IMS Advisory Council 2016

BACKGROUND

What follows is the report of the Advisory Council 2016 meeting. The 2016 AC meeting was important since it was the first evaluation of the Center for Integrative Medical Sciences (IMS) since Dr. Tadashi Yamamoto assumed the Directorship in October 2015 after former Director Dr. Koyasu was promoted in RIKEN to Executive Director. Dr. Yamamoto is supported by two Deputy Directors, Drs. Michiaki Kubo and Haruhiko Koseki.

The AC met for two days. The morning of the first day began with an Assembly Meeting in which overall Center Activities were described. Dr. Yamamoto gave an overview of the Center and this was followed by a description of Core Projects for Genomic Medicine by Dr. Michiaki Kubo and Representative Programs in the Core for Homeostatic Regulation by Dr. Haruhiko Koseki. Finally Dr. Yamamoto gave a brief description of IMS Future Plans. This session was followed by Block reviews, where individual laboratories were evaluated. The AC members prepared individual PI evaluations as well as an overall Block evaluation, which was presented orally to IMS director Yamamoto over the course of day one and two. Written versions of these reports were also sent to Dr. Yamamoto, who is sharing them privately with the IMS investigators. These specific evaluations are not included in this report, although there may be some general comments based on the evaluation summaries. The second day was mainly dedicated to preparation of Block Review comments and closed AC discussions of the Block Reviews and the overall activity and leadership of the Center. Dr. Yamamoto also explained the Terms-of-reference from the new President of RIKEN, Dr. Hiroshi Matsumoto. At the end of the second day's session, Dr. Max Cooper as chair of the AC provided oral comments and advice, summarizing the discussions and opinions of the AC panel. This was an open session attended by the IMS Director and Deputy Directors, RIKEN Executive Directors Drs. Koyasu and Yoichiro Matsumoto (remotely), as well as all IMS PIs.

The AC has been asked to provide comments on: 1) Research activities at the Center as well as the Center's overall research strategy, future plans, organizational policies, and research management, 2) Terms-of-reference from IMS Director Yamamoto, 3) Terms-of-reference from RIKEN President Matsumoto, which establishes criteria that are used in the evaluation of all RIKEN centers. (The AC Comments are summarized in this report and in a separate report for the Terms-of-reference from RIKEN President Matsumoto.)

The AC comments are flanked by ***[AC]***, ***[/AC]***

Cores/Representative Projects

At the 2014 AC meeting held shortly after the merger of RCAI and CGM to form IMS, it was announced that the laboratories in the former centers had been reorganized into three thematic cores and one program: Core for homeostatic regulation, Core for precise measurement and modeling, Core for genomic medicine, and Program for medical innovation. The same structure still exists, and the AC heard a report from

Dr. Kubo on the activities of the Core for genomic medicine (CGM). They also heard from Drs. Yamamoto and Koseki about several Representative IMS projects, which are not strictly based on the cores but are instead major center projects conducted by the collaboration of multiple laboratories.

Core for Genomic Medicine

Dr. Kubo presented recent activities, management and the future plans for the CGM. Their recent activities include publication in top notch journals, the analysis of the BioBank Japan Genome-Wide Association Studies (GWAS) Database for disease association and drug response genes, and many collaborations with international GWAS consortia. In addition, they are performing whole genome sequencing studies in liver cancer as part of the International Cancer Genome Consortium, developing new target sequencing methods to analyze the disease contribution of rare variants, and creating catalogs of genome-wide expression Quantitative Trait Loci (eQTL) for various immune cells. Dr. Kubo's description of the budget situation in CGM was bleak, as discussed below for IMS as a whole. There has been significant personnel turnover and a new IMS Deputy Director from CGM will apparently be brought on board in April 2017, although that was not official at the time of the AC meeting. Dr. Kubo also described the future plans for CGM, but they are described below in the overall IMS Future Plans section.

[AC]
The CGM has been a GWAS pioneer since its inception as the Center for Genomic Medicine. The CGM continues to publish significant findings in high-impact journals and has BioBank Japan as perhaps the premier biorepository in the world in terms of number of patient samples (47 Diseases, 200,000 patients), clinical information and follow-up, and genomic information on the samples (SNP/GWAS). The AC was pleased to note that the CGM has now established a BioBank data sharing and release policy, as recommended at AC 2014.

