

**RIKEN Research Cluster for Innovation Advisory Council 2014 (RCIAC2014)
Report**

May 28, 2014

- I. The RCI is made up of the RIKEN Innovation Center (RInC) and three innovation programs that involve diverse sectors within RIKEN. The RCI Advisory Council is asked to evaluate these components of the RCI as follows.
1. RIKEN Innovation Center (RInC)
 - (1) The RInC manages a Baton Zone Program in which RIKEN scientists work together with corporate scientists in R&D that develops the seeds of basic research into practical applications. The AC is asked to consider whether the Baton Zone Program fully encompasses the whole of RIKEN, and whether its framework is producing effective results.
 - (2) Is the management structure adequate and are appropriate strategies being applied in implementing business development and collaborative activities that link to the Baton Zone Program?
 2. Program for Drug Discovery and Medical Technology Platforms (DMP)
 - (1) Is the program's decision-making structure appropriate and effective in promoting its themes and projects both inside and outside RIKEN?
 - (2) In selecting its themes, has the program built collaborative relationships with clinical medicine researchers?
 - (3) Are the number and contents of the program's research themes appropriate, and is there an appropriate technological infrastructure to pursue those themes?
 - (4) Is the program's exit strategy effectively introducing promising candidates for drug discovery and medical technology to private companies and medical institutions?
 3. Biomass Engineering Program (BMEP)
 - (1) Have the previous Advisory Council's recommendations been appropriately applied to the program's strategies, research structure, and management so as to effectively promote its research objectives?
 - (2) Is collaboration within RIKEN being effectively promoted so as to bring about research that will contribute to "social knowledge"?

(3) Are the proposed future research plans and research management structures based on the past 4 years of research achievements appropriate?

4. Preventive Medicine and Diagnosis Innovation Program (PMI)

(1) Are the measures planned for applying RIKEN's research "seeds" to medical needs innovative and interdisciplinary, and are the implementation strategies appropriate?

(2) Has the program built close, collaborative relations with medical and corporate counterparts?

(3) Is the structure of PMI headquarters and its expertise appropriate?

**Refer to the recommendations of the four working groups attached at the end of this report.*

II. Given your evaluations of its individual components noted under I above, we ask for your comments and recommendations on how the RCI can continue to play a central role in furthering innovation, and your opinions as to whether the RCI's strategies, research structure, and management structure are appropriate for its mission and objectives.

RCIAC 2014 Recommendations on RCI's Strategy, Activity, Structure and Systems

Based on the Terms of Reference for the 2014 RIKEN RCIAC, the AC discussed how the RCI can continue to play a central role in furthering innovation in RIKEN, and the RCI's role, strategies, research structure, management structure, future mission and objectives, and made the following recommendations.

I. RCI's role and strategy in furthering innovation in RIKEN

Given that each research center in RIKEN is now asked to develop innovation by itself, the AC discussed the relationship of RCI and research centers, and the strategy in furthering innovation in RIKEN.

1. Planning offices of each research center should play a more proactive role in seeking out innovative seeds within their own center, and make closer communication with RCI by reporting their strategies for innovation to RCI in a systematic way. RCI should evaluate their strategies and put appropriate proposals in action by mediating contacts with industry, etc.
2. To stimulate innovation in the whole RIKEN, the AC recommends RIKEN sets up Incentives for PIs: these should include both money for their research and assurances for publication of collaborative research with industry. RCI must give PIs guidelines on what is appropriate as an invention or for commercialization, and PIs should report regularly to RCI on their inventions and research with commercial potential. RCI should notify PIs that different levels of collaborative contracts can be made to result in useful efforts. Collaborations with industry that assures that the obtained results can be published, after securing IP related to the project, are to be favored.
3. RCI should make a large, searchable database including such things as declared inventions and grant applications.
4. Last but not least, RCI is encouraged to stimulate discussion on what is innovation in each research center and in the whole RIKEN, and promote all the members of

RIKEN to share the idea that good science and good innovation go together in RIKEN.

II. Research structure and systems

The AC was asked whether new interdisciplinary programs should be set up by RCI in addition to DMP and PMI (and if so, in what areas), and what measures to refine basic research before moving to the baton zone should be put in place. The AC's recommendations are as follows.

1. Hold open competitions for the best ideas. Ask the RIKEN community to come up with new cross-disciplinary programs. This may elicit interesting proposals; as such a bottom-up approach is more powerful than a top-down approach.
2. Advertise on the RIKEN website, in journals, and in discussions with industry. It is important to ensure that industry will be interested for the success of any new inter-disciplinary program.
3. Create a competitive funding system to stimulate pre-baton zone research, similar to the I-Corps initiative in the National Science Foundation in the USA. RCI should promote this new program in RIKEN and choose funding themes among applications by PIs from the Research Centers. Topics for this program should be mostly free but can occasionally set up by RCI.

III. RCI administrative structure

The AC was asked whether RCI's current administrative structure is sufficient and appropriate for an organization playing a central role in furthering innovation. The AC was also asked about the need for a forum for outside experts to advise and guide RCI.

