

BSAC 2016 Report

The BSAC report is divided into two sections: The first section is a Summary of the main points the BSAC wishes to stress, and the second section is a detailed presentation of our findings and recommendations related to the four Terms of Reference provided by President Matsumoto.

Main Points

The Brain Science Institute (BSI) of Riken is a world renowned center of excellence in Neuroscience. It is *the* nexus FOR Japanese Neuroscience, fostering many interactions with foreign universities (e.g. RIKEN-MIT collaboration) and attracting budding and established scientists, from students to Nobel Laureates, to Japan. This extraordinary legacy, we feel, should be preserved and nurtured by strengthening and ensuring its future. The BSAC noted that, under the leadership of Susumu Tonegawa, the internationality and the scientific quality of BSI has been further improved and a truly modern institute has emerged where exceptional researchers, young and old, can pursue their innovative science at the highest possible level, representing a model for how science should be done in Japan and elsewhere.

With this in mind, the BSAC identifies the following critical issues that could threaten the international excellence which has been so carefully built by previous directors.

- **Uncertainty for current PIs** The BSAC noted a high level of anxiety amongst the current PIs owing to the impending restructuring of RIKEN and the BSI. One major area of concern is budget uncertainties. For example, budget cuts are sometimes implemented in the middle of a fiscal year, making planning for experiments and personnel very difficult.

Most importantly, however the PIs were worried about the crucial date of March 2018, which, for them, was an almost magical deadline beyond which no planning was possible. They are under the impression that their contracts end on this date, and moreover that post-docs cannot be told their employment can continue beyond that date. It is crippling to the science of these PIs if they cannot plan for longer than 18 months and if every job advertisement must indicate employment ends on March 2018. The BSAC was assured by the leadership of BSI (Mr. Okouchi) that this is a misperception and that PIs and postdocs can plan until 2023, at the least. The BSAC feels it is imperative to quickly and unequivocally communicate this information to the PIs. It is also essential that the RIKEN central HR department should not require that the March 2018 doomsday is indicated in every job advertisement. These steps are imperative to ensure that the quality of science and the morale of the PIs remain high, despite the inevitable uncertainty about the future.

- **Importance of future Director.** The BSI has a legacy, starting from the first director and continuing unbroken, of fantastic and inspired leadership which has positioned the BSI not only as the leading Neuroscience institute in Japan, but also a globally-recognized hub of innovation and excellence. In order to stay on this stellar trajectory, the choice of the new BSI director is of critical importance. The new director must be, above-all, an internationally recognized leader in Neuroscience with an outstanding track record of cutting-edge innovation in research as well as leadership skills and vision.
- **A minimum “critical mass” for the BSI.** Interdisciplinarity lies at the heart of modern neuroscience and this simply cannot be maintained if entire approaches are unrepresented or minimally represented amongst the faculty. Budget cuts have reduced the BSI size from ~59 PIs at its peak in 2008, to 38 currently. In order to nurture the current cross-disciplinary BSI investigations and facilitate new interactions, the size of the BSI should be not be reduced, but rather increased to include new initiatives. The BSAC thus strongly recommends a size of around 45 investigators.
- **Preserving leadership.** Japan, along with several other notable nations, has recently announced a national brain program. The BSI is in a leading position for the neuroscience community in Japan and is a flagship for brain sciences in the next decade. The investment that Japan has made in BSI over the last 20 years should be preserved.

Terms of Reference

Terms of Reference 1.

The committee feels strongly that BSI has fully achieved its research and training mission. Over the last decade, BSI has developed into a leading international brain research institute. Many young, upcoming scientists of great ability were recruited, and are just gaining the momentum to make research breakthroughs. BSI has developed an admirable track record that includes extensive internal and external collaborations. Despite budget cutbacks, the number of high-profile papers has increased and is very impressive, giving BSI an international stature. Moreover, BSI has developed as a premier institution for the training of young Japanese and international neuroscientists. Overall, by all measures BSI has been a major success.

The committee recommends that BSI should pursue the following goals over the coming 5-10 years:

1. A new BSI director with an outstanding scientific track record and an international reputation should be appointed as soon as possible with the mandate to further develop the institute and reinforce the achieved level of excellence. This director should be provided with the autonomy to make programmatic and budgetary

decisions that allow her/him to respond to and to exploit the most recent developments in the rapidly changing field of neuroscience.

