IMS Advisory Council 2019

BACKGROUND

What follows is the report of the Center for Integrative Medical Sciences (IMS) Advisory Council (IMAC) 2019 meeting. This meeting was important for several reasons, two in particular that are described in more detail later in this report. 1) It was the first evaluation of IMS since it expanded in April 2018. At that time, the Division of Genomic Technologies, part of the former RIKEN Center for Life Science Technologies, was incorporated into the IMS Division of Genomic Medicine. 2) There have been significant changes in indefinite-term (permanent) employment under the new Japan Labor Contract Law that are impacting the hiring and retention of IMS personnel.

Summary of the review meeting

The IMAC met for 2.5 days. The afternoon of the Day 1 began with a Preliminary Executive Meeting, attended by the IMAC chair (M. Cooper), Vice-chair (M. Lathrop), IMS Director (T. Yamamoto), Director of the RIKEN Yokohama Promotion Office (M. Yokota), and members of the IMS Coordination Office (P. Burrows, M. Furuno, H. Iwano, T. Taylor), in which IMAC logistical issues were discussed. This was followed by a larger Preliminary Executive Meeting also attended by the IMS Deputy Directors (P. Carninci, H. Koseki, and K. Yamamoto). During this meeting Director Yamamoto gave an overview of the Center and then the four Division Directors (P. Carninci, K.Yamamoto, H. Koseki, and T. Yamamoto) each gave a condensed overview of their respective Divisions – Genomic Medicine, Human Immunology, Disease Systems Biology and Cancer Immunology. These Division overviews were presented in expanded form on the morning of Day 2. The rest of Day 2 was dedicated to the review of individual PI laboratories by the six Review Groups shown in Table 1.

Table 1	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
	Genomic Medicine 1	**Genomic Medicine 2**	**Human Immunology**	**Disease Systems Biology 1**	**Disease Systems Biology 2**	**Cancer Immunology**
AC reviewers *Group Chair	Ewan Birney* Michel Georges Sarah Teichmann	Mark Lathrop* Hideyuki Aburatani Juha Kere	Max Cooper* David Hafler Arthur Weiss	Bernard Malissen* Rudi Balling Hajime Karasuyama	Ronald Germain* Paul Kincade Yukiko Gotoh	Riccardo Dalla-Favera* Yutaka Kawakami Shimon Sakaguchi

The AC Groups prepared individual PI evaluations as well as an overall Block evaluation, which were presented orally to IMS director Yamamoto over the course of Day 2 and 3. More detailed written versions of these evaluations were prepared by the Groups and were sent to Dr. Yamamoto after the IMAC. He will be sharing these privately with the IMS investigators. Comments about each Division based on each of the Groups evaluation summaries are included in this report, but individual PI evaluations are not. Day 3 also included a lunch where young IMS investigators, postdocs and students working in areas of interest to the different AC members had the opportunity to meet with them and discuss their research. This lunch meeting was new for this review cycle and was considered to be very successful. Director Yamamoto then described IMS Governance and Future Plans at a session attended

by the AC members and all IMS PIs. This was followed by a closed session attended by all AC members and P. Burrows and T. Taylor from the IMS Coordination Office. Director Yamamoto was available if there were any follow up questions. The goal of this session was to assist Dr. Cooper, IMAC chair, in composing a comprehensive oral report to IMS. Thus, each Group summarized its findings and discussed them with the other Groups. The final official IMAC event was the presentation of Comments and Advice at a session attended by all PIs. Dr. Cooper summarized the overall findings of the IMAC review and the chair of each Group provided further details.

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 below are flanked by ***[AC]***, ***[/AC]***

Organization of the Center

At the time of the last IMAC meeting, the research activities of the Center were organized into Cores, the Core for Genomic Medicine and the Core for Homeostatic Regulation, and a Young Chief Investigator Program that provided a mentored, semi-independent position for promising new investigators. Instead of these Cores, there are now four Divisions and two programs (Table 2). The Division Directors also serve as Deputy Directors of IMS.

