IMS Advisory Council 2023

Background

What follows is the report of the Center for Integrative Medical Sciences (IMS) Advisory Council (IMAC) 2023 meeting held August 22-24. This meeting was important for several reasons: 1) The length of time since the last IMAC was longer than usual. Because of the COVID-19 pandemic, this was the first evaluation of IMS since 2019. 2) This was the first opportunity to evaluate the IMS for a full period after the completion in 2018 of the merger of its components the RIKEN Center for Genomic Medicine, the Research Center for Allergy and Immunology, and the Division of Genomic Technologies; 3) There will be a significant reorganization of the IMS research structure, from the current four Divisions into four new Pillars, which are described in more detail below.

Review Terms-of-reference

The IMAC has been asked to provide comments on the Center's general activities (Terms-of-reference from the IMS director) and to address Terms-of-reference from RIKEN President Gonokami, which establishes criteria that are used in the evaluation of all RIKEN centers. The IMAC's comments on the general activities are summarized in this report and separately for the Terms-of-reference from RIKEN President Gonokami.

Summary of the review meeting

The IMAC met for 2.5 days. The morning of Day 1 began with an preliminary Executive Meeting, in which IMAC logistical issues were discussed. It was attended by the IMAC chair (Malissen), Vice-chair (Lathrop), IMS Director (Yamamoto), Deputy Directors (Koseki, Ohno, and Suzuki), Director of the RIKEN Yokohama Promotion Office (Tsunoda), Director of the Center Director's office (Yokota), and members of the IMS Coordination Office (Burrows, Furuno, and Iwano). The IMAC meeting started in the afternoon. In addition to the participants in the preliminary Executive Meeting, all IMAC members, RIKEN Executive Directors (Miyazono and Yoshida) and IMS Team Leaders also attended. Director Yamamoto gave an overview of the Center and the Director's reply to the 2019 AC comments. This was followed by an overview of the four new Pillars of Research for the next term: 1. Integration of genetics and multi-omics data with human immune function (Yamamoto).

2. Non-coding elements in the genome and environmental effects (Koseki). 3. Multi-organ networks and disease systems biology (Ohno). 4. Translation of research findings to novel therapeutics (Fujii). 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**	**Human Immunology & Cancer Immunology**	**Disease Systems Biology 1**	**Disease Systems Biology 2**
AC reviewers *Group Chair	Ewan Birney* Mikiko Siomi Muzlifah Haniffa	Mark Lathrop* Hirouki Aburatani Juha Kere	David Hafler* Akira Shibuya Arthur Weiss	Madhav Dhodapkar* Shimon Sakaguchi Zlatko Trajanoski	Ronald Germain* Bernard Malissen Yasmine Belkaid	Susan Gasser* Rudi Balling Yukiko Gotoh

The IMAC Groups prepared individual PI evaluations as well as an overall Block evaluation, which were presented orally to IMS director Yamamoto over the course of Days 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. (The individual PI evaluations are not included in this report). 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. After a photo shoot, Director Yamamoto described IMS Future Plans and Governance at a session attended by the AC members, RIKEN Executive Directors, IMS Director and Deputy Directors, Steering Committee members, Coordinators, and IMS Promotion Office. This was followed by a closed session attended by all AC members and Burrows 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. Malissen, 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. Malissen summarized the overall findings of the IMAC review, and the chair of each Review Group provided further details.

Organization of the Center

At the time of the last IMAC meeting, the research activities of the Center were organized into four Divisions and two programs (Table 2).

Table 2 - Divisions	**Director**
Genomic Medicine	Piero Carninci
Human Immunology	Kazuhiko Yamamoto
Disease Systems Biology	Haruhiko Koseki
Cancer Immunology	Shin-ichiro Fujii
Programs	**Director**
Other (Young Chief Investigator Program Hakubi Research Team	IMS Director, Kazuhiko Yamamoto

In the next term, the research activities are being reorganized into Pillars (Table 3).

Table 3 – Pillars	**Director**
Integration of genetics and multi-omics data with human immune function	Kazuhiko Yamamoto
Non-coding elements in the genome and environmental effects	Haruhiko Koseki
Multi-organ networks and disease systems biology	Hiroshi Ohno
Translation of research findings to novel therapeutics	Shin-ichiro Fujii

However, the evaluation presented here is principally based on the Research Division structure, since that is what was in existence during the period covered in the reviews and was used by the Center to structure the IMAC review meeting. A separate section of

the report provides comments on the proposed four new pillars for the next term period of 2025-2032.