1. The AC pointed out that to measure appropriateness of administration, RCI should set quantitative indicators, and self-evaluation of their performance based on such indicators. "No measurement, no management; no management, no improvement".
2. As for the proposal for increased staff numbers in the Business Development Office, the AC first recommends closer collaboration with the planning offices of each of the research centers. If RCI still needs additional staff in some field, e.g. biology, then the need for employment can be defined.
3. In assessing innovation within RIKEN, we should be aware that innovation cannot always be measured by number of patents or publications. Below are some examples of qualitative factors which have been reported¹ to help make

¹ References: 1) Making Industry-University Partnerships Work, Science Business Innovation Board (2012); 2) Synthesiology, Vol. 4 –1, Tanaka et. al. (2011)

academia-industrial collaboration successful.

- i) Set goals - Products that will deliver social value are the ultimate goals of innovation
- ii) Be complementary – Partners in innovative collaboration should play complementary roles. When RIKEN researchers and industry combine their efforts, both sides are rewarded, with new scientific advances for the researchers and new products for industry.
- iii) Have common interests – Collaborative partners should have shared interests in development, such as in undertaking research challenges or improving product performance.
- iv) Cross borders - Each program should be crossing one or more disciplinary borders; for example, diagnostics and drug discovery working together.
- v) Create opportunity – Unexpected clients and research subjects may be discovered through active collaboration.
- vi) Consider flexible protection – The role of IP is overemphasized. It is better to seek broad and flexible approaches to handle the knowledge and results generated by collaboration.

IV. Criteria for evaluating and conditions for fixed-term researchers in RCI

Around 85% of RIKEN's researchers are fixed-term employees. We need to take advantage of this to further innovation while at the same time making necessary allowances for the future career paths of our researchers. What are the most effective and meaningful criteria for evaluating our fixed-term researchers and what kinds of incentives can we offer them?

1. It is not good if people are leaving RIKEN without assurance of another job. This must be prevented. RIKEN is science-oriented: if researchers in RCI seek their future career in science, people who have not done good science at RIKEN will have nowhere to go. If they have done good work in innovation and yet have nowhere to go, RIKEN should have career track for those people. The AC discussed such career path in its recommendations to each RCI component. The RCI program promises the 50% royalty to participating researchers, when their patents are licensed. Although this is a huge percentage, given the low success rate, it is not a strong incentive. It is important that RCI should invent a way where good innovation and good science go together (see below).
2. Young researchers with patent track records are popular with universities in Western countries including UK, emphasizing that engineering departments, patents, etc. are

important. There is a changing trend in the world towards more innovation, even in basic research. Publications and technology transfer are often assumed to be incompatible but researchers may have more impact in the community if they are involved in technology transfer. There is a need to make it easy for researchers to present their achievements.

3. It is important not to focus on products only: science and innovation need to be pursued hand-in-hand, at the same time, and such activities need to be encouraged. However, some people are better at one or the other – it is enough if both are covered within each research group.
4. Criteria for researcher evaluation (including basic science and innovation) should be applied to all universities and research institutes so the achievements of individual researcher can be better evaluated in a fair manner.

V. Major social issues RCI should tackle in future

The AC was asked about the major topics or themes in society that RCI should undertake to resolve.

1. Aging is one major problem relating to health and medical care. RIKEN is very close to the field. RCI needs to decide its time-frame to address this issue. The problem may take 20 or 30 years to resolve, but companies need short-range solutions of 5 years or so. So it is important to include both short-term and long-term seeds in the portfolio.
2. Academic research institutes should present a realistic image of science. Society expects innovation to be groundbreaking and sensational. We need to correct this kind of expectation.
3. RCI should reflect on large challenges. In UK Longitude Challenge for 2014 prize was announced for technical solutions to major societal issues. (This is modelled on the original Longitude Challenge from 1714, which a public competition was set up so that ships would not get lost on oceanic voyages.). This may be useful resource: not all will be relevant to Japan but the list should still be informative. The short-list of challenges includes: FLIGHT: How can we fly without damaging the environment? PARALYSIS: How can we restore movement to those with paralysis? ANTIBIOTICS: How can we prevent the rise of resistance to antibiotics? FOOD: How can we ensure everyone has nutritious, sustainable food? DEMENTIA: How can we help people with dementia live independently for longer? WATER: How can we ensure everyone can have access to safe and clean water?
4. Science communication: The scientific community has an obligation to explain itself

to society. It is important to do this to keep society's trust. This involves answering such fundamental questions as: Why is aging a serious problem in Japan and the world? How can science contribute to innovation that will solve the issues of aging and other problems confronting the society? And for each issue that is tackled, what does innovation specifically mean?

RIKEN Innovation Center (RInC) working group discussion summary

Naoto Kobayashi, Eiji Tanaka, Mai Ban

Outline

RIKEN's mission is to promote basic science. At the same time, RIKEN is expected to effectively contribute to society by applying its research outcomes to innovation directed at solving a variety of issues confronting society. In this process, the following are considered important: (1) Making active use of RIKEN's unique basic research outcomes, (2) Clear identification of how RIKEN can effectively contribute to society (in innovation), and (3) Pioneering independent methodologies to achieve this goal. Given these criteria, the RIKEN Innovation Center (RInC) has a major role to play. Although RInC is already performing well despite a limited budget and human resources, it is to be hoped that it will further enhance its contribution through proactive engagement.