2. Strengthen and consolidate the recent advances in research at BSI, and take advantage of the existing research momentum by providing calculable funding and a transparent perspective to BSI's research groups. For this purpose, it is strongly advised that BSI retains its full autonomy in terms of programmatic and budgetary decisions, and that the future of BSI as a research center within RIKEN is clarified as soon as possible.
3. Part of the reason for BSI's success was the strong interdisciplinary collaboration among groups. This should be expanded if possible, but requires that a minimal critical mass of laboratories with diverse types of expertise be maintained.
4. BSI has not recruited new young PI's since 2013. New continuous recruitments are necessary to adapt rapidly to the quickly changing technologies and concepts in neuroscience. The gap in recruitment is already noticeable at BSI. Resuming recruiting at least one PI annually is advised.
5. BSI is not only a full-fledged international research center, but also a hub of Japanese neuroscience – a reputation and prestige that took hard work to build, but can be easily lost. It is advised that BSI strengthens its integration into the international and Japanese neuroscience community as an autonomous research center. For this purpose, collaborations and common initiatives with universities are strongly encouraged. However, the committee warns against trying to mandate specific collaborations in neuroscience because the dynamics of neuroscience render such defined initiatives often unproductive (in other words, trying to tell people what to do is counterproductive).
6. The committee advises that BSI should not focus its research onto a particular area or theme of neuroscience. Focusing on a particular neuroscience area would limit the potential of BSI as a leading research center because neuroscience is increasingly multidisciplinary and is rapidly changing. In this day and age, access to multiple research areas in neuroscience is required for breakthroughs, and most advances happen in the interactions between neuroscience subfields and between neuroscience and other scientific disciplines.
7. Even the most basic neuroscience research aims to address questions of importance for human conditions, in particular diseases, but most major advances in understanding diseases emerged from studies of basic biologies, not of the diseases themselves. Thus, the committee is concerned that too strong an emphasis on translational research without a basic understanding of the underlying biology will not be productive. The committee advises that BSI should continue to emphasize fundamental mechanisms of brain function, and to use an understanding of such mechanisms for insight into diseases. Thus, the committee warns against trying to make progress in translational research without a fundamental understanding of the underlying biology, an understanding largely based on animal studies.
8. In the interactions with the PIs of BSI, the committee perceived a high degree of insecurity about the future of BSI. For BSI to fully and further develop its

potential, it is essential that the RIKEN leadership formulate, if possible, a public plan for the institute that provides a firm perspective for all stakeholders.

Terms of Reference 2

1. Leadership

The BSI is in transition and this is an opportunity to comprehensively re-evaluate its scientific mission.

The future director of BSI should be an outstanding brain scientist with a high international reputation. She or he should have wide knowledge and perspective about brain science and its future applications and should be a strong leader to motivate the members of BSI to understand human brain functions with multidisciplinary collaborative efforts. Brain Science has enormous impact on not only medical sciences but also engineering, physics, psychology, linguistics, education and sociology.

The director should recruit the best researchers from the core neuroscience fields, i.e., molecular and cellular, systems and theoretical neuroscience, and the neuroscience of diseases, and provide them with sufficient freedom and research resources to produce innovative results.

The new director also should encourage PIs to translate their findings into the diagnostics and therapeutics of brain disorders as well as non-disease related various fields of human activities that meet the needs of general society. For this purpose, the director should make the institute open to various types of collaborations with other centers of RIKEN, universities and industries worldwide.

2. Areas of focus (subthemes) within the centers field of research.

It is important for BSI to continue to represent the most exciting areas of modern neuroscience to fulfill its function as a neuroscience hub for Japan, and to maintain a critical mass of researchers in each of these areas.

1. Synaptic and cellular neurobiology (including development) 8 labs
2. Functional circuits and networks (including learning and memory) – 6 labs
3. Sensory and behavioral systems neuroscience – 6 labs
4. Theoretical neuroscience – 5 labs
5. Neurotechnology – 5 labs
6. Diseases and translation research – 5 labs
7. Human neuroscience – 5 labs

The human neuroscience area deserves special mention. BSI already has two excellent labs studying human development and language. The time is ripe to expand this sub-theme because of new experimental approaches to studying humans and bridging with animal models. Relevant research areas include:

- 1) Wearable robotics, sensory substitution & neural prosthetics specifically as a tool for the basic research on neural plasticity.
- 2) Developmental human neurobiology, including sensory-motor development in the human embryo and human brain organoids, with an emphasis on normal development.
- 3) Computational and mathematical theories of embodied intelligence.
- 4) Neuroinformatics and methods for the collection and analysis of big data.

This is also an area that has the possibilities for cross disciplinary integration with AI research.