Terms of Reference from Director Yamamoto

Director Yamamoto listed five specific items to be addressed in the ToR: a) *Overall quality of research activities at the Center*; b) *Development of new technologies that will contribute to medical sciences*; c) *Promotion of young scientists and postdoctoral fellows*; d) A*ppropriateness of future research plans to maximize and mobilize overall research strengths and to promote cross-disciplinary research*; e) *Research management and operating policies of the Center*. Because of the overarching importance of the question, the section of the report dedicated to ToR c) has been extended to include gender balance (see sections c1 on "*Promotion of young scientists and postdoctoral fellows"* and c2 on *"Promotion of gender balance*" below). We summarize the IMAC evaluation of these below.

a) Overall quality of research activities at the Center

The report is based on the existing Center Divisions as shown in Tables 1 and 2, and each section addresses the ToR and resulting recommendations within the Divisions.

The world-class quality of the Center's research activities across all its current divisions can be readily documented. There has been a steady rise in the annual number of publications in the period under review, now reaching almost 300 per year, with more than 35% of papers in journals with an Impact Factor > 10, including the top scientific and medical journals such as Nature, Science, and New England Journal of Medicine. The citation impact and institution rankings presented in the IMS White Paper 2023 show that the Center is top-ranked within RIKEN for its research impact and that the Center's research placed RIKEN as 7th worldwide in the field of immunology. Moreover, IMS makes available over 50 research databases, software, and protocols for the scientific community. An example is the FANTOM database, which as explained in the White Paper, is accessed approximately 10 million times annually and is considered a pioneer in the Open Science movement.

The IMAC congratulates Director Yamamoto and all of the IMS members for these

successes. The following provides evaluations of each of the IMS Divisions

Division of Genomic Medicine 1 & 2

RIKEN has had a long and important position in genomics and genetics delivery in Japan and worldwide. This has emerged from multiple decades of work, innovating in both experimental techniques and computational analysis, to create powerful tools for functional genomics. RIKEN has initiated key worldwide collaborations, such as the global FANTOM projects on RNA analysis, and has been a key partner for global initiatives, such as the Human Cell Atlas, that have pushed back the frontiers of biological knowledge and propelled the development of key genomic technologies with widespread applications. It has organized the Biobank Japan project, and applied leading-edge genomics to it, creating one of the most powerful disease gene discovery resources worldwide. These activities have been a driver for the emergence of Japanese scientific excellence in computational/quantitative genomics and genetics. With the advent of single-cell technologies, there is a bright future for both “traditional” germline and somatic genome sequencing, and single-cell functional analysis to further extend the RIKEN position as a worldwide leader in genomic medicine.

The review panels were impressed by the quality, breadth, and impact of the research in these areas over the last four years as presented by the laboratories in the Group 1 and 2 sections. Examples of note include major contributions to human genetics through research emerging from the Japan Biobank, the exploration of genetic susceptibility to cancer in the Japanese population, the functional characterization of long non-coding RNAs, the development of a novel enhancer activity readout via enhancer RNAs at the single cell level, systematic mapping of RNA/DNA interactions, and the demonstration of interaction between genetic factors and Helicobacter pylori infection in the etiology of gastric cancer. Innovative studies on the role of mobile genomic elements have opened an important new perspective on disease genetics and established RIKEN IMS as a leader in this area.

New national projects such as genomic studies of dementia and cardiovascular disease with the potential for high scientific and public health impact are emerging under IMS leadership. The proposal for a canine genomic program that will enable the use of the

dog as a model system for studying human disease is another innovative approach proposed by IMS investigators. This will advance research in genetics and oncology while also contributing to the structuring of veterinary medicine in Japan.

Immunology is a particularly strong application area of genetics and genomics, with an almost guaranteed impact on biological understanding and healthcare. This is because the immune system is a ‘fluid tissue’ that is naturally present in dispersed cellular form, is often accessible via blood draws, and has a profound impact on all aspects of human disease. The future vision for IMS presented by Director Yamamoto under Pillar 1 (see below) is intended to transform our knowledge of the immune system's role in health and disease using a multifaceted approach that includes in-depth genomic analyses of immune functions. IMS’ expertise in functional genomics, genetics, and data science outlined above will be essential underpinnings for this research and provide it with a strong competitive edge.