The collaboration of this core internationally is at the highest level in both GWA and pharmacogenomics studies. As an example, in 2015 Dr. Kubo became co-leader of the Pharmacogenomics Research Network (PGRN), an international project funded by the US NIH to accelerate pharmacogenomic discovery. Several other IMS PIs are on the PGRN Steering Committee and Scientific Advisory Board. As GWAS has matured as a strategy for genomic analysis, CGM is exploring other approaches including whole genome sequencing, which has the potential to directly identify disease-associated genes, and eQTL, which uses RNAseq to examine mRNA levels of GWAS-identified loci or other genes in various cell types. They also propose to do functional genomics using these and other methods to identify disease-associated and pharmacogenomics-related genes, a goal not easily realized by conventional GWAS.

The CGM future plans are logical and important, although very expensive, which places a major impediment in the way of their successful completion – a severe reduction in funding. A large segment of the CGM budget comes from government-sponsored commissioned research to support their BioBank research activities. This support might cease in 2017, leaving this Core in very difficult financial straits.

The AC considers the Japan BioBank an invaluable resource in Japan and worldwide. Cuts in funding leading to its demise would be catastrophic. Although it may not be necessary to enroll new patients in the BioBank, preservation of the samples and, importantly, continued clinical follow-up on the patients who have contributed the samples, are essential. There is much more important information that can be extracted from Japan BioBank.
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Representative programs for homeostatic regulation

Dr. Yamamoto described progress in mucosal homeostasis. IMS investigators have identified immune modulatory bacteria from mice and humans that regulate specific branches of the T cell mucosal immune system, such as Th1, Th17 and Treg cells. They have also shown that the botulinum neurotoxin exploits the GP2 receptor on M cells to invade the host and inhibit synaptic neurotransmission. This area will continue to be a major focus, based on the premise that dysbiosis contributes to disease pathogenesis.

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The mucosal immunology group has always been very strong and highly productive. IMS has a state of the art germ free facility that is extremely valuable for dissecting the influence of the microbiota on the host. The AC continues to recommend strong support for this very talented group of investigators.
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Dr. Koseki described several programs whose goals are realization of precise and personalized medicine and development of new therapeutics. Diseases being targeted in the former category are atopic dermatitis, rheumatoid arthritis, obesity and Type 2 diabetes, and primary immunodeficiency. Anti-tumor immunotherapy using iPSC-derived NKT cells and humanized mouse technology were the therapeutic development component of his presentation.

Realization of precise and personalized medicine
The atopic dermatitis (AD) project has been running for several years and was originally based on a mouse from the ENU mutagenesis project that spontaneously developed dermatitis on the ears and face. The *Spade* (*S*tepwise *p*rogressive *a*topic *d*ermatitis) mutant was mapped to a point mutation in the *Jak1* gene. There has been a systematic effort to profile gene expression changes during the stepwise stages of dermatitis development in these mice: very early asymptomatic, skin barrier disruption, onset of dermatitis, and chronic inflammation. ChIP enrichment analysis was performed to estimate relative activity of many transcription factors in the ear skin of *Spade* versus WT mice. From analysis of all of these data, IMS scientists have constructed an apparently robust cellular and molecular network map of dermatitis development that is being validated pharmacologically and by gene knockout. In collaboration with the Medical Innovation Hub (see below) and Keio University, they have been testing whether the clinical outcome of AD patients could be predicted by analysis of pretreatment clinical data. By using machine learning they show that in combination, three clinical parameters, blood eosinophils and serum IgE and the chemokine TARC, allowed patient stratification. They will use “reverse translation”, testing these parameters in the *Spade* mutant and other

genetic AD models to define mechanisms.