Terms of Reference 1

The RInC manages a Baton Zone Program in which RIKEN scientists work together with corporate scientists in R&D that develops the seeds of basic research into practical applications. The AC is asked to consider whether the Baton Zone Program fully encompasses the whole of RIKEN, and whether its framework is producing effective results.

1. Are the various programs under the RIKEN Innovation Center producing the intended results?

- (1) RInC is working well. In particular, RInC clearly understands that its objective is to promote innovation while preserving basic science. The excellent results of collaboration with industry indicate that RInC is on the right track. In addition, by effectively appealing the benefits that RIKEN has to offer in terms of technology seeds, RInC can expect to become even more actively engaged in this kind of undertaking. To this end, RInC will need to make even greater efforts to detect internal and potential technology seeds over a broad range of fields, and strive to provide new ideas based on the needs of industry.
- (2) The Integrated Collaborative Research with Industry program is achieving significant results in line with the program's initial objectives. A proactive approach to disseminating the program within industry is needed.
- (3) The Sponsored Laboratories are doing well in furthering the research of

individual talented researchers. For further success, it will be important to prioritize strategic potential in selecting research themes, as well as to effectively promote the research outcomes.

- (4) The RIKEN-TRI Collaboration Center for Human-Interactive Robot Research is achieving unique results. Still, in considering the establishment of similar centers, it is necessary to clarify the significance of the center by referring to other research centers.

2. Effective strategies for getting better proposals for the Integrated Collaborative Research with Industry program

- (1) Barriers to expanding the Integrated Collaborative Research with Industry program have been well analyzed and eliminated where possible. The limited available resources will need to be used as effectively as possible to further disseminate the program within RIKEN among industry.
- (2) For targeting industry, the efforts of the Business Development Office to expand recognition of RIKEN's technology seeds through direct contact with individual corporations is effective, but could be enhanced by broadly disseminating information on successful collaborations to date, as well as focusing on existing corporate partners with whom RIKEN has had successful collaborations in the past. In addition, since there are only a limited number of corporations appropriate for applying RIKEN's research outcomes to innovation, an effort should be made to build up a database on such companies and their needs.
- (3) It might be useful to form a RIKEN-Industry consortium for collaboration and regularly issue to members, an email magazine with the latest hot topics.
- (4) RIKEN researchers must periodically be informed of the latest industrial trends and the outcome of on-going Integrated Collaborative Research with Industry programs. Education of researchers is also important, such as lessons to foster curiosity for innovation, and training programs that will encourage researchers to interact proactively with researchers from industry side at workshops.

3. Measures to enhance the RIKEN "baton"

- (1) To create a "baton" that can be more easily passed on to industry, it is necessary to improve the quality of RIKEN's research proposals by acquiring a better understanding of diverse business needs, and excavating internal technology seeds and proposals, before performing the 3-step process for selecting corporate partners, identifying corporate needs, and working together to draft

effective research proposals.

- (2) It is important that industry is able to “see” the potential of RIKEN’s research seeds. RIKEN should help researchers to provide relevant economic data as well, to connect research results to innovation
- (3) To enhance the RIKEN “baton”, RIKEN researchers must fully understand the purpose and significance of Baton Zone research and have high motivations towards the goal. One approach would be to create a program similar to the NSF I-Corps.

(Refer to: http://www.nsf.gov/news/special_reports/i-corps/)

- (4) Substantial resources, budget, people, and time, are required to complete technology transfer from research seed to commercial product. Effective options for achieving this include creating a team of experts from industry within RInC, provide funding within each center that is dedicated to enhancing the RIKEN “baton”, and other such measures.

Terms of Reference 2

Is the management structure adequate and are appropriate strategies being applied in implementing business development and collaborative activities that link to the Baton Zone Program?

1. Are the Business Development Office activities appropriate for getting grasp on industry needs?

- (1) The Business Development Office is well prepared with appropriate strategy and operational formation to respond to industry needs and is operating well under the strong leadership of its director, despite the Office’s limited resources.
- (2) The Business Development Office will need to be reinforced to achieve the goals of collaboration with industry. In particular, 1 or 2 additional collaboration coordinators are necessary, preferably in the fields of biology and life science.
- (3) The Business Development Office needs to clearly define what has to be done to achieve successful cross-organizational collaboration. The best practices of the past need to be applied to build conceptual models for the future.
- (4) Information exchanges with the Industry-Academia-Government Collaboration Promotion Committee of Keidanren and the Council on Competitiveness-Nippon (COCN) will help the Business Development Office better understand the latest topics of concern in industry.