3. Integration of research between Centers.

BSI is in a unique position to develop synergies between its laboratories and those of other Riken Institutes. The reason is that over the past decades Neuroscience has come to encompass virtually the whole range of disciplines of the natural sciences and now extends even into domains classically covered by the humanities. The subdiscipline of cognitive neuroscience offers naturalistic explanations of mental functions, some of which are specific for human subjects and have previously been the exclusive domain of Psychology, Linguistics, Sociology and the Philosophy of the Mind. It is because of this comprehensive coverage of scientific disciplines, - a necessary prerequisite for research of normal and disturbed brain functions – that Neuroscience has become an autonomous domain of research that can no longer be considered as a subfield of biology, medicine or psychology. The BSI fulfils in an ideal way the requirements for the concentration on a singular campus of subdisciplines ranging from the analysis of molecular processes all the way up to investigations of mental phenomena.

Obvious opportunities are collaborations between the BSI and other RIKEN institutes for the development of novel tools of analysis in the domains of molecular biology, genetics and diagnostics of brain diseases. A particularly fruitful collaboration is expected to take place in the domain of artificial intelligence, in the design of self-organizing autonomous robotic systems and in the development of advanced mathematical tools for the analysis of complex systems with nonlinear dynamics.

The Scientific Advisory Board unanimously agrees that such collaborations cannot be imposed by top down measures or administrative mergers of institutes. Cooperation can only emerge from the initiative of individual researchers sharing common scientific interests and visions, as documented already by the numerous international collaborations in which BSI scientists are engaged. However, incentives should be given to facilitate such synergies. This can be accomplished by organizing joint symposia in order to raise awareness of available opportunities and by setting aside a special budget to provide seed money for cooperative projects. Scientists of different Institutes of RIKEN should have the opportunity to apply for such seed money on a competitive basis in order to be able to start a cooperative research project.

Terms of Reference 3

Pioneer a research management model for maximizing research and development results

Evaluation. From its inception in 1997, RIKEN BSI has been on the cutting edge of developing new research management models in Japan for maximizing research and development results. Most importantly, BSI has given young team leaders (i.e. faculty equivalents) unprecedented freedom pursue their most ambitious research ideas, eliminating hierarchical obstructions that discourage creativity. BSI has successfully attracted a significant cohort of foreign scientists as team leaders, who bring new ideas, techniques, and experimental approaches to the entire RIKEN community. Under the leadership of Director Tonegawa, BSI has given highest priority to scientific excellence in its hiring and promotion decisions. Standards are very high, and junior Team Leaders have had confidence that their performance will be judged fairly by outstanding peer researchers who are experts in the field. The high standards ensure regular faculty turnover and a fresh flow of new ideas and techniques into BSI. The confidence of the junior Team Leaders in the fairness of the process has been shaken recently with the announcement that BSI procedures for evaluation and promotion will be abandoned in favor of new RIKEN-wide committees whose standards and criteria are as yet unclear. This uncertainty is harmful to the morale of junior Team Leaders and must be addressed as soon as possible (see recommendation below).

The current governance structure of BSI is healthy, with input being received and seriously considered at multiple levels from the BSI Board of Directors, the Executive Committee, the PI Assembly and the Academic Council. From our interactions with multiple faculty over our two-day visit, we conclude that faculty of all levels feel that their views are heard and that they have a strong stake in BSI governance. This creates a sense of ownership among the faculty that is vital to maximizing research and development productivity.

External research funds have also been a source of remarkable success. In FY2015 BSI partnered with 26 companies and received a total of 632 million yen. This resource is well-poised to continue to grow, and should be encouraged and fostered.

Recommendations. In a period of declining funding, BSI leadership has performed exceptionally well in maintaining core programs and laboratory support while cutting expenses where possible. The cuts have been draconian, and we are impressed by the loyalty of the faculty and their continued commitment to BSI during a very difficult time. This sense of identity and commitment to BSI among the faculty is a precious asset in maintaining BSI productivity and morale.

- **BSI leadership is to be commended in creating this culture; it speaks eloquently for the structure that has been put in place, and should be preserved and encouraged by the RIKEN administration.**

- **We strongly urge RIKEN to clearly articulate the new procedures for evaluation and promotion of faculty, and also we urge that these procedures be based on scientific excellence as judged by competent peer scientists.**

Lead the world in pre-eminent research and development achieved through scientific excellence.