Division	**Director**
Genomic Medicine	Piero Carninci
Human Immunology	Kazuhiko Yamamoto
Disease Systems Biology	Haruhiko Koseki
Cancer Immunology	Tadashi Yamamoto
Programs	**Director**
Young Chief Investigator Program	IMS Director, Tadashi Yamamoto
Genome Immunobiology RIKEN Hakubi Research Team	Director, RIKEN Cluster for Pioneering Research, Shigeo Koyasu

[AC] The new Divisions provide a better description and a more useful structure for integration of the research activities of the Center than did the previous Cores. The Division of Genomic Medicine is an expanded version of a previous Core and thus has been in existence the longest. Other Divisions, especially Cancer Immunology, are newly formed. The following sections contain specific AC comments about each Division, general comments applicable to most or all Divisions, and comments about the YCI Program. Note: IMAC Group 5 reviewed the research activities of Dr. Nicholas Parrish, an IMS-associated member of the Genome Immunobiology RIKEN Hakubi Research Team. However, IMAC did not review the program itself since it is RIKEN-wide. ***[/AC]***

Division of Genomic Medicine

In his overview, Division Director Carninci described several ongoing projects, including FANTOM and Human Cell Atlas (see below for details). He also described ongoing efforts to integrate genomics and genetics, as well as an intriguing effort to integrate biological models and genomics technologies, which he termed matrix-driven science. The efforts to integrate genomics and genetics are driven mainly by the fact that in April 2018, the Division of Genomic Technologies, part of the former RIKEN Center for Life Science Technologies, was incorporated into the existing IMS Division for Genomic Medicine, which had a major research focus on GWAS and related genomic analyses. The current Division has 18 laboratories, 12 of them coming from Division of Genomic Technologies. Because of these significant changes in the Division of Genomic Medicine structure since the last IMAC, it was given the most detailed evaluation.

[AC] Overall, the IMAC was enthusiastic about this new Division of Genomic Medicine structure, which combines the strengths of genomics and genetics. On the genetics side, the FANTOM project has been a longstanding success for RIKEN. Now in its sixth edition, the current goal is to systematically elucidate the function of long non-coding RNAs (lncRNAs) in the human genome. Another important international project is the Human Cell Atlas, which aims to provide a comprehensive map of human gene expression at the single cell level. The Division of Genomic Medicine has taken an important lead in coordinating this project in Asia. The Division of Genomic Medicine also includes one of the best genomic protocol development groups in the world. On the genomics side, a common theme is to apply genomic approaches to identify genetic factors that are involved in human disease, particularly complex, polygenic disorders. The principal approach has been to analyze large numbers of samples, mainly from Biobank Japan (BBJ), which is a major national resource for disease genetic studies. BBJ is composed of ~250,000 samples covering ~50 different disease areas that have been collected over a 15-year period. The Division of Genomic Medicine has been a world leader in the area of complex disease genomics, and this has led to many new international partnerships and heightened the global visibility of RIKEN in the area of Precision Medicine. The AC was pleased to see that the RIKEN has adopted a policy of “open science” in which the key data are made freely available to the scientific community after publication to aid these efforts beyond the initial publications and collaborations. The AC noted further that the whole genome sequencing that has been started on Biobank Japan samples is also leading to important new knowledge about genetic variability within the Japanese population.

The arrival of the new Division of Genomic Technologies groups with strong genomic expertise provides an opportunity to take disease genetics at RIKEN to a new level. The AC found that the groups had made an excellent start on integrating the FANTOM expertise with the disease projects, for example, in the area of long non-coding RNA biology. New methodologies such as NET-CAGE are very promising for advancing into a new generation of disease studies. Considering inter-divisional collaborations, the experimental expertise in the immunology groups could provide mechanistic insights from the large scale work being done in the Division of Genomic Medicine. Some of these joint genomics/immunology projects are already occurring,

but the AC believes that more could happen. One strategy to encourage collaboration within and between Divisions would be to provide financial support for such collaborative projects, although the AC recognizes that the current IMS budget situation may not make this feasible.