2. *How should the Business Development Office apply RIKEN's resources (particularly research funds and people) to accelerate joint research with industry?*

- (1) The various activities and issues at each stage are well analyzed and understood by the Business Development Office. However, for projects requiring substantial resources, it may be useful to study the practices of foreign institutions in providing incentives under a system of commissioned research.
- (2) Ideally the income derived from collaboration with industry should be re-invested to expand and accelerate the research. As for securing the necessary personnel to drive the project, RIKEN should look to its own tenured researchers and researchers who have working experience in corporations.
- (3) Corporations are unlikely to collaborate with RIKEN given their constraints on human resources and research budget, unless RIKEN's research seeds seem extremely beneficial for their business and licensing alone is not enough to secure those seeds. RIKEN must decide whether to cultivate good seeds that will be attractive to certain corporations in industry, or to emphasize innovation and hire innovation-oriented personnel

3. *What are the merits and demerits of proactively seeking out new opportunities for collaborative research with industry?*

- (1) RInC is currently considering the merits and demerits in collaborative research with industry. There are a variety of collaborations depending on when and at which stage of the project the corporation decides to collaborate. Awareness is developing within RInC of how best to achieve collaboration that will lead to innovation.
- (2) There is a need to share among RIKEN Headquarters and all the RIKEN centers an awareness of the substantial aspects of innovation, such as how long to wait until innovation emerges, and what type of impact innovation has and on whom. This will help the RIKEN Research Cluster for Innovation (RCI) to optimize strategies, organize and manage research, and decide on appropriate topics.
- (3) Step 1 (corporate research) of the three steps for open innovation presented in the discussion points for this working group must continue to be prioritized, and emphasis must be placed on creating new seeds that will connect to innovation that is important for industry and society.
- (4) Step 2 (research on prototypes that will lead to new business lines) requires a large budget, not only for research but to cover costs related to planning, sales,

engineering, and manufacturing. Special care should therefore be taken, especially in selecting research topics, in this step.

- (5) In addition to collaborating with major companies, there is also the option of jointly launching startup businesses with collaborative funding from both RIKEN and the partner corporation. Although it is not easy for startup businesses to be successful in Japan, RIKEN has spun off a lot of startup companies successfully in the era before the Second World War, and there are still excellent business seeds to be found inside RIKEN. Serious consideration should be given to actively starting up new businesses.

Others

- (1) **Clear definition of the kind of innovation RIKEN is pursuing and striking a good balance between basic research and innovation**

As described in the Outline, RIKEN is expected not only to strive in basic research related to the natural sciences, but also to contribute to innovation by transferring basic research seeds to industry. It is necessary to clarify the time frame, extent, and impact of innovation as well as achieving a balance with basic research.

- (2) **Creation of an innovation mind-set for researchers**

RIKEN researchers, most of whom are fixed-term employees, are expected to achieve excellent research outcomes in basic science. They therefore have a tendency to ignore the need to contribute to innovation. However, basic research must contribute to innovation, and RIKEN researchers must be more highly motivated in this regard. Centers, for example, could be encouraged to provide incentives for contributing to innovation, by offering special incentive funds. It is also important to secure intellectual property rights at the same time as research results are published. Finally, for talented researchers who are suited to innovation, appropriate future career paths should be offered.

- (3) **Proposal to pioneer “science for innovation” as a methodology for technology transfer of basic research**

There must be a variety of approaches to contribute to innovation. RIKEN must recognize that one of its important objectives is to “apply basic research seeds in society through Baton Zone research” and pioneer ‘science for innovation’ through analyses of the processes involved. It is hoped that the RInC will pioneer new methodologies for the science of innovation.

Report on Program for Drug Discovery and Medical Technology Platform

The AC is pleased to see advances in several areas since the last meeting in 2011:

- Program exits exceeding objectives
- Progression of cell therapy to the clinical trial stage, establishing precedents to facilitate this important treatment modality
- Implementation of recommendations from the 2011 AC with respect to medicinal chemistry resource, and interactions with external clinical groups. Some seeds were picked up from actual clinical practice.

The AC is also pleased to see the integration of structural biology, synthetic chemistry and computational chemistry activities to provide an important resource, giving RIKEN DMP a big advantage in drug discovery.

Program Objectives

Success of DMP should be assessed based on three outputs:

- Number of products generated for further development towards the clinical study
- Development of novel technologies that can be utilized by other groups for the generation of novel therapies
- Translation of drug discovery into target identification and elucidation of new disease mechanisms

Existing objectives seem to be focused on the first of these outputs: performance metrics need to be devised that can capture the remaining outputs. To efficiently achieve the second and third outputs, DMP should promote collaborations with other RIKEN centers/programs to develop new practical technologies and investigate new disease mechanisms.

Target Selection:

The ALK2 target for FOP is a clear example of added social value contributed by DMP. This target is not attractive to pharmaceutical companies because of the small number of patient, and an academic group in the US working on the same disease has struggled to raise funding to progress drug discovery. The work being conducted within DMP will hopefully lead to a novel treatment for this rare but debilitating disease.

It is important that DMP does not compete with the pharmaceutical industry: it has unique resources at its disposal and should preferably select drug targets for small-molecule drug discovery that take advantage of these resources, including

structural chemistry, and the K computer. Novel drug discovery technologies that utilize these resources are encouraged: for example, development of novel methods to address protein-protein interaction targets and lipidic mesophase technology for membrane protein structure could add significantly to the group's capabilities.

Portfolio Management

Management of the portfolio seems to be going well: programs are closed down when necessary and there is a flow of new themes/projects to fill the available slots. While DMP should not compete with the pharma industry, it should look to learn pharma best practices: comparing DMP progression metrics and success rates with industry averages may identify areas where a significant improvement in DMP efficiency can be made.