[AC]
The *Spade* mutant mouse has been extensively and very well characterized and the network map highlights the complexity of AD. These results should be published soon, since they validate this approach, which is also being used at IMS in other disease models. Their foray into the clinical realm is admirable and the preliminary data suggest that the IMS investigators have identified biomarkers that may be quite useful for predicting the clinical outcome of AD therapy.
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The CGM has identified many rheumatoid arthritis (RA) susceptibility genes by GWAS. In this project, transcriptome analysis will be performed on blood cells and synovial fibroblasts from human RA patients and controls and from multiple tissues and cell types from RA model animals. The initial mouse model to be analyzed is the SKG mouse, which develops a T cell-mediated chronic autoimmune arthritis immunologically resembling human RA. (These mice have a hypomorphic mutation in *Zap70*.) By integrating these data with genomic, transcriptomic, epigenomic and protein-protein interaction datasets, they plan to construct network models and use them to infer the key pathways commonly affected both in mice and humans leading to the onset and progression of RA. The goal of this project is to identify relevant biomarkers and potential drug targets for RA.

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Although this is a very ambitious project, the IMS scientists have already begun to accumulate transcription factor data in the SKG mouse, indicating that approaches similar to those used in the AD project can be applied here.
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Another IMS center project aims to study the role of host-gut microbiome interactions in the pathogenesis of Type 2 diabetes (T2D), using their comprehensive multiple omics approach. The IMS laboratories for Metabolic Homeostasis, Intestinal Ecosystem, Metabolomics, Integrative Genomics, and Integrated Bioinformatics will mainly be involved in this project. This is a collaboration with clinicians at the University of Tokyo who will collect blood, saliva, urine, and feces from individuals classified as normal, obese individuals with no metabolic abnormality, and those with impaired glucose tolerance.

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The proposed multiomics approach has been used very successfully by IMS investigators in mouse studies. The T2D project is exciting but is a huge investment in human and financial resources and will ultimately require follow up studies as, for example, when certain of the obese individuals develop diabetes. In the face of an ever shrinking budget, there is concern about the sustainability of this project. There is also some concern that heterogeneity in humans will make it difficult to extract meaningful information from the massive amounts of data that will be generated.
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In the Primary Immunodeficiency Database in Japan (PIDJ) project, IMS will

continue its collaboration with Dr. Ohara at the Kazusa DNA Research and the network of clinicians throughout Japan to assist in the diagnosis of PID and to identify new PID-causative genes. In some cases IMS investigators will create mouse models that mirror the human gene defect for mechanistic studies.

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The PIDJ is the longest running translational research project, established during the RCAI era. It has been very successful in the somewhat difficult task of establishing a network of clinicians to provide patient samples and also in identifying new PID genes. This project merits continued support.
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Development of new therapeutics
The use of iNKT cells in cancer therapy is another long running translational research project that has gone through several small clinical trials. One limitation has been the number of autologous iNKT cells that can be harvested from cancer patients. The therapy is also complicated by the fact that NKT cells from cancer patients often are functioning suboptimally. To circumvent this problem, iNKT cells are being used to generate iPSC, which can then be cultured and re-differentiated into iNKT cells. These iPSC-derived iNKT cells have been shown to have potent *in vivo* anti-tumor activity in a mouse model.

[AC]
The iNKT cell studies fit well with IMS goal to perform research that has near-term clinical application.
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Humanized NSG mice have been used to study normal human immune system development as well as to understand leukemia and attempt to develop leukemic stem call targeting therapies. IMS has been developing better humanized mice by introducing human genes such as HLA, cytokines and niche factors such as stem cell factor. Such strategies have been successful such that, for example, tumor antigen specific CTLs can be generated in HLA-containing NSG mice.

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The humanized mouse improvements are likely to be very beneficial for some of the proposed IMS studies. However, the position of these efforts in engineering humanized animals in the context of larger international efforts in this area by a group funded by the Gates Foundation is unclear and this was an issue raised in the previous review cycle as well.
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Future plans

Dr. Yamamoto described five areas of IMS focus for the future.

1. *The science of adaptation to environmental changes*

The goals of this program are to understand mechanisms and effects of immune responses to pathogens and long-term environmental responses in order to prevent

chronic inflammation, cancer and other multifactorial diseases induced by dysregulated immunity, environmental stimulation and aging, with the long term goal of sustaining healthy longevity. The concept emphasized here and throughout many presentations is the existence of multiple layers of homeostasis, which must be each understood separately and then understood *in toto* in order to develop useful models of health and of disease prediction, prevention and therapy. Significant funding has been requested for an all-RIKEN project "Comprehensive Understanding of Microbiome-Host Interaction - for the promotion of bioindustries". IMS has a major role in this project: Dr. Ohno is on the governing board, Drs. Fagarasan, Honda and Amagai are in the Basic Science section, Drs. Nakagawa and Kitano are in the Applied Science section, and Dr. Taylor is in the Fundamental Technologies section.