Internationalization is extremely good in Division of Genomic Medicine, particularly in the former Division of Genomic Technologies laboratories, with a very high proportion of international PIs and with a strong recruitment across the world. A number of PhDs and Postdocs have been drawn to RIKEN IMS due to the international reputation of this group. On a less positive note, there is an issue about recruiting and promoting female PIs. In discussions with other Review Groups and according to information provided by Director Yamamoto, this is not a Division of Genomic Technologies- specific issue.

The AC noted a number of subjects that are likely to require further attention in the near future:

1. Biobank Japan is a major national resource for precision medicine research and it will be extremely important to have a continued follow-up of the participants, otherwise it will be a lost opportunity. The AC was disappointed to learn that, although funding is in place for continued long-term storage of existing samples at the University of Tokyo, there is no solid plan yet in place for the follow-up phase. Ideally, there would not only be follow-up, but also a strategy for the sequencing and other large-scale analysis (such as metabolomics) of the full cohort. This would be quite expensive and require the negotiation of additional outside resources, governmental as well as perhaps from pharmaceutical companies that might benefit from the outcomes of these studies. Garnering of such funds will require a concerted effort by IMS, the RIKEN administration, and other entities.

2. The AC was pleased to see the positive effects of the integration of the sequencing groups originating in the IMS and arriving from the Center for Life Science Technologies. We felt it would be important to have further planning and clarification in the operations and development of core support in areas such as single-molecule sequencing and single-cell genomics which seemed currently dispersed and, in some instances, with efforts that may be duplicated in different laboratories.

3. The AC noted that the IMS environment is most suited to disease projects that draw upon high throughput genomic technologies and expertise in advanced genome analysis. In light of this, the IMS should consider if some of the on-going activities, such as the development of diagnostic sequencing panels, might better be transferred to other academic structures or to spin-off enterprises in order to focus better on these strengths.

4. The AC also noted the importance of providing an organized approach to mentorship and support for young scientists. In some cases there are substantial differences in internal support and team size of these young investigators when compared to more established Team Leaders.

5. There is clear tension and angst among some laboratories in the Division of

Genomic Medicine about the nature of the current AC review format. By focusing almost exclusively on evaluating PIs individually, the concern is that the process does not fully capture the central importance of team science in the area of genomic medicine, and that there is a need to evaluate the contribution of PIs to the overall program or programs in addition to the productivity of the individual laboratories. This issue is exacerbated by the changes in the Japan Labor Contract Law (See page 11), which will result in stiff competition for the limited number of indefinite term PI positions that will be available in IMS; it will be difficult in this situation to evaluate a PI based on team rather than individual accomplishments. ***[/AC]***

Division of Human Immunology

In his overview, Division Director Kazuhiko Yamamoto described the gap in knowledge of human immunology, with most of our knowledge derived from mouse studies. The goal of the Division is to establish a pioneering Human Immunology research area in which the immune systems of mice and humans are compared, and basic science and human disease science are connected.

[AC] Overall, the Division of Human Immunology does excellent work with several outstanding investigators and programs. The question becomes what defines Human Immunology. Clearly, some groups focus on human immune physiology or diseases. The eQTL analysis by the Laboratory for Autoimmune Diseases and plans in the Laboratory for Innate Immune Systems to examine idiopathic pulmonary fibrosis using single cell RNA seq from patients are excellent examples of true translational immunology. However, some investigators remain focused on mouse systems, exclusively, although their work may be instructive regarding the human immune system and disease pathogenesis and therapy. While the animal models relate to fundamental aspects of the immune system that could be relevant to clinical issues, there is a sense that there could be more effort/emphasis on focusing on humans with disease. However, this would require a close working relationship with patient cohorts. Perhaps long-term recruitment of active physician scientists connected with medical facilities but with their laboratories at RIKEN would be a model to incorporate immunology studies that directly involved human subjects in a more integrated fashion. A good example of where this has already been put in place at IMS is with Masayuki Amagai, who is an M.D., Ph.D Team Leader of the Laboratory for Skin Homeostasis in the Division of Disease Systems Biology. In addition to his outstanding basic research on skin biology, he is a Professor and Clinical Dermatologist at Keio University where he sees patients.