Evaluation. The BSI faculty has produced major new discoveries that transcend existing fields of research. Director Tonegawa's research on the circuit level mechanisms of memory has been particularly elegant. The ability to implant memories artificially into the mouse brain and have the animal act on those memories is an acid test of our understanding of the neural mechanisms underlying memory. Dr. Tonegawa's fusion of molecular, circuit, and behavioral techniques transcends traditional disciplinary boundaries. Dr. Miyawaki's laboratory has developed important new molecular tools including fluorescent proteins that are fused to functional proteins to trace intracellular signaling pathways. Dr. Miyawaki's new tissue clearing technique, Scale, has been applied to the rodent brain during the past year as originally intended, but strikingly, has also been applied productively to multiple tissues including heart, lung, GI system, lymph nodes and animal embryos. This is a salient example of tool development facilitating research in totally unanticipated ways. The Brain/MINDS project, hosted and spear-headed by BSI, is an important project to develop transgenic primate models (using the common marmoset) for the study of human disease, bringing the power of genetic tools developed in the mouse to primate neurobiology. An important first stage of this effort is mapping gene expression patterns across the entire marmoset brain and comparing these patterns to those measured in mouse at the Allen Institute for Brain Science. The Brain/MINDS project has already discovered substantial differences in expression patterns of certain genes between primate and rodent brains in addition to many patterns common to the two species. This project transcends fields by providing a unique resource that will support multiple unforeseen investigations far into the future.

Recommendations. Without a doubt, RIKEN BSI is one of the premier neuroscience research institutions in the world. BSI has an enviable balance of experienced senior Team Leaders with established international reputations and talented junior Team Leaders who are brimming with new ideas for advancing all areas of neuroscience from molecular disease mechanisms, to higher primate and human cognition, to technological innovation that will enable fundamentally new types of experiments to be performed in the future.

- **This critical base of human talent is BSI's most precious resource and must be protected at all cost.**

Hub of science and technology innovation

Evaluation. The advisory council accepted Director Tonegawa's description of the strong steps taken by RIKEN BSI to drive creation of a hub for neuroscience-focused science and technology

innovation. Particularly striking examples included numerous interactions with industrial partners such as Olympus, and within-RIKEN/cross-center interactions: Prof. Miyawaki interacting with the RAP center for advanced photonics, Prof. Tonegawa collaborating with the BRC Bioresource Center in circuit genetics, Profs Saido and Kato working with the RIKEN –omics CLST, and Prof. Tanaka’s use of the K-ray cyclotron at the RIKEN Spring-8 Center. Director Tonegawa also highlighted areas of expected further growth in this direction, including with the CAII Center for Advanced Integrative Intelligence Research, and neural circuit simulation in the AICS (Advanced Institute for Computational Science). Finally of course we note the strong interactions, including via Prof. Miyawaki, with the exciting national Brain/MINDS effort.

Recommendations. While we find these efforts to be exciting and potentially transformative, the council did have a recommendation for driving further hub-like integration of BSI within RIKEN. While some of the more senior PIs (Miyawaki, Tonegawa, Tanaka) as noted above were engaged in these cross-Center interactions, many of the younger PIs were not engaged in such efforts, or were unaware of mechanisms that could facilitate interaction.

- **A specific recommendation for new policy is initiation of a small seed-grant program for pilot studies that would require involvement of at least two PI from at least two different centers.**

The impact of such cross-cutting programs has been highly successful at other institutions in the US, and often leads to initiation of novel conversations and collaborations that simply would not have otherwise happened, often between young PIs for whom the impact would be biggest and for whom the small seed grants are most motivating. Typical magnitude of such programs need not be greater than the salary for a postdoctoral fellow for two years along with some discretionary money for basic supplies. It is important in such programs to explicitly state that these are for out-of-the-box ideas that would not be competitive for external funding, and may be high-risk at the level of $>2/3$ expected to fail, but which have the potential for attraction of major external funding if successful. Such programs can be highly cost-effective in the sense of paying for themselves many times over while at the same time serving the central goal of driving interactions across the institute from the hub-like BSI center. Neuroscience is now playing such a hub-like role at major institutions around the world due to its inherently interdisciplinary nature.