2. *Functional genomics*

This will be a major effort to move beyond GWAS to identify genes or gene variants responsible for common diseases. This goal will be pursued by **1)** expanded bioinformatics analyses, **2)** experimental validation and functional analysis of disease causative genes or drug-responsive genes, **3)** whole genome sequencing (WGS) analyses, and **4)** developing new methods for genomic analysis by utilizing artificial intelligence technology. For **1)**, the plan is to link GWAS results to various epigenome/expression databases, which have expanded exponentially and contain data from many of the different layers described above, in order to define networks and critical disease causative genes. These can then be tested in **2)** by methods in widespread use at IMS, e.g., CRISPR-Cas9 gene editing of iPS cells. In terms of **3)**, WGS is a more powerful method than SNP GWAS for identification of disease causative gene variants.

3. *Genomic science and human immunology*

Recognizing the importance of understanding the human immune system as they pursue more clinically oriented research, IMS has set the following goals. **1)** Perform comprehensive analyses of genetic, epigenetic and proteomic data, as well as functional analysis at the level of cells and tissues. This program will involve collaboration with the functional genomics studies described above. **2)** Create high-resolution imaging technology for human tissues. As with many of the other projects, this will involve extensive collaborations with other RIKEN institutes. **3)** Develop a new platform for analyzing human samples. **4)** Create next-generation humanized mice to understand the *in vivo* behavior of multiple human cell types. **5)** Create and analyze immune-genomic profiles from human cancer tissues and develop stratification models of immune responses in cancer. **6)** Perform sequential integrative analysis of clinical data from patients suffering from immunological disorders. Two examples of projects to achieve these goals were described, the first is to create eQTL catalogs. These would be derived from different immune cell types by SNP genotyping and RNA-seq to determine the risk for immunological diseases. In a similar strategy, an individual's genotype data would be used to create an eQTL catalog that would be predictive of drug responses. The second project involves humanized mice reconstituted with human specimens to understand the *in vivo* behavior of multiple human cell types.

4. *Bridging medical care*

This is a very broad area that was mostly described in the White Paper, where four goals were presented.

1) Creation of low molecular weight (MW) compounds, antibodies and other biologics for drug development
This program aims to identify drug targets based on the disease-associated factors, regulatory factors or environmental response factors discovered by the basic science, new big data computational methods, and disease-association research in IMS.
2) Development and verification of immune cell therapy.
This program aims to evaluate the efficacy of novel therapies in humans, and also to accumulate and integrate data from human samples in clinical testing by collaboration with the Medical Sciences Innovation Hub Project (See below). IMS plans to promote development of new therapeutic technologies to stimulate and regulate lymphocytes and non-antigen-specific effector cells that are potential novel drug targets. The therapeutic efficacy of these new technologies will then be verified by clinical trials with collaborating hospitals.
3) Development of medical informational technology.
In collaboration with the RIKEN Medical Sciences Innovation Hub and the Artificial Intelligence Project, IMS plans to collect and analyze clinical data from patients with atopic dermatitis, rheumatoid arthritis, and other immune-mediated diseases and develop technologies and informatics for stratification of patients, prediction of therapeutic effects and prognosis. One proposed approach, to be done in collaboration with QBiC, CLST and other RIKEN institutes, is to develop technologies for tissue imaging and single cell analysis. The idea here is that these technologies will ultimately result in personalized evaluation for clinical practice.
4) Development of therapy targeting leukemic stem cells
IMS investigators have had successes in reconstituting human leukemia in humanized mice, which led to their identifying leukemic stem cells (LSC) as well as a small molecule inhibitor that is in clinical trials. They now plan to develop new therapies to target LSCs by combining single cell genomic/epigenomic analyses and humanized mice technologies.