Another issue is that collaboration and synergy between groups in the Division was not readily apparent. Based on comments at the closed session where all the AC members gathered to summarize their reviews, this is an issue with most of the Divisions. ***[/AC]***

Division of Disease Systems Biology

In his overview, Division Director Koseki described their efforts at stratification of patients by building up human data sets, extrapolation of these data to mouse-based models and the modeling human disease pathogenesis in mice.

[AC] The studies described by Dr. Koseki are important and will involve establishment of collaborations with the RIKEN Medical Sciences Innovation Hub Program (MIHub), the Agency for Medical Research and Development (AMED), and various university hospitals that will provide patient samples and clinical data. Establishment of close interactions with these groups will be essential going forward as IMS strengthens its translational research programs.

Overall, the Division of Disease Systems Biology is a strong group of scientists. Both the senior and YCI investigators all are producing, or are capable of, a high level of scientific output, though with varying degrees of productivity reflecting in part of size of their laboratory groups. There was good evidence of group collaboration in terms of the SPADE AD project, with at least 4 different groups involved in the analysis of this mouse model, although the degree of effort by some groups was modest. The AC was also impressed by the strong effort made to connect basic animal studies to human disease, for example with respect to AD, allergic diseases, cancer treatment, and cutaneous biology.

An impressive attribute of the teams in this Division is that each one has command of a cutting-edge technology such as proteomics, imaging, metabolomics, or genomics. At the same time, neither the written reports or the presentations put special emphasis on efforts to either share these methods extensively with other Divisions or IMS members or to foster within-Division collaborations leveraging this substantial array of technologies. In this regard, it was unclear to the AC panel whether the Division of Disease Systems Biology actually constituted a formal mini-department or was assembled for review purposes, given this limited programmatic interaction. It was also noted that while the Division is supposed to be pursuing systems biology approaches to key biological questions, there was little evidence of either of the two main systems methods (big data / bioinformatics or quantitative integrated modeling) apparent in the ongoing work.

The Team Leader of the Laboratory of Integrative Genomics will leave his IMS PI position by next year due to his growing responsibilities for clinical DNA evaluation. This left open the question of the plan going forward to provide the remaining IMS investigators the genomic, proteomic, analyte methods, and informatic assistance his group has traditionally supported. Presumably the Division of Genomic Medicine will be taking care of providing genomic services (bulk and single cell sequencing), but how the remaining core technical services, including informatics, will be covered is unclear. Although the departing Team Leader indicated that he would support proteomic studies in his outside laboratory, this does not seem an optimal solution.

As a major recommendation, the panel felt strongly that more extensive interactions among the groups should be encouraged, especially given the current fiscal limitations. High profile work is more and more multi-disciplinary in nature and the optimal use of the various technologies available in the division to produce major findings on important questions in a timely manner seems a valuable path forward.

Other specific comments:

1. IMS integrative research on atopic dermatitis. For historical and

strategical/societal reasons, IMS devotes a fair amount of efforts to data-driven integrative research on atopic dermatitis. This is a highly competitive field and several academic and industrial research groups are also tackling this condition with the aim of developing new drugs; a few trials investigating the efficacy of drugs for disease-specific pruritus and AD are already running. In view of the very innovative and exciting models in the process of development at IMS it might be interesting to consider the possibility that some of those models supersede the IMS SPADE AD model and will put IMS in a better competitive advantage.

2. There is a need to bring in or solidify some expertise in neurobiology to boost projects such as the one headed by Sidonia Fagarasan aiming at characterizing how immune and metabolic changes modulate brain functions.

3. The IMS should increase its efforts to stay at the forefront of data science, computational disease modeling. This might involve a major initiative on the "FAIRification" of data (https://www.go-fair.org/fair-principles/fairification-process/), such as data accessibility, interoperability and sharing of in-house data and of data from collaborators. Particularly with clinicians and hospitals this will become a key issue and potential bottleneck for future development. ***[/AC]***

Division of Cancer Immunology

The Division of Cancer Immunology is a recently formed unit within IMS. In his overview, Division Director Tadashi Yamamoto described his vision of creating a next-generation cancer immunology platform. This will involve creation of cancer therapeutic model animals, single-cell analysis of tumors, cancer genome analysis, and quantitative analysis of cancer immunity.