The review panel has several comments and recommendations that are intended to help IMS achieve its objectives within the Division of Genomic Medicine and also extend to the novel Pillars-based reorganization:

1. While recognizing the current excellence and near-future potential in functional genomics as highlighted above, the panel had significant concerns that the leadership in this area at RIKEN is largely now happening via people with joint appointments. Although these individuals can - and we are fully confident will - continue to contribute to RIKEN science and its global integration, we believe that IMS would be best served in evolving its functional genomics efforts by having predominantly full-time RIKEN scientific leaders in the field. These individuals should be encouraged to work in close collaboration with jointly appointed researchers, and they should be fully integrated into the scientific decision-making at IMS, for example, by forming an internal strategy group of senior investigators. Importantly, functional genomics (e.g., CAGE, NET-CAGE, single cell analysis) is a rapidly evolving scientific field, not a production-only endeavor; it requires leaders to drive the development of new methods and analysis, and in the context of the ambitions of IMS, with the experience and background needed to successfully conduct large-scale studies. Additional remarks about the

evaluation procedure for team-based science are included below in the section below *Research management and operating policies of the Center*.

2. The expertise in data science and artificial intelligence (AI) in medicine and biology positions IMS to contribute significantly to the RIKEN vision for the TRIP (Transformative Research Innovation Platform of RIKEN platforms) program in the next seven-year term (FY2025-2032), on the condition that the expertise for data engineering is maintained, and indeed reinforced, within the multidisciplinary environment of IMS. These points are elaborated on further elsewhere in our report.
3. Following remarks in the 2019 IMAC report on the importance of reinforcing interactions between components of IMS, the review panel was pleased to see an increased number of collaborations between different laboratories for research falling broadly under the umbrella of genomic medicine. We would recommend that the RIKEN examine possibilities to strengthen these interactions further as they are crucial to the success of the IMS's future vision. For example, as also mentioned in the 2019 report, internal funding schemes should be used to prioritize multidisciplinary collaborations.
4. The proposed new IMS programs, particularly Pillar 1 (see below), will involve the production of massive, multifaceted datasets. To assure the highest standards of scientific quality (and lowest costs), some activities that are currently undertaken in individual laboratories will undoubtedly require harmonization, and they would benefit strongly from a center-wide approach. New core facilities like those now available for genotyping, genome sequencing, and some other activities should be considered to achieve the necessary scale. Equally important would be a center-wide approach to data management and analysis of these massive datasets. IMS now has a cadre of very competent and innovative data scientists, and we would encourage that they be brought together with a mandate to create and implement such a data plan.
5. The financial implications of new programs, such as dementia and canine genomics, in addition to expanded activities such as those discussed under Pillars, need further evaluation to assure that they are sufficiently resourced. Strategies to obtain the

additional funding needed should be defined and pursued with the help of the IMS Director.

6. The 2019 IMAC report noted that some ongoing applied genomic activities in areas such as diagnostics are at the stage that might best be transferred outside the RIKEN so IMS can focus on its research strengths and others can build upon the work for clinical applications. Following this suggestion, the IMS Director has successfully implemented such transfers in the four years following the report, and the panel recommends that this continues as a policy in instances where it is appropriate.

Divisions of Human Immunology and Cancer Immunology (3 and 4) and Division of Disease Systems Biology (5 and 6)

The Divisions of Human Immunology, Cancer Immunology, and Disease Systems Biology have been reshuffled into a four pillar-based structure and comprise an outstanding group of investigators, especially with respect to world-class microbiome research, novel studies of immuno-metabolites, understanding of cutaneous cell biology, cutting-edge metagenomics, and dissection of sensory neuron function in the skin and gut. Exciting results relating the human microbiome to disease were obtained using causality-determining animal models and isolated microbial strains or products thereof. These studies led to highly impactful findings about bacteria that influence major diseases like diabetes, multiple sclerosis, asthma, and other conditions of importance to Japanese (and indeed world) health. Major areas of investigation also range from basic studies in cancer immunology, including novel vaccines and clinical trials, to analyses of cancer genomics and the cancer microenvironment. Studies of the cancer microenvironment via spatial methods are well aligned with Pillar 4's overall focus on translating research findings into therapeutics. State-of-the-art humanized mouse models are also developed to study normal and malignant human hematopoiesis *in vivo*. Since its origin as RCAI, IMS has hosted world leaders in the use of iNKT cells to fight human cancer and this unique knowledge has been further extended to the use of promising artificial adjuvant vector cells. Along the same lines, an ambitious program has been developed to harness iPS-derived NKT cells for head-and-neck cancer treatment. This further led IMS to acquire an extensive knowledge of GMP-grade NKT cell production. IMS also hosts a leader in