At the AC meeting Dr. Yamamoto described a new initiative; the Medical Innovation Hub (MIH) that he predicts will be very helpful in achieving the goals of this "*Bridging medical care"* part of the future plan. The purpose of this initiative is to establish data-driven medical sciences by promoting a collaborative network involving IMS, university hospitals, companies and other RIKEN centers. IMS investigators appear to be well integrated in the three cores of this initiative, Multi-layered measurement, Data integration and disease modeling, and Reverse translation by animal models.

5. Research structure

This part of the future plan dealt with IMS infrastructure rather than particular research projects. IMS has a unique research structure that is mandated to function at the interface with clinical medicine. This is quite different from other RIKEN centers or Japanese universities. In order to support that structure, IMS proposes to:
1) Develop platforms for measurement of environmental responses, data integration, analysis pipelines and modeling (mathematical modeling and validation using

experimental animals). This activity will be promoted by the four cores in IMS, Core for Homeostatic Regulation, Core for Precise Measurement and Modeling, Core for Genomic Medicine, and the Program for Medical Innovation.
2) Expand and update a technical support section (animal experiments, mass spectrometry analysis, imaging, bioinformatics, etc.) to support and develop new technologies. The current "Group Director" system will be reconsidered, and highly competent researchers will assume responsibility for this technical support section.
3) Conduct RIKEN Medical Sciences Innovation Hub Program projects, national projects, MEXT projects and AMED projects by linking the four cores mentioned above.
4) Develop an IMS research system that will enable seamless collaboration with other RIKEN centers. (QBiC and CLST for the measurement of environmental responses, the chemical biology and protein structure analysis groups for drug development, AI for stratified medicine)

[AC]
Specific comments on the future plans

1. The all-RIKEN project "Comprehensive Understanding of Microbiome-Host Interaction - for the promotion of bioindustries" should provide a substantial funding boost that increases the feasibility of the "*Science of adaptation to environmental changes*" project. As well, mucosal immunology/microbiome research is a major IMS strength.
2. The "*Functional genomics*" project builds in some parts on existing IMS expertise, but details are lacking when this is not the case, e.g., developing new methods for genomic analysis by utilizing artificial intelligence technology.
3. The "genomic sciences and human immunology" project suffers from a similar lack of specifics in areas not already in use at IMS.
4. The "Bridging medical care evokes similar concerns.
5. "Research structure" As noted above, the infrastructure improvements **(1, 2)** are very important for the future of IMS and can be easily solved by supplemental funding. Points 3 and 4 are more difficult since they deal with scientific cultural issues.

General comments on the future plans

The future research plans (1-4) are imaginative, thoughtful and address important questions and issues; moreover they build on some of the existing IMS research strengths. There are several common features in all of the projects, for example, multi-level, multi-omic analyses that will be integrated into larger, comprehensive models predicted by systems biology approaches and then validated experimentally. On the surface, such an approach is justified and logical given the overall research strengths existing at IMS. The research structure part of the plan (5) is very important for the future success of IMS and seems to be a particular passion of Director Yamamoto.

These strong points are counterbalanced by several perceived weaknesses. Each of the future plans on its own is very ambitious and taken together are scarily so. The AC is concerned that, even with an unlimited budget and the existing highly competent IMS researchers, these projects would totally consume the IMS research

portfolio, leaving individual PIs with little time to pursue their own independent, curiosity-driven research interests. Moreover, integration of the complex datasets that will be generated and the proposed experimental validation of relevant genes will require very close interaction between IMS genomic and biological scientists. In reality of course the IMS budget is far from unlimited and the integration of the genomic and biological scientists at IMS has not yet taken place (discussed further below).