[AC] The research accomplishments of the Division vary from very mature, fully developed projects (e.g. in the Laboratories of Human Disease Models and Immunotherapy) to "in development" efforts (e.g. Laboratories of Immunogenetics and Cancer Genomics). Overall, the quality of research and the productivity is generally high both in terms of quality and quantity of published papers. Area of particular relevance are represented by the novel findings of the role of CCR-NOT in RNA regulation by the Laboratory of Immunogenetics, by the excellent genomic studies in liver cancer by the Cancer Genomics laboratory, and the outstanding innovative bioinformatics analysis by the Laboratory of Medical Science Mathematics.

The Division includes research groups with marked heterogeneity in terms of background, objectives, and approaches. This diversity could represent a strength since there is also significant complementarity in the expertise and technology provided by the several groups. However, evidence of interaction is still lacking, possibly due to the relatively short time during which the various groups have been brought together. Thus, it is recommended that dedicated mechanisms be implemented to promote interactions. These may include: I) the selection of one or more broad-based research topics or cancer types that may lead to the synergistic convergence of the efforts of the various groups and exploit their complementarity; II) the implementation of scheduled research presentations by group leaders as well as young scientists (students and post-doctoral fellows), thus allowing the dissemination

of expertise, approaches and technologies.

The general focus of the Division is clearly translational research in cancer, focusing on immunotherapy-based approaches. It would be very useful to complement the available expertise by interactions on one side with the basic research in Immunology, as provided by the Division of Human Immunology, as well as with well-structured contacts with clinical collaborators providing access to human pathology samples, ideally from clinical trials. In this vein, it would be useful to establish a mechanism, e.g., an email list serve, to let other IMS investigators using human material know when such valuable samples are coming into the Center so that they might possibly be shared. ***[/AC]***

IMS Divisions: General Comments

In the review of the IMS Divisions there were some issues noted that were common to many/all of them and they are therefore described here.

[AC] The AC felt that the goals of the new Division structure at IMS should be twofold: **1**) Promote synergistic interactions among PIs within a Division, drawing on each other's research strengths. Ways to achieve this goal could include informal "work in progress" meetings attended by all researches in a Division, not just the PIs. Development of a Division-wide common research project would also be effective at integrating labs within a Division. **2**) Promote inter-Divisional collaborations. The Division of Genomic Medicine could provide a hub for such collaborations, since much of its technology, currently available or in development, would be useful for other Divisions. Some of this is already occurring, e.g. various types of single-cell analyses are being performed by several laboratories. Overall though, the IMAC felt that much more needs to be done to achieve these goals, in particular the first one. We do recognize, however, that this Divisional structure is still relatively new and a work in progress and that it will take some time to fully mature.

The recruitment and promotion of female PIs at IMS is not adequate.

Many laboratories are using mouse models to study human disease pathogenies and treatment. This approach has sometimes been informative, but unfortunately in many cases had only limited translational research value. It has been recognized for some time, in large part due to studies performed at IMS, that the microbiota has a significant impact on the host immune system. Recent studies, in which C57BL/6 embryos were transferred into wild mice so that the offspring had the microbiota of the wild mice at all body sites, have shown that these "wildling" mice are a better model for human diseases [Rosshart et al., Science 365, 461 (2019); https://www.the-scientist.com/news-opinion/new-mouse-model-predicts-two-clinical-trial-failures-in-humans--66223]. The most striking finding was that the wildlings, but not laboratory mice, phenocopied human responses in two preclinical studies One example, in previously published studies, treatment of laboratory mice with an agonistic CD28 mAb promoted Treg expansion and reduced inflammation. However, a clinical trial based on this finding had to be halted when the first group of patients suffered life-threatening inflammation. The wildling mice responded similarly to the humans. Setting up such a system at IMS would not be trivial, but is well within the expertise of the state-of-the art animal facility headed up by Dr. Koseki. As a long

term goal, IMS might consider adopting such an approach, which should move their translational human immunology research into the forefront of this area.

