Report on the 2nd Meeting of the RIKEN Centre for Life Science Technologies Advisory Council

Executive Summary

The Centre for Life Technologies has developed significantly since its nascent plan and vision was first considered by the AC in 2014. The CLST is still relatively early in terms of its overall development and operation as a cohesive management unit, nevertheless significant progress has been made to breakdown barriers. Collaborations at the interfaces of the technologies have started, both top-down and bottom-up, and the Centre's cadre of PIs are engaged and excited about the opportunities.

The CLST-AC continue to be impressed with the achievements of the divisions, the prominence of their leadership and of the Centre itself. The component Divisions were world class organizations before they were combined to form CLST in 2013, and their international prominence has continued.

Our observations are that in addition to the main strategic thrusts, there are a very large number of smaller projects and collaborations which all require active and constant management. The CLST is urged to define and maintain a strategic vision, particularly as technologies like NGS, bioinformatics and single cell genomics become commodities. Associate with this and perhaps to encourage some discipline, strategic budget allocations in terms of categories of spend may be helpful in deciding on priorities.

We urge the continuation of high standards for recruitment, exploiting the CLST world-class reputation and facilities. We further suggest that targeted head hunting and/or a focus on younger internationals and/or female scientists, may enhance the internationalisation and female ratios in the 5-10 year horizon.

The CLST-AC support the laudable concept of the drug discovery programme but advises caution to manage expectations on potential outcome(s). We further advise that such efforts be enhanced by collaborating with pharmaceutical companies and biomedical facilities, as they will understand the markets and unmet clinical needs.

The CLST-AC supports the future plans of the Centre, although we recognize that these are still being developed. We endorse the desire to continue to invest in basic science but focused the normal (non-diseased) human state. To achieve this we recommend that the CLST *establishes a clinical capability and/or closer contacts with healthcare-oriented facilities.*

We remain concerned about legacy of the past leadership of DSSB. Undue and inappropriate influence is apparent which is a major distractions and on-going challenge for the management team. This needs to be urgently and decisively solved

1.0 Summary of the preparation and conduct of the 2nd meeting

The second meeting of the RIKEN Centre for Life Science Technologies Advisory Council CLST-AC took place over four days from May 24th to 27th at the RIKEN Yokohama Campus. Prior to the site visit itself, the committee were provided with a comprehensive and exceptional high quality white paper describing the activities of the Centre's various Divisions and Collaborative Programmes before the meeting. We also were provided with the CVs of the PI's.

The whole committee were initially given the context of the review process, starting with a cascade of presentations beginning with the history of RIKEN and RIKEN's mission. The AC was reminded of our Terms of Reference, followed by an overview of the Centre including its mission, management, national and international activities as well as a summary of the responses to our 2014 recommendations. The presentations then were focused on a high level review of the different Divisions, followed by the Director's Strategic Programme and Strategic Funds projects. Before breaking into separate sub-committees with a divisional focus, the whole committee received presentations from groups formerly associated to the Centre for Developmental Biology, which had been assigned to the Centre some months after the last Advisory Committee Meeting. These PIs would normally have been reviewed by a different Advisory Council and in an entirely different context.

All of the CLST-AC were present for these high level sessions, but were split into three parallel sessions to review each of the three Divisions. Drs. Bradley, Juha Kere and Chieko Kai focused on the Division of Genomic Technologies (DGT); Drs. Cheryl Arrowsmith, Lucio Frydman and Masami Hagiya focused on the Division of Structural and Synthetic Biology (DSSB); Shigekazu Nagata, Christer Halldin and Noboru Yumoto focused on the Division of Bio-function Dynamics Imaging (DBDI). Following the presentations from the PIs in each division the AC reconvened together to hear and discuss the ideas and projects for the next mid-term plan. Throughout the presentation the site visit committee asked many questions ranging from high level strategic questions to the Centre and Division directors, to probing the scientific programs and exchanges of individual principal investigators. In all cases, comprehensive replies and data were furnished in response to the AC queries.

In this Report we have summarized our considered views on the performance of the CLST as a whole and at an individual level, under several sub-headings: Centre, Division, inter-Divisional programmes as well as individual PIs. The evaluation of the individual PIs is provided as an Appendix. We have also commented on the CLST future plans as we currently understand them, acknowledging that these are still very nascent and are likely to change.