General Comments

Under the Directorship of Dr. Yamamoto, IMS is a thriving, international recognized research institute, particularly in genomic medicine and immunology, the areas of excellence of its predecessors, RCAI and CGM. IMS PIs continue to publish seminal papers in top quality journals, participate actively in international collaborations and are invited to prestigious international scientific meetings. All of these factors contribute to the success of both IMS itself and RIKEN as a whole. There are however external and internal forces that may be disruptive of this success. The AC was surprised and very concerned by the continued decrease in the IMS budget, given its stature. Since 2013, there has been a 65% reduction in the research budget available to IMS laboratories. We are frankly amazed at the continued high level productivity given this financial impediment. The AC would emphasize, however, that it may take several years for the existing severe budget cuts to be reflected in a noticeable deterioration of IMS, manifested by the loss of highly qualified and productive investigators and a decline in publication quality. By that time recovery is likely to be quite difficult. A second issue is a sensitive one, the integration of genomic and biological science at IMS. These are two quite different scientific cultures, the former thriving on team science to answer large scale questions and the latter on individual/small group science to investigate basic issues that may have clinical applications. The merger of these two groups was expected to be difficult and there have been some small successes. In general, however, the perception of the AC is that these two groups continue to exist as separate entities. This is unfortunate since together they could synergize in a powerful fashion. These are both problems that Dr. Yamamoto has inherited and he is very committed to efforts that will increase the IMS budget and to promoting the successful merger of the genomic and biologic scientific cultures.
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Terms of Reference from RIKEN President Matsumoto

1. Status of the Center based on international standards

1) Strengths

IMS is a thriving, internationally recognized research institute, particularly in genomic medicine and immunology, the areas of excellence of its predecessors, RCAI and CGM. IMS researchers continue to publish seminal papers in top quality journals, participate actively in international collaborations and are invited to prestigious international scientific meetings.

Of 279 publications in 2015, 25% were in high impact (IF>10) journals and 15% were in *Science*-, *Cell*- or *Nature*-related journals. Thomson InCites™ provides an unbiased external evaluation of the impact of IMS publications. In 2013-2014, the latest reporting period, more than 25% of IMS publications were ranked among the top 10% worldwide and 8% were in the top 1% of papers. These remarkable accomplishments are especially impressive given the severe annual decreases in the IMS budget.

The uniqueness of IMS is the combination of very strong immunology and a comprehensive project in genetics of common human disease. If this expertise is exploited appropriately, then IMS will be well positioned to understand the functional basis of genetic factors contributing to the burden of inflammatory diseases. The projects on atopic dermatitis and rheumatoid arthritis illustrate this, and they are discussed in the report.

2) Weakness

As IMS research becomes more translational in nature, a potential weakness is that the Center has no hospital affiliation and thus obtaining patient samples and clinical information and expertise may be difficult. There seem to be appropriate collaborative efforts in place or in the works that make this less of a concern. Moreover, there is already demonstrable success in a number of translational research projects outlined below in section 2, “Center’s achievements”, subsection 2).

3) Suggestions for mid/long-term

There is very little regular communication or interaction between the Core for Genomic Medicine and the Immunology group. There needs to be more in order to establish better integration in the Center and to take full advantage of the strengths of the two groups. This is probably best done via a bottom-up mechanism rather than top down (i.e., from the Director). A regular research forum that brings PI’s and postdocs together would likely work best. Interesting results relevant to the immune system from the genomics group could be shared in such a forum with the goal of

discussing mechanisms, pathways and tests of hypotheses. A faculty lunch or a Research in Progress-like session for the postdocs and graduate students would also be worth considering.

Dr. Yamamoto is very committed to expanding and updating the technical support section (animal experiments, mass spectrometry analysis, imaging, bioinformatics, etc.) to support and develop new technologies. This is an important goal for the continued success of IMS, but may be difficult to accomplish if budget reductions continue. Since the budget for all of RIKEN appears to be recovering, the AC hopes that the IMS budget will similarly be restored.

2. Center's achievements for the RIKEN Initiative

1) Pioneer a research management model for maximizing research and development results

Since the best measure of success of a research institute is publications, the publication record provides compelling evidence of the effectiveness of the IMS research management model. The Center is now in the process of developing a unique experimental strategy that will attempt to achieve integration in precise measurement at multiple levels, e.g., metabolome, proteome, transcriptome, and genome. Many investigators worldwide use one or two of these approaches to generate big data to try and understand a particular biological system. An integration of multiple levels of this type of analysis will be a big challenge, but ultimately this will be required to understand the complexities of human diseases, where both genetic and environmental factors play a role. In addition to the basic biology and clinical studies, which provide the input for such big data analyses, there will need to be major investments in bioinformatics, computational sciences and artificial intelligence for this bold initiative to succeed. To take this approach to an even higher level IMS investigators will attempt to integrate human and mouse studies. This will be difficult because of species differences in biological response, but promises big rewards, since pathways conserved between mice and humans are likely to be critical and ultimately drug-targetable.