Young Chief Investigator Program

The purpose of the Young Chief Investigator (YCI) program is to provide a career path for young investigators who conduct multidisciplinary research that will bridge immunology with other fields. The YCI is expected to become an independent leader in a new research area. The YCI runs an independent laboratory in terms of funding and research. The laboratory, however, shares space, equipment and facilities with a host laboratory in the Center. The YCI is supported by Advisors from related fields and receives guidance for research, preparation of papers, presentations and obtaining research funding (https://www.ims.riken.jp/english/jobs/yci.php).

[AC]
The YCI, which at RIKEN is unique to IMS, has been quite successful as judged by the fact that three of the original cohort have obtained independent positons at universities and at the new (April 2018) RIKEN Center for Biosystems Dynamics Research.

Coaching of Young Chief Investigators. Young Chief Investigators will greatly benefit from IMS inputs external to their group in the form of regular discussion/coaching by senior IMS PIs. Although this is activity listed in the description of the YCI program, it was not entirely clear whether IMS makes optimal use of the expertise of senior faculty, for instance in long-term strategy planning and grant writing, to maximize the success of its more recent faculty members. Such meetings should occur regularly and more often than they apparently do at present.

Format of IMS Young Chief Investigators laboratories. Is the small format of the IMS Young Chief Investigators laboratories viable given the level of international competition? In many European countries and in the US, the packages that are allotted to Young Investigators allow them to develop teams of 4-5 persons. If the IMS YCI has only one other person in the lab, s/he will be spending most of the time at the bench, with little time left for creative thinking. ***[/AC]***

Terms of Reference from Director Yamamoto

Director Yamamoto listed three items to be discussed for the future development of IMS.

1. What is the right size for our strategic project oriented center and the divisions/labs given our limited budget?

[AC] Specific recommendations concerning individual divisions/labs are provided in the IMAC Group Reports. The AC is concerned, though, that some laboratories are too small to maintain stability and productivity. A typical single PI lab should have 4-6 members, and some are smaller than this. With a few notable exceptions, it seems that many IMS PIs are having difficulty recruiting students and postdoctoral fellows. It could be helpful to have some sort of RIKEN office to coordinate recruitment of qualified individuals, particularly at the postdoctoral level. Maintaining an active and attractive website for each PI that includes a listing of

open positions might be helpful. ***[/AC]***

2. Which areas should be strengthened for the future?

[AC] In the effort to identify human disease genes, it would be well worth expanding the analysis of diseases in infants and children, in addition to the current focus on the adult population. One area in which IMS already has a foothold is the analysis of primary immunodeficiency disease genes in children. The Primary Immunodeficiency Database in Japan (PIDJ) was established several years ago as a collaborative effort between RCAI, the Kazusa DNA institute and the Japan PID Study Group and involved creation of a network of hospitals and clinics where suspected PID patients were sent for evaluation. Many PIDs are first manifest in newborns and young children, thus many PID genes have been identified in this patient population. Since it is well known that other disease genes, for example those causative for autoimmunity, also become manifest in children, we encourage the IMS to broaden their in-depth genetic analyses to other childhood diseases.

With the exception of Dr. T. Okada, the IMS has lost some of the expertise it previously had in the area of optical imaging. Especially with respect to tissue imaging, this is a burgeoning area and such methods are now commonly incorporated into many of the large scale studies one sees in the top journals. It would be important to add capacity in this area and to integrate such activities into the efforts in such areas as cancer immunology, contributions to the Human Cell Atlas, and even studies of the microbiome and metabolism. This is especially cogent because new technologies now permit direct visualization of specific bacterial species *in situ*, where the interaction with specific host cells can be mapped or assessment of the cell metabolic state can be probed, permitting this information to be related to ongoing cell-cell interactions or to a cell's location within a tissue setting.