lipidomics, who contributes to establishing lipidomic standards worldwide. Promising studies of autoimmune diseases, atopic dermatitis, the role Aire plays in medullary thymic epithelial cells during the establishment of self-tolerance, and ILC2 immunobiology were also presented. Finally, to achieve the aim of the 4 four pillars, it is also important to stress the importance of the presence within IMS of world leaders in the fundamental study of polycomb group-mediated repression and of the transcriptional and epigenetic mechanisms permitting T and B cell functional diversification.

IMS researchers involved in the integration of data-and hypothesis-driven science in human immunology benefit from state-of-the-art research platforms that provide key technologies, including proteomics, metabolomics (recently expanded to include lipidomics), imaging, flow cytometry/cell sorting, mouse experimentation (sperm and embryo cryopreservation, production of genetically modified mice, humanized mice, germfree, and gnotobiotic mice). A BSL3 facility has been also developed, permitting IMS to contribute to fighting the global COVID-19 pandemic. For instance, IMS used basic mouse models of long-lived plasma cells and memory B cells to provide invaluable information on the generation of antibody responses to subdominant Omicron epitopes. The BSL3 facility allowed IMS to be selected as the Strategic Center for Biomedical Advanced Vaccine Research and Development for Preparedness and Response and will permit IMS to develop research on dangerous pathogens for future preparedness. A Cell Processing Center has been developed permitting the manufacturing of pharmaceutical-grade cells to be used in the IMS cancer immunology programs, including conventional and iPS-derived NKT cell therapies. Along the same therapeutic line, a promising Drug Discovery Antibody Platform has been developed. The possibility of raising advanced mouse models under germ-free conditions or to co-house SPF with wild mice in germ-free isolators (‘wildling’) will help compensate for the lack of environmental diversity in the SPF condition and of genetic diversity resulting from the use of standardized inbred mice. It will also facilitate the evaluation of the large numbers of unannotated microbial products on human health. This unique IMS-integrated knowledge environment is highly congruent with the TRIP initiative and it appropriately fits the novel four pillars-based reorganization in that it will allow the production of well-controlled, massive, high-content datasets. As described above, consolidation of the bioinformatics and computational biology present

at IMS will be vital to achieve these challenging and scientifically exciting goals of high relevance for human health.

The review panel has a few comments and recommendations that are intended to help IMS achieve its objectives within the novel Pillars-based reorganization involving the former Divisions of Human Immunology, Cancer Immunology, and Disease Systems Biology:

1. The generation of increasingly quantitative, high-quality biological datasets will play a foundational role in supporting the TRIP initiative. Such high-quality, quantitative data are needed before large-scale data *per se* can be optimally employed for Artificial Intelligence/Machine Learning analyses. Importantly, these emerging data need to remain tightly linked to the biological insights in complex systems provided by the researchers belonging to the former divisions of Human Immunology, Cancer Immunology, and Disease Systems Biology. Such insights cannot be replaced with just large amounts of genomic data in the search for a predictive understanding of healthy versus diseased states.

2. While there is a lot of expertise in omics technologies including spatial technologies and downstream bioinformatics in most IMS laboratories, some other laboratories seem to have limited access to bioinformatics and data analysis. Therefore, the TRIP initiative offers a unique opportunity to enhance such interactions between data science-based labs and experimentalists to enhance synergy. Expanding core facilities for bioinformatics might also facilitate initial data pre-processing so that the data science experts could focus on higher-level analyses.

3. We support an increase in the collaborative work among the groups belonging to former divisions of Human Immunology, Cancer Immunology, and Disease Systems Biology, as it is clear that there is a close relationship between microbial and immune cell products/metabolites in supporting tissue homeostasis or driving disease, and further, between these elements, the immune system, the nervous system, and the tumor microenvironment.

4. The benefits of such a unique and integrated IMS knowledge environment might also be actively promoted at the global IMS level and via collaboration with RIKEN DMP and

RIKEN Innovation to reinvigorate the interest and support of domestic pharmaceutical companies.