2) Lead the world in achieving new research and development results through scientific excellence

Again, the publication record attests to the scientific excellence of the Center. IMS has many areas of deep strength, particularly in mucosal immunology, where exciting new discoveries in microbiome-host interactions are at the forefront of international research. It is noteworthy that three of the six recent papers highlighted at the AC meeting that were in the top 1% of the Thomson InCites™ rankings were in this area. The Core for Genomic Medicine has also been a leader in genome research. Finally, the Center has evolved to include basic and pre-clinical studies as well as early clinical trials in collaboration with university hospitals. Given the

increased focus on bench to bedside research at IMS, it seems appropriate to highlight some of the ongoing projects that have clinical/translational components.

The longest running translational research project is the primary immunodeficiency project (PIDJ, Primary Immunodeficiency Database in Japan), which was established in 2006 as a collaboration between RIKEN RCAI, the Kazusa DNA Research Institute and clinical immunologists in the clinical study group for primary immunodeficiency from 13 universities and colleges throughout the country. The original goal, which has succeeded remarkably well, was that PID experts at these institutions would serve as the first contact point for primary care physicians in the surrounding local hospitals and provide patient samples to the PIDJ for molecular diagnosis and identification of new PID genes.

The use of NKT cells to target human cancer has also been a long-standing translational research project. Based on studies in mice, Dr. Taniguchi and colleagues set up a clinical trial in collaboration with Chiba University Hospital. Phase IIa clinical studies were completed on advanced lung cancer (Stage IIIB, IV, and recurrent tumor) patients by using α-GalCer/DCs, and on head and neck tumor patients by the combination of α-GalCer/DCs and activated NKT cells. There was significant clinical efficacy in both cases. Based on these promising results, the NKT cell-targeted therapy was approved for the advanced medical care assessment system B in 2011 for advanced lung cancer and in 2013 for head and neck tumors by the Japanese Government. A problem with NKT cell therapy using patients' autologous cells is that they are often few in number and suboptimal in function due to, e.g. effects of the tumor or tumor chemotherapy. A novel solution to this problem being used by Dr. Koseki with several IMS collaborators is to reprogram human NKT cells into iPSCs and then re-differentiate NKT-derived iPSCs into functionally mature NKT cells *in vitro*. The results so far of these studies have been quite promising and may increase the number of cancer patients that can be helped by NKT cell immunotherapy.

Another translational research project that is moving rapidly to the clinic is Dr. Fjuii's artificial adjuvant vector cells (aAVCs), which use CD1d+ allogeneic cells loaded with αGalCer and transfected with antigen-encoding mRNA for the induction of antigen-specific T cell responses. The advantage of this approach is that it combines the adjuvant effects of NKT cell activation with delivery of antigen to DCs *in vivo*. A human version of aAVCs has been established using Wilms tumor-1 (WT-1) antigen-encoding mRNA. For the purpose of going forward with a clinical study, there have already been multiple consultations with the Pharmaceuticals and Medical Devices Agency (PMDA). A collaboration has been established with the Department of Hematology of the Institute of Medical Science, The University of Tokyo for the first clinical trial using aAVC-WT-1 for two hematological malignancies, acute myelogenous leukemia and multiple myeloma.

Using humanized mice, Dr. Ishikawa has developed a small molecule inhibitor of the src-family kinase HCK to target chemotherapy resistant human acute myeloid leukemia stem cells. The “in vivo” preclinical evaluation of this compound on human leukemia samples transplanted into humanized mice has been very promising and clinical trials are expected to begin in the future.

Apart from the cancer immunotherapy studies described above, the studies of Honda and colleagues demonstrating that a select mixture of Clostridia strains isolated from the human microbiome can induce intestinal T-regs, so far only shown in mice, is likely to be on the forefront of new therapy for human inflammatory bowel diseases.

