RIKEN IMS Advisory Council 2014

BACKGROUND

What follows is the report of the Advisory Council (AC) 2014 meeting. This AC meeting was very important since it was the first evaluation of the new Center for Integrative Medical Sciences (IMS), which was formed in April 2013 by merging two existing RIKEN centers, the Research Center for Allergy and Immunology and the Center for Genomic Medicine. The AC met for two days. On day one there were block reviews, where individual laboratories were evaluated. The second day was the Assembly Meeting, where there were presentations from each of the four IMS cores (see below) followed by a presentation outlining the Center's Future Plans.

IMS STRUCTURE

Dr. Koyasu has been acting Director of IMS since its inception. He is supported by two senior advisors, Dr. Taniguchi, former RCAI director, and Dr. Akira from Osaka University, who is very well known for his seminal studies on innate immune sensing mechanisms. There are also Deputy Directors, two from the former CGM, Dr. Kubo (former CGM acting director) and Dr. Tanaka, and two from the former RCAI, Drs. Saito and Koseki.

AC GENERAL COMMENTS

IMS is a logical joining of two great institutes and a wonderful opportunity. The merger creates the capacity to perform functional genomics, which could set IMS apart from other genomics institutes in the world.

In terms of moving the IMS center forward during this transition period, a permanent Director is urgently needed. There will be many difficult decisions to make and new strategies to implement. An "acting" Director will not have enough power to accomplish these in an effective manner. RIKEN should either name Dr. Koyasu as Director or conduct an expedited search for a new Director. There is a critical need at this point for designating a permanent IMS Director. It was not clear to the AC whether IMS is taking advantage of the expertise of the senior advisors as the Center moves forward.

There are outstanding investigators present in the new institute, and there has been some integrated planning and the potential that this will succeed. It is still early days and more time is needed to see. The AC recommends the formation of a committee, two members from each former center, to figure out how the future plans will actually be implemented.

The AC is disappointed that funding for the new center was cut, when logically it should have been increased or at least maintained at a stable level to help creation of a new center by fusing two formerly successful centers. Extra funds are needed to facilitate the marriage that created IMS, perhaps with direct support from the RIKEN president.

TERMS OF REFERENCE

The AC was asked to provide general comments in the following five areas in this Assembly Meeting Review and also make comments based on the Terms-of-reference from RIKEN President Noyori.

Terms-of-reference from the IMS Director (Acting)

1 Overall quality of research activities at the center.

The overall quality of research at IMS is very high. The two founding institutes, RCAI and CGM, had outstanding publication records and this appears to have been maintained in the new center. It is a little too soon to objectively evaluate IMS in this category; the continued success could be a carryover from the previous institutes. The next year should be telling.

2 Development of new technology that will contribute to medical sciences.

There is some new technology development but, perhaps because of budgetary constraints, it does not appear to be centralized or to constitute a major focus. Dr. Ohara continues to perfect his single cell analysis platform. The genomics core has developed an automated SNP analysis system.

3 Promotion of Young Scientists and Postdocs

This issue was not specifically addressed during the AC. The former RCAI established a young chief investigator (YCI) program shortly before the IMS merger. These young scientists share equipment and space in a host lab and have senior PI mentors in RIKEN or at other institutes/universities. The AC recommends that the budget for the YCI be increased to promote success of these young researchers. The YCI program does not appear to have been adopted center-wide at IMS; it does not exist in the Core for Genomic Medicine but should be implemented. There was insufficient data to allow comment on the situation for Postdocs at IMS.

4 Appropriateness of future research plans to promote cross-disciplinary research and those to mobilize overall strength for problem solving research.

Projects are in place that will promote cross-disciplinary research between PIs in the former RCAI and CGM. It is critical for the new IMS that these interactions are fruitful since they will

be objective indicators of the successful marriage of the two former centers into a cohesive new one.

5 Research management and operating policies of the Center
During this transition period, Dr. Koyasu has done a remarkable job of trying to fuse the former RCAI and CGM into an integrated IMS. However, being acting director is not an acceptable option for his future or that of the institute.

Terms-of-reference from RIKEN President Noyori

1 Is the center's research output and personnel up to international standards? Is the center a world-leader in its field? Please make concrete proposals that could lead to quantum leaps.
The new center was formed by joining two already great institutes. As of now these high standards have been maintained.