Another area to pay attention to is 'real' systems biology. This means attention to the integrated functioning of a tissue, organ, or host addressed by measuring many parameters at one time and relating the state of these measured entities to an outcome that none of the individual elements achieves on its own ("emergent properties" of the system). Such systems analysis will be critical if one is to develop a true understanding of polygenic diseases that have largely been mapped to eQTLs or regulatory elements that affect expression of an otherwise wild-type protein by only 1.5-2 fold. How such small changes in expression lead to disease that typically develops over many years, in contrast to the explosive disease seen with full knock-outs in animals or humans, will involve new thinking and investigational approaches. IMS is well-positioned to undertake such work in terms of the institute-wide expertise available, but currently lacks a strong effort to conduct such integrated, comprehensive studies and to develop the quantitative models that put the pieces together to achieve insight into complex behavior. The latter models can provide a way to identify key control nodes in the system that would be amenable to drug manipulation to prevent or ameliorate disease. Although the Future Plan discusses efforts in this direction, it was unclear how this vision was to be initiated and the review of the Division currently charged with leading in Systems Biology did not provide a strong plan for full development of efforts in this direction. ***[/AC]***

3. PI evaluations: Are they competitive enough considering current world standards?

[AC] Overall, the AC was very impressed by the quality of the research being done at IMS. Evaluations of individual PIs were provided to the Director in the IMAC Group Reports. ***[/AC]***

Indefinite Term Employment under the New Labor Law

[AC] This law is apparently meant to provide job stability for employees and requires that they be offered indefinite term (permanent) positions after a certain period of employment. Since this is a government policy beyond the official purview of the IMAC, our comments will be brief. Based on the information we received, the majority of those who will become indefinite term employees are assistants and technicians. There will be very few such positons for PIs, and researchers will mostly be fixed-term employees. The AC foresees at least three potential problems here. There may be stagnation if indefinite term employees no longer have the motivation to excel. With a fixed number of permanent positions, most already filled, it will be difficult to retain highly talented individuals. The indefinite term system will further strain the already limited IMS operating budget ***[/AC]***

Budget

[AC] A declining operating budget has been a chronic problem for IMS since its inception in 2013. The last IMAC in 2016 noted with concern that the continued severe budget cuts could lead to a significant deterioration of IMS manifested by a loss of highly qualified and productive investigators and a decline in publication quality. Although the number and quality of IMS publications remains high, among the best at RIKEN, there has been a downward trend in the percentage of papers ranked in the top 1% and the top 10% by Incites Research Performance Profiles. When Division of Genomic Technologies joined IMS, one might have expected at significant, even if only temporary, increase in the budget to fund new intramural research projects, but this did not occur. Once again, the IMAC urges the RIKEN Central Administration to increase the IMS budget so that the Center's groundbreaking research can continue. On a positive note, recently the IMS budget has been stable, not suffering from the severe annual cuts that occurred in previous years. ***[/AC]***

Future Plan

Director Yamamoto emphasized the development of new technologies at IMS and their role in ongoing and future studies focusing on human health, in particular studies of complex diseases such as cancer, metabolic disease and inflammatory diseases, which impact the quality of life. The IMS future plans include integrated efforts by the IMS Divisions and Technology Platforms to understand the role of genetic variants and environmental factors in the pathogenesis of such diseases. Precise measurement of disease states and individual genetic variants are proposed as the foundation of this effort, on which data integration, modeling, validation and ultimately medical implementation will be built upon. Director Yamamoto also proposes to promote collaboration and exchange of human resources with institutions in Europe, North America and Asia as another mechanism to achieve the

goals set forth in the future plans.

[AC] Director Yamamoto has a clear vision of the future IMS. Although not very many details were provided, most of the research underpinnings needed to achieve the future plan are already present, some more mature than others, at IMS. The Director noted several times the importance of integration, within and between Divisions and also between technology platforms to optimize their use and promote development of new technologies. The AC is in complete agreement here. The promotion of international collaborations with RIKEN IMS serving as a hub is also underway and should be encouraged. ***[/AC]***