4. Owing to his key contribution to the development and operation of the IMS state-of-the-art research platforms, broad vision on IMS activities, and charisma, the review panel emphasizes that H. Koseki could be the catalyst to organize cross-cutting programs of research with medical collaborators and encourage and expand the teamwork across technologies and expertise within IMS.

b) Development of new technologies that will contribute to medical sciences

To fulfill its mission to be a national focal point for large-scale biomedical research, IMS has pioneered the development and integration of new technologies in areas of genomics, metabolomics, imaging, FACS, animal experimentation, and informatics. A few examples (one from each of the group reviews) will be used to illustrate IMS technology contributions: the development of novel experimental techniques and associated computational methods revealing the biological roles of long non-coding RNA (Division of Genomic Medicine-1); genetic screening technology to accelerate the adoption of precision medicine for cancer (Division of Genomic Medicine-2); advanced technology for human immunology as part of the national Vaccine R&D Centers project to protect against the new coronavirus and further emerging infections (Division of Human Immunology); new analyses methods to predict neoantigen candidates from cancer genome data with results being applied in several types of cancer with a pharmaceutical industry partner (Human Immunology & Cancer Immunology); new methods to identify and potentially modulate the effects of the microbiome on human disease (Disease Systems Biology-1); and new technologies for advanced lipidomics (Disease Systems Biology-2).

The IMAC encourages IMS to continue to aggressively pursue technology development and integration. For example, we strongly recommend the Center consider equipping its core with the appropriate staff and modern confocal instruments capable of high-resolution multiplex imaging (Disease Systems Biology - 1) as this is a major emerging technology that will enhance its multi-omics efforts. This technology will soon be compatible with multiplex RNA FISH, enabling data from single-cell transcriptomics to be used to develop optimal probe panels to complement antibody panels to cell markers,

phosphorylated proteins, and transcription factors. It will allow cells to be deeply phenotyped while also accessing their signaling state, vital information for creating an understanding of immune function in the tissue context and for relating bacterial species to the local immune environment. Recent advances in 3D multiplex high-resolution imaging will further extend such studies, permitting the mapping of branching structures such as nerves, blood vessels, and lymphatics that are poorly visualized in thin sections.

c1) Promotion of young scientists and postdoctoral fellows

At present, there are ~46 PIs at IMS. Their research is supported by 120 scientists and 17 postdoctoral fellows (Table 4). The research of a few laboratories is also supported by graduate students (64); thus, these young scientists make up 53% of IMS personnel (214/404).

For the purposes of this commentary, we will also designate a subcategory of team leaders who, although PIs, are young researchers in the early stages of their independent scientific careers (appointed 4/2021 or later). Finally, there is the Young Chief Investigator (YCI) program, which currently has two participants.

Category	Number
PhD students	64
Postdoctoral Fellows	17
Young scientists	120
Young team leaders - appointed since 4/2021	11
Young Chief Investigator (YCI)	2
Total	214

Table 4. Distribution of young researchers at RIKEN IMS (Data from IMS 2022 Annual Report)

The IMAC believes that more could be done to create exchanges and interactions between and among the students, postdocs, young scientists, young team leaders, and YCI across the institute. These groups can share a substantial level of their own

mentorship if they freely interact and discuss science and their careers.

Some specific suggestions mainly for postdocs/graduate students:

1. Create a Postdoc Association involving all of IMS (and a graduate student association if there are enough students). Give them a budget for weekly or biweekly events (either purely social or linked with posters or short talk presentations). Give the Postdoc Association the right to invite and host a seminar speaker or two each year. The same could be done for students, although to have a critical mass it may be necessary for IMS PhD students to team up with PhD Student Associations at Yokohama City University or Keio University,
2. Postdocs and Students should have an internal chat group or websites for shared communication.
3. Encourage self-organized social events - without PIs, just postdocs, and students.
4. Organize practice talk sessions so that students, postdocs, YCI, and even team leaders can practice their presentations and get feedback before meetings or interviews.
5. Organize job interview practice sessions for postdocs (e.g., for team leader or university faculty positions)
6. Distribute information on how to go abroad for a postdoc or for training visits – where to apply for fellowships, the timing of finding a position, draft letters for PIs, and how to interview. Have team leaders give advice to graduating students.
7. At the next IMS review, the IMAC would like to meet with the presidents of the (future) Postdoc Association and PhD Student Association to hear directly from them what their desires or needs may be.

The “Young scientists” identified in Table 4 need career guidance, which likely would come from their PIs. Whether they stay at IMS in the same position or attempt to grow their scientific careers here or elsewhere needs to be openly discussed, and the issue is complicated by the Indefinite Term Employment System. It is important for these individuals to have a clear career path.