The AC feels that the number of themes and projects is appropriate for the resources available.

Chemistry Capabilities

The computational chemistry capability is an excellent resource, and the virtual screening library will be a key contributor moving forward. However, the current chemical library available to DMP is sub-optimal. The chemistry team should work to ensure access to a good quality HTS library of sufficient size.

Biology Capabilities

High-content phenotype screening is an important drug discovery technology, and some evidence suggests that it is more likely to generate drugs than target-based drug discovery. Therefore, the AC is pleased to see that this approach has been incorporated into DMP's capabilities. This method however requires strategies and technologies to be in place to determine the target of active molecules. These will inevitably utilize the CLST omics expertise available to DMP, another example of excellent technologies providing an edge to DMP drug discovery.

Exit Strategies

The exits achieved to date at exits 2 & 3 have been to academic collaborations/venture companies funded by government agencies. It is important for DMP to understand the requirements of pharma companies so that future exits can be made to these important stakeholders directly.

Recruitment and Incentives

Progression within RIKEN is based on scientific output alone, and insufficient regard is given to innovation. To counter this, DMP policy is to distribute 50% of its financial returns to the researchers involved in the program. This incentive alone is not enough for career development of people involved in RCI activities. The RIKEN should consider introducing new career path based on the innovation achievements by individuals.

In addition, RIKEN should find ways to promote and fund spin-out companies as another incentive for researchers hoping to engage in entrepreneurial ventures.

Interactions with PMI

There is significant opportunity for synergy between DMP and PMI:

- Identification of potential drug response biomarkers, either for target engagement (important for translational research) or as candidates for patient stratification in subsequent clinical development.

The AC recommends that DMP and PMI produce a joint strategy on these opportunities.

RCI BMEP Advisory Council Review

Reviewers:

Vice Chair, Professor Dirk Inze – Scientific Director and Head, VIB Department of Plant Systems Biology, Ghent University, Belgium

Professor Carl J. Douglas – Professor, Department of Botany, University of British Columbia, Canada

Professor Friedrich Srienc – Director of the Biotechnology, Biochemical and Biomass Engineering Program, National Science Foundation (NSF), USA

The RIKEN Research Cluster for Innovation (RCI) Bio-Mass Engineering Program (BMEP) advisory council would like to thank all presenters for their excellent, very comprehensive presentations, which were didactic and clear. The style and structure of the reports show that BMEP members are working as a team.

Observations and Recommendations:

1. We were impressed by the **very high quality of research** at BMEP and the project's emphasis on **taking advantage of RIKEN's strengths**. Each team **collaborates extensively** with other groups, both within RIKEN and with external partners to achieve program project goals. We **congratulate the management and all PI's** for this impressive output.
2. We recognize that the BMEP management **took into account previous recommendations of the 2011 RCI Advisory Council report** by, for example, adding new teams that significantly broadened the BMEP research scope; most notably the Cell Factory team. The bringing forward of Dr. Numata's Enzyme team was also noteworthy.
3. We acknowledge BMEP's **well-defined research goals** and we further encourage the management to **create more concrete timelines** for each individual project for delivery of practical outcomes. **Defining timelines and expected deliverables** will help the management monitoring individual project progress and keep teams focused on BMEP's broader goals. Example questions for the poplar project that would lead to such definitions are: - What would the target be for increased productivity in terms of biomass per unit time, including improvement of the plants and improvement in defining cultivation techniques? - What are the timelines to include Eucalyptus based research as well?
4. In the reports and presentations we saw **top quality research** by BMEP in plant sciences, synthetic genomics, biocatalysis, plant biomass use, metabolic engineering,

bioresources and other fields. To compare this program with those in other countries, it is **very competitive internationally** and of the highest caliber. BMEP is a world leader in the field of biomass engineering, accomplished by combining fields ranging from plant science to chemistry, microbiology, synthetic biology and metabolic engineering to name a few. We strongly advise BMEP to **effectively benchmark BMEP activities with others around the world** as Biomass engineering is rapidly emerging as a recognized and competitive field.

5. We feel BMEP is comprised of excellent scientists and we have only seen the beginning of what they can achieve. Clearly BMEP is a **model for what RIKEN Research Cluster for Innovation** can produce. BMEP scientists have just started to know each other and already created synergy. BMEP's research area has **huge opportunities for further innovation** and should be further nurtured.
6. **BMEP's cross-disciplinary nature is a major strength** with the highest potential to generate novel and innovative solutions for creating a sustainable, clean society. We saw a lot of **innovation from cross-disciplinary thinking** in BMEP. To build on this strength we ask BMEP to consider how to promote cross-disciplinary research even more. What mechanisms can you use to promote this kind of thinking? Will BMEP repeat activities like the retreat held a year ago? We **encourage you to create novel ways to brainstorm on solving scientific problems across disciplines.**
7. The cross-disciplinary nature of BMEP is likely to generate **game changing technology**; BMEP should especially strongly support these types of achievements and discoveries to maximize their impact, including handling related intellectual property issues. **In fact, we already found examples of game changing technologies in the BMEP presentations.** For example, BMEP has created an important method for delivering double stranded RNAs into plant cells. This is a potentially new enabling technology for many areas of plant science like gene discovery and genome editing for any plant at any developmental time. Many companies are starting to use double stranded RNA as a chemical agent to target insects, nematodes and other organisms. **The advisory council advises BMEP to prioritize finding and using ways to pick up on such potentially game changing technologies and to broaden their impact.** These can change the whole way of thinking. **There may be high risk but also possibly high gain**, so BMEP should really push for these. **It's a matter of making them bigger, broadening their impact and making the process faster.**
8. We propose that BMEP takes a more **systems analysis approach**, as practiced in

