobiology; Mechanisms of Learning and Memory; Neurobiology of Disease) aimed specifically at RIKEN students and post-doctoral fellows and offered on a rotating basis over a period of several years would be a major benefit to post-doctoral fellows by expanding their knowledge base of neurobiology. It would also encourage contact and collaboration between groups.
- c. RIKEN BSI might explore the possibility of hiring a full time science writer who could work with fellows to improve their writing of manuscripts and reviews in English.

6. Students. RIKEN BSI should encourage and expand its opportunities for graduate students. Perhaps the best solution would be to strengthen ties with universities. An alternative possibility to consider is the establishment of a graduate training program at RIKEN BSI similar to that seen at National Institute for Physiological Science at Okazaki.

7. Animal facilities. The provision of high quality facilities for animals, particularly mice and non-human primates, is often a critical factor in the success of modern biomedical research institutions. In view of the increasing use of transgenic mice and the growing need of behavioral analysis, we recommend that RIKEN BSI analyze its projected needs and to develop a plan for future facilities, if they are needed. Included in the analysis should be an examination of whether RIKEN investigators are using the present facilities with maximum efficiency. Outside consultants or professionals from other institutions might aid RIKEN to evaluate its future needs.

8. Future reviews by the Advisory Council. We have several suggestions that might improve future reviews by the Advisory Council.

- a. We would like to have separate meetings with one or more groups of post-doctoral fellows and students, and with unit leaders and laboratory heads.
- b. We would like the short CVs (one page summarizing training and important publications) of all laboratory heads and unit leaders. This would better help us in the evaluation.

We support the use of the outside review mechanism to evaluate RIKEN BSI investigators. We caution, however, that frequent reviews sometimes have the inadvertent effect of encouraging investigators to publish many small papers rather than fewer, more substantial papers in major journals.

### **Thematic Areas:**

#### **UNDERSTANDING THE BRAIN**

We are pleased with the overall strength of the RIKEN BSI program in ‘understanding the brain.’ The program consists of two major laboratories—Neuronal Circuit Mechanisms (Group Director: M. Ito) and Cognitive Brain Science (Group Director: K. Tanaka)—in addition to the RIKEN-MIT joint program. These research efforts have considerable vitality and are contributing substantially to our ongoing efforts to understand the basic principles by which the brain gathers and processes information, learns from experience, and produces behavior.

#### Neuronal Circuit Mechanisms research group

The expertise accumulated in the Laboratory for Memory and Learning headed by Dr. Ito on cerebellar circuitry is unique. The Advisory Council urges that this expertise be continued at BSI. The development of fluorescent indicators in the Laboratory for Neuronal Circuit Dynamics is highly promising, and several recent advances seem now ready for wider application. The unit leaders are well integrated in the Group and interact at different levels with each other and the laboratory heads. Specifically, Drs. Endo and Hirabayashi have developed interesting mouse models for detailed analysis. Similarly, the GAD knockout mice available in Dr. Obata’s unit provide tools that will allow important questions to be tackled.

Cognitive Brain Science research group This research group emphasizes empirical research on the organization and function of the cerebral cortex, employing an impressive array of modern physiological, anatomical and modeling techniques. The electrophysiology and optical imaging efforts of the Tanaka and Tanifuji groups are world class, and the technical development of optical coherence tomography in the Tanifuji lab may provide access to deep regions of cortex that have been heretofore inaccessible to optical imaging technologies. The anatomical investigations of the Rockland laboratory are interesting, and are particularly powerful when combined with physiological techniques that provide simultaneous information about function. Thus we are particularly impressed with the collaboration between the Tanifuji and Rockland labs in which optical imaging of IT cortex is used to guide the placement of anatomical tracer injections.

We are pleased that the high resolution fMRI studies are now progressing beyond “proof-of-principle” demonstrations (i.e. human ocular dominance columns) toward addressing new and interesting issues in visual cortical function (i.e. adaptation, temporal tuning, motion vision). This facility for high resolution fMRI is a world-class facility, and we hope to see a stream of high-quality research publications emerge from this group during the next few years. Unfortunately, the Advisory Council received little information during this meeting concerning the current status of the MEG research effort. An original motivation of this imaging group was to combine fMRI with MEG in order to obtain functional information from the human brain at both high spatial and temporal resolutions. One publication has appeared on this topic during the past year (NeuroImage, 2003), and this is encouraging. We suggest, however, that an explicit review of the human imaging effort be included in the agenda of next meeting of the Advisory Council in 2006. It may be appropriate to invite an ad hoc member with expertise in human neuroimaging to participate in the next Council meeting. We again raise the possibility of creating an additional laboratory directed by a researcher who uses fMRI and/or MEG to investigate hypotheses concerning human cognition.