The RIKEN system provides new team leaders with one year of mentorship. While a good start, the IMAC believes that the mentorship should be more open-ended. Based on individual laboratory reviews, it was clear that some young team leaders are well on their way to becoming independent established investigators, but there are others who would benefit from some mentoring, e.g., to help them focus their research. The duration of this mentoring could be mutually decided by the mentor and mentee. Importantly, the YCIs already have permanently assigned mentors and the IMAC hopes that there is active participation in this activity.

In addition to mentoring support, it is important to provide adequate financial start-up packages to allow new young investigators and YCI to make their teams internationally competitive. The IMAC recognizes that the IMS budget is tight, but these young investigators, unlike their senior colleagues, will not yet have had the opportunity to apply for external funding.

c2) Promotion of gender balance

Although not listed as a separate category in the original ToR, the IMAC believes that strong action should be taken on this issue, which has been one at IMS and elsewhere in Japan for many years. We recognize that there are numerous factors that have contributed to the problem. A major difficulty in increasing the number of female PIs, especially Professors, results from the fact that the pool of qualified female candidates is not large enough, stressing the importance of nurturing young researchers, particularly females, across Japan.

The IMAC recommends the following measures to enhance the gender balance and generate an atmosphere that is even more creative and cooperative.

1. Set a goal for the number of women to be hired for each year over the next four years, at either YCI or team leader level, and stick to it. Aim for 25% female leaders overall in 5 years. A demographics analysis that takes into account retirements and probable turnover rates should help guide the plan.
2. Identify talented young women at the postdoc level and create an active career promotion plan for them. These can be internally mentored, and their careers

promoted (although, admittedly, open calls for new collaborators are generally a better policy). Nonetheless, to improve the gender balance, targeted career development is a good idea for talented female postdocs.

3. Create an internal working group whose only goal is to increase the number of female PIs. Its membership should more-or-less reflect the current gender distribution in the institute, i.e., this would not be a female committee.
4. Use the women on the IMAC as consultants and advisors for mentoring and candidate interviews or searches.
5. Create a seminar series of outstanding women scientists. Have the guests talk with female students, postdocs, and PIs about their careers, in addition to giving a scientific seminar.
6. Create an office or contact person within the administration who provides information on childcare, sets up shared care for sick kids, and informs about daycare opportunities on the RIKEN campus (or other family-friendly needs).
7. Create joint positions with universities like the University of Tokyo and other nearby universities for women who are hired to fulfil the quota for professorial hiring. Joint positions with medical faculties might be particularly useful, as they bring medically relevant research questions, fulfil the female hiring quota, and provide the nearby university with access to some RIKEN high-level infrastructure. Such positions will be highly desirable, making RIKEN more competitive for the top female candidates.

d) Appropriateness of future research plans to maximize and mobilize overall research strengths and to promote cross-disciplinary research.

As articulated in Director Yamamoto's future vision for the IMS, the plans are to build upon the strengths reviewed above in a series of high-impact multi-disciplinary programs (the four Pillars) intended to significantly advance biological knowledge and medical translations. (We comment separately on each of the Pillars.) The IMAC 2023 noted that these plans were supported by increased collaborations between IMS laboratories, the positive impact of new team organization and platform structuring, advances in areas such as statistical genetics and computational genomics, and strategic new recruitments

in the period under review. Moreover, IMS is collaborating with many Universities and hospitals in Japan and internationally to implement its programs, and it has strong interactions with the RIKEN Drug Discovery and Medical Technology Platform Program (DMP) for therapeutic development. IMS has contributed to this effort by setting up a facility for the development of antibody drugs, the Drug Discovery Antibody Platform Unit, and the artificial Adjuvant Vector Cell (aAVC) Drug Translational Unit. The Pillars and these other activities clearly address the goals of maximizing and mobilizing overall research strengths and promoting cross-disciplinary research.

e) Research management and operating policies of the Center.

Organization

The progressive merger of the RIKEN Center for Genomic Medicine, the Research Center for Allergy and Immunology, and the Division of Genomic Technologies was a visionary step that has created a powerful multidisciplinary environment in which basic research is closely integrated with large-scale genomics and computational/quantitative methodologies. IMS is now one of the largest research centers in RIKEN in terms of the number of PIs (~46). Under the leadership of Director Yamamoto, three additional Deputy Directors have been appointed as group heads. The IMAC believes that this configuration provides strong scientific coordination for IMS. The role of the Director and Deputy Directors has been particularly important, not only in developing/managing cutting-edge IMS teams and platforms but also in conveying/promoting an IMS spirit of collaborative team science that will be crucial for the success of the next stage of IMS research.