GWAS studies are by definition designed to identify disease-associated genes with the objective of modifying their activity to prevent disease. This goal has been difficult to achieve, but some GWAS performed by the Core for Genomic Medicine have had translational outcomes in the area of pharmacogenomics. For example, Carbamazepine (CBZ), a commonly-used antiepileptic drug, is the main cause of cutaneous adverse drug reactions (cADRs) in the world. Association of HLA-A*31:01 with the risk of carbamazepine-induced cADRs was observed in Japanese and Northern European populations. The GENCAT study was designed to test the clinical utility of prospective HLA-A*31:01 screening to prevent carbamazepine-induced cADRs. A clinical intervention trial validated the clinical utility of the HLA-A*31:01 genetic test, since there was a 40% reduction in the incidence of CBZ-induced skin rash when patients with this HLA allele were treated with an alternate drug. Warfarin is the most commonly used oral anticoagulant for treatment of thromboembolism, but adjustment of the dose appropriate to each patient is not easy because of the large inter-individual variation in dose requirement. In another study, genome guided warfarin maintenance dose prediction based on two genetic markers was superior to standard dosing with respect to rapid achievement of therapeutic anticoagulation.

3) Become a hub for science and technology innovation

The Core for Genomic Medicine is involved in many international collaborations at the highest level in both GWAS and pharmacogenomics studies. As an example, in 2015 Dr. Kubo became co-leader of the Pharmacogenomics Research Network (PGRN), an international project funded by the US NIH to accelerate pharmacogenomic discovery.

4) Serve as a focal point for global brain circulation

IMS has comprehensive research agreements in place with nineteen institutions worldwide and has three more in progress. These programs will provide opportunities for collaborative research as well as exchange of research personnel. The turnover of PIs in the Center is 23%, meaning that new talent and perspectives can be incorporated into IMS research. Some IMS investigators come from outside

of Japan, but this number is small and could be increased. On the flip side, PIs leaving IMS and joining the brain circulation mainly are recruited within Japan. IMS PIs have been quite successful in obtaining academic appointments at Japanese universities.

5) Foster the development of world-class leaders in scientific research

IMS has been quite successful in this area. They originated the Young Chief Investigator program to promote the development of talented young researchers; one IMS YCI, Dr. Shiroguchi, was recently promoted to PI at the RIKEN Quantitative Biology Center. Another important program has been the RISP, RIKEN IMS Summer Program. Here talented graduate students and newly minted postdoctoral fellows from abroad and from Japanese universities participate in a week long program consisting of an immunology course with a distinguished panel of national and international lecturers, poster and oral presentation sessions by the students, and participation in the two day RIKEN IMS-JSI International Symposium on Immunology. This program helps develop world class research leaders and fosters international collaborations. It also contributes to point 4 above.

3. Recommendations for the RIKEN Initiative

The research management of IMS is efficient and directed to continued improvement of the center. RIKEN plans to reform its personnel system in 2017 when they will introduce a conversion system of fixed-term workers to permanent employment. This transition will provide job security for a number of IMS personnel, and insecurity for others. It was not entirely clear to the AC how this decision process was being handled but we hope that those most directly affected by it, the laboratory heads, are deeply involved in the decision about who to retain as permanent employees. Depending on how this process is handled, there could be a potentially damaging loss of well-trained technical staff. If the IMS budget continues its precipitous decrease, it seems that labor costs for the permanent employees will consume a larger and larger percentage of the Center's overall budget.

To nurture young researchers who will become the leaders in future multidisciplinary research, IMS established its unique Young Chief Investigator (YCI) system. This system has had some notable successes and was approved as an official RIKEN system in 2015, thus making it easier to request budgetary support from RIKEN. Increased YCI funding was suggested in the last AC report and continues to be recommended.

4. Center's activities towards maximizing RIKEN's achievements as a whole, including collaboration between centers.

Many of the Center's representative projects involve significant collaboration within IMS and externally with other RIKEN centers. IMS is a major participant in the RIKEN Medical Sciences Innovation Hub (MIH) which should be of great benefit for

RIKEN's overall achievements. They will also be participating in the new RIKEN-wide interdisciplinary program on aging, which will involve several RIKEN centers.