2 Evaluation of the center's management policy
-appropriateness of the research roadmap
The future plans are exciting and bold. There is concern that at this point they may be overly ambitious and will need refinement to be successful.

-Measures for attracting top international human resources
The AC was pleased to see that the international summer program (RISP) that began in RCAI is continuing in IMS. This program, together with the outstanding science being done, helped bring international visibility to RCAI. IMS is not well known yet and such programs are very important for raising its international profile.
No specific plans to attract senior researchers from abroad were presented during the AC meeting.

-Budget allocation system (balance between research and human resource costs)
Based on personnel and budget data provided to the AC, several conclusions can be drawn. In terms of personnel categories, IMS is a very efficient operation, with administrative staff accounting for only 6% of total employees. Of the government funding for operations, 55% is budgeted for research and 45% for human resource costs, which is reasonable. Moreover, in terms of the overall budget, which includes commissioned research and external competitive funding, human resource costs account for only 30%.

-System for personnel turnover
The former RCAI had a very robust system for personnel turnover, but it was unclear how this was being done in the former CGM, or how it will be handled in IMS.

-Collaboration with groups inside and outside RIKEN, progress in building collaboration, including global efforts
IMS has been quite successful in this regard.

3 RIKEN will be operating under a new system for Independent Administrative Institutions, starting in April 2015. As such, RIKEN's primary objective will be to maximize its research and development capabilities and define goals for creative, outstanding world-class results in selected areas of problem-solving research. Each center advisory council is asked to recommend specific research topics by which the center can apply its special attributes to contribute to those areas of specialty (not only issues confronting society, but also those specific to science and technology) in which RIKEN should be dedicating its comprehensive resources.
Because implementation of the new system for Independent Administrative Institutions is not yet accomplished, the AC withholds comments on this point.

IMS FUTURE PLANS
The center plans to analyze the human genome to identify disease-related genes and then develop predictive models that will allow for intervention prior to disease onset. By instituting lifestyle changes or performing some sort of medical intervention, the disease will be prevented. These are ambitious plans and will require input from many laboratories in the center. To make this work, they have introduced a split laboratories concept, whereby individual labs will pursue their own research program but devote a certain percentage of their effort to center-wide goal-driven projects. A number of projects fall into this category, the most visible being the atopic dermatitis (AD) model. Others are the cancer genome, microbiota in diabetes and inflammatory bowel diseases, and the primary immune deficiencies (PID) project. There will be multiple levels of analysis – DNA, RNA, proteins and cells and tissues. As an example, for the AD project they will perform such multi-tier analysis superimposed on a time course analysis of disease development, from before the onset of symptoms to full blown disease. The massive data generated will require high powered computational analysis, higher mathematics, new algorithms and a new modeling strategy. At the same time they plan to develop a pipeline for mouse-human network conversion. This essentially means developing a system by which studies in mice can be easily extrapolated to human, which is currently not the case. Humanized mice, human iPS cells carrying disease-associated SNPs, and eQTL analysis will play major roles in this effort.

The future plans for the institute are bold and exciting but suffer from being overly enthusiastic; they need to be more realistic. The proposed functional analyses are highly

dependent on the humanized mouse, which needs more thought and more manpower if it is to be successful. Although the plans look good, there was a shortage of detail to allow for critical evaluation. This is understandable given that some of the programs are new, and it is expected that a year from now the plans will be better fleshed-out and some may have been abandoned. On the other hand, some projects, e.g. the AD project, have been underway at some level for a long time. In that regard, the AC is not convinced that the *spade* AD project is the best one for the proposed systems biology launch, since it is so complex.

AC COMMENTS ON EACH CORE & THE PROGRAM

The laboratories in the former RCAI and CGM have been reorganized into three thematic cores and one program:

1. <u>Core for homeostatic regulation</u>

The goal of this core is to elucidate mechanisms of disease onset using animal models and information from human genomic sciences. The core should also create new scientific paradigms and validate disease models established by core 2. The mission of this core is quite broad and includes, under the rubric of "create new scientific paradigms", the heart of what led to the great success of the former RCAI, i.e., investigator-initiated, curiosity-driven research. The other goals are related to the new mission of IMS, to generate systems biology models of disease onset and progression.