RIKEN-MIT Center The presentation by Dr Tonegawa illustrated several examples of exciting projects being conducted by the groups at the Picower Center at MIT. These focus on mechanisms and functions of activity-dependent synaptic plasticity from AMPA receptor recycling and receptor-associated protein-protein interactions as well as behavior studies and multiple single-unit (“tetrode”) recording in awake mice, including genetically

modified mice. There is no doubt that the work of this center is state-of-the-art, notably Tonegawa's use of brain region-specific conditional knock-out techniques and their application to network level issues in neuroscience such as pattern completion. Two specific examples of collaboration and technology-transfer between MIT and BSI-RIKEN were mentioned (use of FRET imaging, and conditional gene-knockout technology to exploit the discovery of the cerebellar L7 gene); other opportunities of this kind may emerge as the American and Japanese labs get to know each other better. We urge RIKEN to encourage these interactions. The Advisory Council shares Dr Tonegawa's view that this venture between the two institutions is exciting and mutually beneficial.

Future opportunities. We note that significant opportunities exist for enriching the RIKEN program in understanding the brain. The existing programs in neural circuit mechanisms and cognitive brain science are very impressive, but new research programs in several areas would enhance the effort of RIKEN BSI to understand how the brain works. We suggest consideration of a program that studies behavior and systems level electrophysiology in rodents, as suggested above.

## **PROTECTING THE BRAIN**

This section has been recently reviewed and received a generally excellent evaluation. All groups within « Protecting the Brain » are excellent and several laboratory heads have attained world recognition, although a slight note of caution exists in some laboratory.

Many laboratories have interactions with hospital units. Interactions with some hospitals should be formalized to ease these interactions so that greater advantage can be taken for opportunities of working on problems related to patient populations. For some MD investigators, it may be appropriate to include some commitment for clinical time in their responsibilities as RIKEN investigators.

## **CREATING THE BRAIN.**

The 2002 Council of Advisors stressed the need for the Creating the Brain section to fully develop meaningful collaborations with experimentalists across BSI, and welcomed Dr. Amari's plan for restructuring the Creating the Brain program. While applauding Dr. Amari's world leadership in the

mathematical theory of neural networks, they recommended hiring as a Group Director a world-class computational neuroscientist committed to building bridges to experimentalists throughout BSI. They also recommended that appointments should address all levels of modeling from the synaptic to circuits to systems level. The 2002 Council also suggested a review of the focus and function of the Brainway group, a task made more urgent by the untimely death of Gen Matsumoto.

The present Council notes with approval the plan to hold an international workshop followed by a full-scale re-evaluation of all Creating the Brain laboratories in September 2004. We stress that the review committee should be offered alternative plans for major restructuring which fully address the 2002 Council recommendations. Interactions between neuroscientists and non-biological researchers in Creating the Brain must be increased to prevent isolation and to provide further opportunities for computational modeling or mathematical analysis in BSI's experimental groups. To give just one example, we see the opportunity for a major effort in cerebellar modeling.

The 2002 Council recommended the integration within laboratories of work on computational neuroscience, robotics and brain-style computing but the present Council favors the formation of more focused laboratories with a strong plan for cross-lab collaboration.

We recommend that the theoretical laboratories in RIKEN engage further with major laboratories overseas in computational and cognitive neuroscience as well in experimental neuroscience. There could be a great payoff, at low cost, through collaborations targeted on specific BSI efforts at Wako, e.g., through visiting relationships with researchers at other institutions.

### **ATDG and RRC.**

We welcome the reorganization of ATDC into the Advanced Technology Development Group (ATDG) and the Research Resource Center (RRC). We note that Neuroinformatics has been established as part of ATDG. It has a focus on visual mechanisms. However no clear plan has been explained either for extending work on the Visiome Platform beyond that just completed under 5-year funding elsewhere, nor for offering a more general support function within ATDG to provide a federation of databases and data analysis and modeling tools for BSI generally. Given its overlap with computational neuroscience, we recommend that Neuroinformatics be reviewed in

September 2004 as part of the plan to restructure Creating the Brain, and that a plan for Neuroinformatics be presented at that time.

## **NURTURING THE BRAIN**

This section has also been recently reviewed with a very favorable evaluation. The council applauds the formation of the new section on Nurturing the Brain as it brings together a talented group of investigators in the Brain Development and Critical Period mechanisms groups that are addressing timely and important issues. The overall quality of research in both groups is high. In addition, each group brings together researchers with diverse approaches and levels of analysis but with conceptually overlapping interests that should provide a rich interactive environment. The Critical Period Mechanisms Group is especially commended for developing structures, including journal clubs and monthly reports of individual labs to the entire group, that should facilitate research interactions and provides an optimal training environment for postdoctoral fellows and graduate students. We also noted the strong thematic connections between those in the Nurturing the Brain section and the Recovery Mechanisms Group and hope that strong interactions between these groups will also be encouraged. In addition, the success of Dr. Furuichi in the Brain Development Group in developing several interesting and independent lines of research from his cerebellar genetic screen was noted and the council strongly encourages him to pursue these endeavors. Finally, with the creation of the Cognitive Development and Human Learning Groups within this section, it would be advisable to identify an internationally known scientist with expertise in human cognition and language development to provide guidance in effective development in these groups.

**Conclusion:** RIKEN BSI is an exciting, multidisciplinary research institute of world-wide stature at the forefront of contemporary brain research. The Council trusts that its suggestions will aid planning for the future development of the Institute. We are confident that RIKEN BSI will continue to flourish as an exciting focus for obtaining knowledge about the brain and using that knowledge to the benefit of society.

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