Policy on joint appointments

For several years, many IMS senior team leaders have had affiliations as adjunct/visiting faculty at university graduate programs in Japan. This allowed them to teach classes and recruit graduate students to perform their dissertation research at IMS. In 2022 there were 33 adjunct professors/associate professors affiliated with eight domestic graduate programs, and 64 students had studied at IMS.

For a number of IMS PIs, these types of affiliations have recently been upgraded to joint appointments. In this case, the PIs have laboratories at both IMS and the respective

universities. The IMAC notes advantages to this type of arrangement. 1) If the university has an affiliated hospital, it allows access to cohorts of patients and medical samples, which are important as IMS expands its translational research studies. 2) It allows better and more direct access to graduate students, who can perform their dissertation research both at their home university and at IMS when advanced technologies are required.

The IMAC also has some concerns, most notably that the PIs with joint appointments spend enough time at IMS. This is essential to provide leadership for the IMS laboratory, for managing its scientific activities, and to contribute to the overall activity of the center, e.g., through internal seminars and student tutorials. An average of 2.5 days/week at IMS was judged by the IMAC to be a reasonable goal.

Some issues regarding joint appointments are particularly acute within the Division of Genomic Medicine and require attention as discussed above in the evaluation of this Division.

Criteria for evaluating IMS scientists

The panel reiterated concerns voiced in the 2019 Advisory Council report about the almost exclusive focus on evaluating PIs individually, given the nature of the large team science that is conducted at IMS. As stated in the 2019 report "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". While recognizing the difficulties involved in adapting the evaluation system, the panel recommends that RIKEN look at procedures used to successfully address this issue in other organizations, such as the Wellcome Sanger Institute, that also support life sciences infrastructure and associated large team science.

Computational and quantitative biology within the TRIP concept

The advent of machine learning, AI and the presence of more sophisticated computational resources, such as GPUs and Quantum computing is a great opportunity for biology. We are confident that AI and high-end computing will continue to contribute fundamentally to biology, which has already started (e.g., the AI system to predict protein structure from

the amino acid sequence, AlphaFold). However, this AI work requires well-understood, “compute-ready” data, and there is still a large need for data preparation, QC, analysis and biological insight, currently executed by expert bioinformatics and computational biology groups. Thus, it is of key importance that scientists with primary bioinformatics/computing/data profiles are embedded within IMS and that an appropriate scheme be used to evaluate them (see above).

In this context, we believe that expertise consolidated at IMS should be mobilized to make an important contribution to the success of TRIP, but that this project should not be considered a replacement for the bioinformatics and computational biology now present in the Center.

Bioethics

The medical and other life sciences research pursued by IMS has important Ethical, Legal, and Societal Implications (ELSI). The creation of a Bioethics Working Group in 2019 was an important step to address these issues. The IMAC fully supports the formation of a new laboratory that will be installed later in 2023 to pursue research on the ELSI of genomic medicine and related disciplines. Embedding this laboratory within IMS will create an interdisciplinary environment that will benefit RIKEN, and impact medical research in Japan more broadly, by addressing important societal aspects of genome-based biomedical research. The IMAC noted that collaborations have already been initiated between existing IMS laboratories and the new ELSI laboratory, a positive first step towards this interdisciplinarity.

Funding

The need for increased core funding from RIKEN remains a chronic issue that was highlighted in previous reviews from 2016 and 2019 and is reiterated again by the 2023 IMAC. In particular, the mergers of different RIKEN Centers to create IMS were not accompanied by aggregating the corresponding budgets, although efforts in this sense would have been expected in such a major restructuring. Sufficient investment is essential for the IMS to maintain its infrastructure at world-class levels, and to expand it as appropriate into new areas such as the imaging described above. While IMS PIs have been successful in obtaining outside grants for specific projects, this is not a substitute

for the core support that is needed to assure that IMS remains at the leading edge of international research in genome-based medicine. And, while we support the Center's Direction in the efforts to identify strategies to address a decline in the Yen value of industry support, this too cannot substitute for an increase of the RIKEN component budget which the IMAC would urge upon the Central Administration.