The presentation during the AC describing this core focused on:

1) Recent studies by IMS investigators of the mucosal immune system and its interaction with the microbiota.

2) Analysis of primary immunodeficiencies (PID) in the Japanese population. The PIDJ has been a remarkable success, wedding primary care clinicians and basic researchers. They have gathered DNA samples from ~1400 PID patients and are conducting a systematic screen to identify causative mutations, with a focus on identifying new genes.

Future plans of Core 1.

On the mucosal front, the Center plans to focus on gut microbiota-related diseases. Based on the fact that different ethnic groups seem to have different microbiome compositions, they argue that it will be important to do this sort of analysis in Japanese. They have preliminary results showing altered composition of the microbiome in IBD versus healthy controls, and also plan to include type 2 diabetes/metabolic syndrome in the analysis. No specific future PID plans were presented, but it is anticipated that the identification of new PID genes will continue to be a major goal.

[Recommendation]

The mucosal group at IMS is clearly world class. Their discoveries have been many and of very high quality. Metagenomics to correlate the composition of the microbiome with disease states are ongoing worldwide. Given the expertise in genomics at IMS, it is anticipated that high quality data will emerge from these analyses. These data should be freely shared with the scientific community worldwide.

The PID research at IMS has been impressive and should continue in this vein.

2. Core for precise measuring and modeling

The goal of this core is to elucidate the mechanisms of human disease onset through building a predictive network of the process, systems biology in other words. Data to feed the models will be generated by quantitative measurements including high resolution imaging and gene profiling. The core will attempt to fill the gap between genotype (e.g., information generated by Core 3) and phenotype and between animal models and human diseases.

The presentation focused on skin homeostasis; IMS is vested in atopic dermatitis (AD) as a model in which they will collect data from multiple perspectives to ultimately incorporate into a predictive systems biology model. This decision has an historical backdrop since the ENU mutagenesis project generated an AD mouse model (*spade*). Since then, IMS has developed a number of projects that deal with altered skin homeostasis. Multiple loci for human AD have been identified by genome wide association study (GWAS). The filaggrin knock out mouse develops dry and scaly skin, a keratinocyte-specific SOCS3 knockout leads to skin inflammation, and Foxp3 mutations lead to multi-organ inflammation, including skin. The ongoing AD project is focusing on the *spade* mutant and will gather time course data at multiple levels during disease onset and progression. They have already established an RNAseq pipeline that has detected genes with significantly different expression patterns in WT vs *spade* mice.

Future plans of Core 2.

The goal is to incorporate the data on the *spade* mutant into a comprehensive and predictive systems biology model.

[Recommendation]

IMS is heavily invested in the *spade* AD project, pinning its hopes on this being the first successful systems biology application since they ventured into this area a few years ago. There is concern that the strength of the former RCAI investigators is in immune system cells but the *spade* mutant directly affects skin cells and not directly immune cells. The addition of Dr. Amagai to IMS has provided needed expertise in the area of skin biology.

A second concern is more general. The AD project is top down and multiple IMS PIs are being asked to participate in it. It was not clear that there is much enthusiasm for this approach, since the PIs have achieved their success by following their own curiosity-driven instincts. AD in the *spade* mutant is also very complex and development of a predictive systems biology model will take a long time and may not be successful. Perhaps a simpler, inflammation-related disease with immune system

pathology should be the proof of concept target for systems biology at IMS. A rapid return would allow the IMS PIs to see the value of the systems biology approach.

3. Core for genomic medicine

The goal of this core is to implement Personalized/Preventive Medicine by using genomic approaches that will be experimentally validated by the two other cores. This core is essentially the former CGM, which has a distinguished record in genomics and GWAS. A critical resource is the Japan BioBank, which has 200,000 patients with 47 diseases. This is one of the largest disease-oriented BioBanks in the world. A new iteration of the BioBank will recruit 100,000 more individuals with 37 diseases. They have begun to perform whole genome sequences on samples from the original BioBank with a goal of 1,000 patients. The core also has a large genome-guided drug treatment optimization program for carbamazepine (skin eruptions), warfarin (maintenance dose) and tamoxifen (breast cancer treatment dose). The core also participates in many international genomics projects.

Future plans of Core 3.

The future plans for this core include:

-Implementation of genomic medicine project to ultimately provide predictive genetic markers for various diseases.