engineering, for some projects where appropriate, by really quantifying how the individual parts are interconnected. It's important to analyze the whole from a global point of view, **including translating this into an economic model.**

9. **Cross-disciplinary activity creates a lot of value and a lot of technology transfer.** Identifying potential value is not easy. BMEP must be alert and careful how to get value from their discoveries.
10. **Green innovation will only gain in importance** in the next years, with sobering predictions for climate change that will affect food, climate and social structure from the recent IPCC report. This will increase pressure to go to carbon neutral and carbon negative policies as recently introduced by President Obama in the US. Biomass development work over the next 30-40 years will be very valuable as we look to 2050. Looking that far ahead, the effect on the green economy of BMEP research and translational activities will be very good. **This will require sustained long term investment. RIKEN needs to start now to be ready for BMEP to have the needed foundations.**
11. BMEP needs to develop **incentives for researchers' involvement in technology transfer**, especially considering the careers of young scientists. Keeping a balance between scientists' desire to produce top quality papers with the goal of technology transfer is a real challenge. There are institutes comparable to RIKEN that use the principle "what you measure you can gain". They evaluate all young PI's on the following criteria: 60 percent based on scientific output, 30 percent on technology transfers (industrial collaborations, spin-offs and patents), and 10 percent for education (PhDs). This motivates young people to be active in translational research.
12. **BMEP is an example within RCI of how to successfully achieve tech transfer with Japanese companies.** The AC advises BMEP to **stimulate tech transfer** not only to Japanese Companies, **but also to other companies world-wide where appropriate (that is, when there isn't an immediate update by Japanese companies).** We feel that BMEP working together with the Center for Sustainable Resource Science (CSRS) will lead to many more possibilities in the future. At present, it's very difficult for companies from outside of Japan to see inside the "black box" of RIKEN, but international companies represent a very great potential to benefit BMEP, CSRS and RIKEN researchers, including funding. Perhaps BMEP could define a set of molecules they want to produce together with the industry, and actively pursue partnerships with foreign companies if partnerships with Japanese companies on these are not forthcoming.

International companies recognize the excellent work done in RIKEN. Although there are many companies that would be interested in working with RIKEN, our impression is that they do not find working with RIKEN is very easy. As mentioned, an acceptable policy for promoting RCI activities internationally would be for RIKEN to first apply to Japanese companies, and then seek transfer to international companies. Cooperation with international companies will generate value for Japan, including benefits from royalty sharing.

13. The advisory committee **strongly supports the integration of BMEP together with CSRS**, which will have a **huge impact on synergy, value creation, maximizing resources and for improving visibility to the outside world**. The complementary activities of BMEP and CSRS together should **maintain and grow a very strong capability for technology transfer**. The addition of BMEP research activities to CSRS will create further synergy to extend the capabilities of both groups; between polymer science and catalytic chemistry, for example. It will be possible to take more advantage of the strength of interdisciplinary work in bio-catalysis of valuable compounds and their further possible conversions. Metabolic engineering will benefit from collaboration with those working on pathway design, as in the case of Dr. Saito's metabolomic research and Dr. Kondo's Cell Factory research. Biomass research will benefit from cooperating on super-plants and super-trees, and so on.

The AC strongly recommends that the **integration of BMEP and CSRS should be accomplished without any net reductions in budgets** as this would only weaken the impact of this merger. As one organization BMEP/CSRS will further strengthen its very competitive position on a global scale.

14. We suggest that the BMEP management considers setting up a program to study methane emissions and alternate ways of fixation and CO₂ fixation along with CSRS. This field has a potentially huge societal impact. For example, an approach should be considered to **study organisms that use methane** (natural gas) to help stabilize the environment.
15. The use of GMO plants for biomass is an important potential deliverable. **Establishment of appropriate GMO field trials to assess BMEP plant biomass innovations at the field level in Japan in very open communication with Japanese society** about potential benefits, associated with the use of genetically modified plants for biomass and bioenergy purposes, could make a difference in practice, and increase the acceptability of GMO related scientific development. **Engaging in field trials on biofuel and bioenergy would be a way to**

communicate with society by example. We believe **it's important to perform such field trials in Japan**, at least for research purposes; the experience locally will create a lot of value. It could demonstrate that GMO based technologies can contribute significantly to creating a green, sustainable and healthy society.