We offer a second specific recommendation regarding the extension of hub-like properties to universities in Japan:

- **Joint faculty appointments with universities could have the dual effect of providing some budgetary relief to RIKEN while at the same time extending the impact of RIKEN’s work on the broader academic community in Japan, and provide an infusion of ideas and tools that could help maintain “critical mass” at RIKEN even in a time of downsizing.**

Focal point for global brain circulation

Evaluation. The advisory council evaluated Director Tonegawa's description of the successful steps taken by RIKEN BSI to improve recruiting methods and the outcome of migrations from RIKEN to the international community. We took note of the summary of BSI researchers that have been appointed as professors at major institutions both at Japan (18, including 10 at the University of Tokyo and Kyoto University) and around the world (2 at Harvard, 1 at Stanford). Internationalization efforts have included global recruitment trips by Charles Yokoyama, launch of a blog, and the BSI-international program associate (IPA) process for recruitment of international graduate students. We also noted with approval the upgraded on-site daycare facility "RIKEN kids".

Recommendations. We noted and agreed with Director Tonegawa's comment that the male to female ratio at RIKEN needs to improve (261:195), especially among PIs (33:5). This is not out of step with other major non-university Japanese research institutions such as OIST (51:8 among PIs) but nevertheless needs to improve.

- **We recommend evaluation of satisfaction among the female PIs and postdocs, particularly with regard to issues that may be addressed soon and which may help with international recruitment of both men and women** (daycare placement support, lactation rooms, etc). **We suggest that the recruitment efforts carried out for international faculty be explicitly modified with particular attention to recruiting talented young women.**

We also note that the current uncertainty with regard to the tenure-track (or not) nature of the appointments is likely to have an enormously negative impact on recruitment of international PIs, who will be expecting and accustomed to bona fide tenure-track positions, and the best of these potential recruits will find the lack or instability of such positions to be a deal-breaker.

- **Steps must be taken to minimize damage already done by the current uncertainty, which could have effects derailing international recruitment not just at RIKEN for the present time, but at RIKEN for many years to come, and even reverberating across Japan.**

Foster and train world class leaders in scientific research; provide researchers and engineers in industry and academia with opportunities for research and training to improve their skills

Evaluation. The advisory council were impressed by Director Tonegawa's description of the strong steps taken by RIKEN BSI to address the previous BSAC recommendations in this regard. We noted not only the excellence of the BSI laboratories and the number and quality of the papers carried out by trainees (which in many ways is the best evidence for fostering of world class researchers), but we noted other efforts that will have the effect of broadening the training of young BSI scientists. These efforts include the Harvard-RIKEN BSI program (8

students/year), the UCSF Exchange program with bidirectional visits, and the Waseda Internship Program targeting 5-6 3rd year undergraduate students/year. We also noted the BSI collaborative Centers with industry, including the RIKEN-BSI Olympus Collaboration Center (BOCC), the RIKEN BSI-Toyota Collaboration Center (BTCC), the RIKEN BSI Takeda Collaboration Center (BTaC) and the RIKEN-BSI Kao Collaboration center (BKCC).

Recommendations. We advise continuation of this rich and diverse set of programs for fostering young scientists who will have a broad impact on the world, and link industry and academia. As noted above:

- **Joint appointments with universities could have the dual effect of providing budgetary support while at the same time broadening impact of RIKEN's work on the academic community in Japan, provide bidirectional infusion of ideas and tools, and enrich the training of the next generation.**

Terms of Reference 4.

BSI already has many important collaborations with other RIKEN Institutes/Centers, which include:

- Dr. Atsushi Miyawaki collaborating with RAP (RIKEN Center for Advanced Photonics) for new cellular imaging,
- Dr. Susumu Tonegawa collaborating with BRC (BioResource Center) for circuit genetics research
- Dr. Takaomi Saïdo and Tadafumi Kato collaborating with CLST (Center for Life Science Technologies) in omics analysis
- Dr. Motomasa Tanaka collaborating with RCS (RIKEN Spring-8 Center) for structural analysis of amyloid beta
- Collaboration projects with "Program for Drug Discovery and Medical Technology Platform" in RIKEN for drug screening.
- BSI Participating in a group collaboration with other Institutes/Centers (IMS, CDB, BRC, QBic, CSRS and CLST).

There is also active collaboration with outside industries, which include;

- Collaboration projects with companies (TOYOTA and Olympus) for application of neuroscience in industry and also for facilitating personnel exchange.
- Collaboration projects with pharmaceutical companies (Takeda Pharmaceuticals and Astellas Pharma) for drug screening project.

In our experience, cross-disciplinary collaborations are most effective if the ideas are originated from investigators. RIKEN can consider establishing new funding scheme to solicit collaborative grant applications on a competitive basis. In order to facilitate collaboration with other RIKEN Institutes/Centers, BSI must retain its identity with a certain critical mass and strong

foundation. PIs should be encouraged to submit proposals that require cross-disciplinary collaborations.