-Reverse translational pharmacogenomics research to identify biomarkers of drug efficacy or adverse reactions.

-Cancer genome research to understand the cancer genome and cancer biology and to provide personalized medicine for cancer patients.

-Catalog of genome-wide expression Quantitative Trait Loci (eQTL) for immune cells and tissues.

-Continue international collaborative efforts.

In terms of their integration with other IMS cores, the basic plan is for the genomic core to identify new disease susceptibility genes which will then be experimentally explored by the other cores *in vitro*, e.g. by introducing the SNP into iPS cells and inducing their differentiation along a disease relevant pathway, and *in vivo* in humanized or conventional mice.

[Recommendation]

The Genomic Medicine Core has continued to very productively leverage on the Japanese BioBank to pursue GWAS analyses, including by merging them with other datasets in meta-analyses, to identify an increasing number of risk loci for a broad panoply of diseases. The group should be commended for these outstanding achievements. The Core plays a unique role as a resource for

large-scale medical genomics in Japan and the AC encourages the RIKEN to continue its long-term support of the Core. The completion of whole-genome SNP genotyping of the Japan BioBank cohort is an important milestone in disease genetic studies. The AC recommended that efforts be made to make a combined analysis of all the Japan BioBank data with a variety of advanced statistical techniques, and that new opportunities for meta-analyses should be actively pursued following the models of rheumatoid arthritis and some other diseases that have led to major publications in Nature and Nature Genetics. As pointed out in previous AC reports, a formal policy to allow sharing of all the data with other groups should be established given the importance of these to the scientific community. This would align with policy in institutions in other countries. Whole-genome sequencing studies with selected groups of Japan BioBank patients (such as the 200 myocardial infarction patients with age <40 years) should also allow novel and potentially important disease loci to be detected.

The AC recommended that the choice of samples to sequence be investigated further. Two points were stressed: sequencing of 1,000 samples as presently proposed may be insufficient; the samples should be careful selected to be representative of the Japanese population. The AC supported the suggestion that the Core consider coordinating efforts with other groups undertaking sequencing in the Japanese population.

Merging of the Immunology and Genomic Medicine Centers into a single Center for Integrative Medical Science provides opportunities to exploit the Core's genetic results and expertise in new and innovative ways. The AC lauded progress to create a more systematic integrated approach for functional genomic studies of GWAS loci. Some specific studies that are already underway (myocardial infarction, primary immune deficiencies, atopic dermatitis) were noted. It felt that priority should now be given to further defining the general program with members of the other IMS cores. Would the focus be principally on creating iPS cells, mouse models or using other approaches? What would be the baseline characterizations that could be undertaken? How many loci would be investigated and within what timeframe? Can proof-of-principal data be obtained for some loci in the near future?

Apart from the efforts for the development of a procedure for targeted sequencing and automated SNP analysis for the clinic, the Core lags in technological development. The AC recommends that the Core consider integration of additional leading-edge genome instrumentation and new technologies. Moreover, the use of such technologies could make important contributions to microbiome studies that are planned by other Core groups.

Given the vast amount of data being produced, there seems insufficient statistical/bioinformatics power to take full advantage of the available data set and to explore new opportunities. New staff

and/or collaboration networks with outside scientists may be needed. Some re-organization may be necessary, particularly to assure that the laboratories for “Medical Science Mathematics” and “Statistical Analysis” are closely coordinated.

Finally, the AC noted that some of the individual projects seem now to have reached a stage where the genomic studies are over, or their role diminished to the extent that the RIKEN high-throughput facilities may no longer be required for the project. It would be useful to have a defined mechanism that would allow turnover of projects and groups in such instances.

4. Program for medical innovation.

The aim of this program is to target research discoveries made at the center to the clinics for medical applications. This will be done in collaboration with the RIKEN Program for Drug Discovery and Medical Technology Platforms. Several of the projects bear the mark of the former RCAI director Dr. Taniguchi in implementing iNKT cell therapy in various clinical applications. The others are leukemia stem cell therapy, histamine-releasing factor as a potential biomarker for food allergy, and artificial adjuvant vector cells for cancer therapy.

[Recommendation]
All of the projects are well under way, and the NKT cell therapies are in clinical trials. The other projects should strive to maintain a translational focus and develop strategies to get these promising discoveries into patients, since that is the goal of this program.