RCI BMEP AC Review summary

- 1. The very high quality of BMEP research takes advantage of RIKEN strengths by collaborating within and outside to achieve program goals.**
- 2. BMEP answered 2011 RCIAC report recommendations, including broadening the scope and adding teams effectively.**
- 3. We recommend BMEP to create more defined timelines and expected deliverables to monitor progress and keep teams focused on BMEP goals.**
- 4. BMEP is a world leader and very competitive in plant sciences, synthetic genomics, biocatalysis, plant biomass use, metabolic engineering, and bioresources. Please benchmark BMEP performance internationally in this competitive field.**
- 5. BMEP is a model example of what the RCI can produce based on synergy and knowledge from knowing each other and working together. The huge opportunity for future innovation should be further nurtured.**
- 6. Cross-disciplinary thinking at BMEP leads to a lot of innovation, one of its major strengths and has the highest potential to create solutions for a sustainable clean society. BMEP should strive to find novel ways to brainstorm solving scientific problems by working across disciplines.**
- 7. Cross-disciplinary research at BMEP has already generated game changing technologies, such as delivering double stranded RNA into plant cells via peptides. Please consider the mechanism to recognize discoveries like these, take them beyond the group, and develop them faster, in order to broaden and increase their impact.**
- 8. Propose that BMEP, where appropriate, takes a systems analysis approach as practiced in engineering to quantify how individual parts of research are interconnected, from a global point of view and considering also the economic model.**
- 9. Be alert and careful in extracting value from discoveries made by cross-disciplinary tech transfer.**
- 10. BMEP will need sustained long term investment in order to create deep**

foundations for biomass development over the next 30 to 40 years to meet the vital challenges created by climate change from global warming.

- 11. BMEP needs to develop incentives, especially for young scientists, to produce achievements in technology transfer projects, not only to create academic impact.**
- 12. BMEP should consider stimulating tech transfer to companies worldwide based on its successful experience with Japanese companies, to benefit research, researchers and create revenue for Japan.**
- 13. The advisory council strongly supports complementary integration of BMEP with CSRS. BMEP funding should be maintained in full to continue its unique activities together with CSRS to create further technology transfer, create value, maximize resources and improve visibility in the world.**
- 14. BMEP should consider a methane emissions research towards alternate ways of fixation and CO₂ fixation, to help stabilize the environment.**
- 15. BMEP should be open with respect to the potential benefits of GMO technologies by establishing open and appropriate field trials in Japan where there are useful applications for bioenergy and biomass. These would serve as examples to influence acceptability of GMO technologies locally in Japan, toward a green and healthy society.**

ADVISORY COUNCIL REVIEW OF PMI

THE TASKS given to the AC for PMI to answer read as follows:

- 1) Are the measures planned for applying RIKEN's research "seeds" to medical needs innovative and interdisciplinary, and are the implementation strategies appropriate?
- 2) Has the program built close, collaborative relations with medical and corporate counterparts?
- 3) Is the structure of the PMI headquarters and its expertise appropriate?

GENERAL CONSIDERATIONS OF ADVISORY COUNCIL IN RELATION TO TASKS

PMI is a recent center started in 2013. It has a staff of 11 Individuals and is led by a prominent RIKEN scientist, Yoshihide Hayashizaki. The background competence of the staff recruited seemed in general quite high providing coverage of many of the areas needed for successful developments of projects into products. There is, however, a need to strengthen the PMI headquarters with regard to business-development capacity as exemplified in the RECOMMENDATIONS. During the short period since creation PMI has in a commendable way rapidly proceeded along several routes in line with the vision(s) of RIKEN to create social as well as commercial value via innovative projects stemming from research at the institute.

Benefitting from the Director's long stay at RIKEN a very impressive survey covering most areas of RIKEN's research has been carried out. A large number (64) of potentially promising seed projects were thus identified. The individual projects were then categorized according to the specific possibilities of the respective project with regard to medical need, company interest, collaborations, economical support etc. Many of these projects contain innovative cross-overs between different research disciplines having potential to create unique new products.

A significant handicap for RIKEN and PMI in relation to performing innovations in the area of clinical medicine is the lack of a hospital of its own. This has been largely remedied by the signing in 2012 of a close collaboration between RIKEN and the Juntendo University Hospital. The Director of PMI has over the period had

regular monthly meetings with the clinical management of the hospital. To analyze the medical needs a large number of interviews of clinicians at Juntendo amounting to several hundred hours of meetings have been done, Attempts of matching of the identified medical needs with the potential seed research projects at RIKEN have thus been started. Already projects reported to the AC stem from such deliberations. However, several projects, in particular those covering biomarker studies in relation to oncology require that PMI does arrange for possible access to samples from established biobanks, preferentially where long clinical outcome follow-up is already recorded. This may well require significant international collaborations. One option would be to develop an international research consortium or center to ensure mutual benefits. A commitment to build a new research center for biomarker discovery in collaborator's institution by transferring RIKEN's technologies could be a potential strategy to explore world-wide sample availability.

In short summary, the review performed by AC in relation to tasks given to analyze concludes that PMI has made a rapid start and is performing very well along the 3 lines of tasks analyzed. Below we will provide some more specific observations in relation to the activities of PMI.

SPECIAL NOTES OF OBSERVATION

Given the fact that PMI has been given an unexpectedly low budget for 2014 a drastic reduction in the number of projects explored had to be carried out leaving 5 projects in significant development whilst letting the large majority of potential projects (45) idle. The AC considers this quite unfortunate as this will with time reduce or even totally eliminate the present potential value of several of these latter seed projects.

The AC received a thorough presentation of the 5 prioritized projects in PMI and had time to discuss and question the individual projects and their potential future. In general, the AC was very impressed by the high quality and innovative height of the interdisciplinary research seed projects coming out from the research at RIKEN constituting a good basis for successful product candidates. The area where PMI has the most interesting and unique seed projects come in the area of biomarker discovery and detection. The AC got a practical demonstration of one project that had produced an extremely rapid and sensitive kit for the detection of serious virus infections, here flu

infection of humans. This project represents a beautiful example of cross-discipline basic research where researchers at RIKEN including international collaboration and a company in Japan together have created an outstanding diagnostic system now ready for commercialization. The AC considers that the biomarker research seed projects do also clearly fulfill the special wish mentioned in the vision of RIKEN to via interdisciplinary research create results that have the potential to dramatically change ways in which clinical medicine in the future can be done.

The biomarker seed projects have furthermore already started to generate highly interesting clinical results such as the capacity to very rapidly diagnose from a biopsy of a colon cancer the metastatic potential of that tumor thus directly influencing the treatment modalities to be taken. These biomarker technologies coming out of RIKEN's interdisciplinary "seed" projects contains a multitude of future possibilities to perform personalized medicine in a paradigm breaking way. Although quite advanced from the research point of view we found most of the projects and attempted systems to not yet be ready for commercialization. Research and development coordination to further refine these interdisciplinary based projects and to structure these complicated systems into functional products will thus constitute a most important task for PMI in the coming years.

RECOMMENDATIONS AND CONCLUSIONS

PMI has already successfully defined a clear and problem-solving oriented mission and recruited a skilled and motivated staff under strong leadership of Dr. Hayashizaki. They constitute a freshly started unit compared to other units in RCI and have already highly promising technology seeds at various phases of development.

The AC for PMI has some recommendations as outlined below to further improve the function of PMI as an optimal unit developing superior commercial products producing significant values for RIKEN and society.

The AC is impressed by the achievements of PMI during its short period of existence, nicely delivering according to our analysis on the Terms of References. A major problem for PMI to develop more of its identified projects into functional projects and products is the very harsh financial situation for PMI. Without improving the budget for PMI it will only be able to explore a small minority of identified innovative

seed projects for their commercial potentials. PMI is trying very hard to explore the opportunities to obtain the external funding or the financial support from partner companies especially in the field where the PMI head quarter has its own expertise, and this effort has to be encouraged. International funding opportunities will also be a potential solution. However, it is essential and maybe the only way to provide RIKEN's institutional budget to PMI in order to start the cross-center projects which could make real innovations from the technical seeds of RIKEN. Accordingly, we strongly recommend that RIKEN will increase the budget for PMI.

PMI has successfully built collaboration networks for commercializing their technology with leading entities, for example, Juntendo University Hospital and companies, to accelerate developing products and services for health care. However, there exist also a highly obvious situation with significant enhanced potential synergies within RCI between PMI and DMP. The AC recommends that this latter potential is further explored.

Regarding the overall achievements of PMI, our recommendation is that RIKEN and PMI collaboratively strengthen the activity in technology transferring function in two specific ways not to significantly diminish the huge opportunity they already have in their hands to provide fruitful impact on society and people wellness.

Our first recommendation is that dedicated senior personnel should be recruited to PMI with entrepreneurial mindset and expertise of market competitiveness, possible business models in medicine and health care. A person who has experience of starting or working for biotech ventures could be suitable for the position. He/she will manage a development process of PMI pipelines, draw a business scheme for each PMI technology and IP, and negotiate with partners for PMI's interest. This would be of particular importance in situations when potentially quite complex products with diverse possible implications like the biomarker systems are coming forward. Simple licensing deals would here quite likely be commercially inferior to more sophisticated solutions.

We fully understand present regulatory restrictions for RIKEN with regard to not being allowed to create a TLO. We thus recommend as the first step, for PMI by itself to hire a person as indicated above under its budget or RIKEN's financial support, a successful commercial outcome of this function would with time be helpful also for RIKEN to work with policy makers. The aim would be to in the future for RIKEN to be allowed to have its own TLO or alternatively help to create a TLO-like structure outside

RIKEN to improve the capacity of RIKEN to more efficiently convert its basic science into socially valuable products.

Our final recommendation is based on our opinion that PMI has amongst its potential seed products a truly unique situation with its biomarker based system to make personalized medicine truly function, in particular in the oncology field. Due to the long history of the creation of this system within RIKEN several cross-disciplinary areas have become involved. The potential of these biomarker technologies IF made into clinically functioning systems is enormous with regard to clinical consequences. The principles of many technological parts of the system are well established, the preliminary results are most impressive but the AC concludes that there remains significant remaining requirements for coordination of R&D activities to make this into a optimally commercially functioning test system. The AC would thus strongly recommend that such a coordinating activity of R&D for this is allowed to take place within PMI.

We hereby conclude the report from the AC for the PMI.

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