2.0 Background

The advice provided has been distilled from a large amount of high quality and comprehensive written and presented materials and interactions. They are provided in the context of the President Matsumoto's Terms of Reference, and of our desire to give helpful and constructive guidance. We recognize that there may be overriding constraints and other considerations that may prevent and/or alter the implementation of this advice. In assembling our comments we again focused on the macro level (Centre and Division) but we also have, as requested, provided specific feedback for each PI. In the latter instance we took the view that the more recently appointed PI's should not be comprehensively evaluated at a very early stage, as progress in the Life Sciences is not rapid. It would be fortunate indeed if any had amassed a substantial number (or indeed any) publications from their independently initiated research activity after their appointment dates. Therefore, we have provided comments to guide them where possible and appropriate to do so.

The Centre for Life Sciences is still a very new organisation formed in April 2013 under the leadership of Dr. Yasuyoshi Watanabe, by fusing the activities, facilities and staff of three formerly separate Divisions. At the same time the leadership of two of these Divisions changed with the appointments of Drs. Shirouzu and Carninci, both rising from within ranks in the previous Divisions to their directorship. The three Divisions have widely different but complementary technological foundations, focusing on structural biology tools, genomics (particularly RNA) and whole body imaging, respectively. This amalgamation is an attempt to foster cross-disciplinary research, promoted by former RIKEN President Noyori. The Centre also has to deal with an additional challenge in that it is geographically split. In addition, the Centre recently had to integrate several research groups with a very different technology focus and biological curiosity, separated from the Centre for Developmental Biology.

3.0 Response to recommendations of the 1st CLST-AC

The 1st meeting of the CLST-AC took place two years ago, merely one year after CLST was formed. *Overall, we are very pleased with the response to our previous recommendations.* Commendable efforts have clearly been made to overcome some of the challenges presented to the newly formed Centre, particularly in terms of scientific emphases and PI management.

- *Collaborations*: As a result of efforts to promote communication and understanding of the different scientific disciplines in the Centre there appear to be a large number of bottom-up collaborations developing in addition to the top-down Molecular Network Project uniting inter-divisional teams and units.

- *Appointments*: An appointment committee has been established consisting of senior management and external members for all new PIs.

- *Clinical expertise*: The number of researchers who are clinically trained or are undergoing clinical training, has massively increased.

The AC also recognizes the effort that has been undertaken by Drs. Watanabe and Shirouzu, in response to our previous recommendation with respect to supporting the independence of Dr. Shirouzu, and the need to help establish her authority and leadership of the DSSB. With two years elapsed we note, however, that this not only remains an unsolved issue, but that matters have in fact escalated. It remains critically important for CLST and RIKEN to resolve this issue, as the AC views Dr. Shirouzu as a key intellectual and leadership pillar of the CLST. Furthermore, Dr. Shirouzu's scientific prominence makes her a role model for female scientists in Japan generally and RIKEN in particular.

We notice as well that the CLST has elected to not respond to our specific 2014 recommendation regarding engaging with clinicians in a focused area. The AC accepts the reasoned response to this recommendation, which is addressed in the Centre's future plans.

4.0 Response to Terms of Reference:

***Term of Reference 1**. Consider whether the Centre:*

- *Has achievements and human resources that meet international standards*
- *Produces World Leading research in its field*
- *Engages in research that contributes to society*
- *Elucidate the strengths and weaknesses*

The component Divisions of CLST were at a very high international standard before they were combined to form CLST in 2013. In fact all three components could be considered as international leaders in their respective fields, and are therefore by definition World Class. The facilities, research output and human resources are all internationally competitive, and in several cases unique. For example, super high magnetic field NMR, expanded genetic codes, the genomics of RNA (in particular non-coding RNA), the development and use of new PET probes and of multi-mode imaging methods, are disciplines and technologies in which the CLST is second to none.

Still, the Centre is newly formed and at the last review in 2014, inter-divisional scientific programmes were just being developed. These programmes have begun to gain traction, but it is too early evaluate which among all of them will ultimately be successful. Still, the quality and quantity of publications and achievements stemming from individual PIs as well as from joint intra- and inter-Centre projects in the 2014-2016 period, is extremely promising.

The CLST has a very strong technology base by any standards. This provides a foundation for intra-Centre basic research, for cross-RIKEN researches, as well for

interactions with non-affiliated groups in Japanese academia and industry. The CLST platforms thus support multiple aspects of basic and applied sciences in Japan. The societal benefits that emerge from such investments is elaborated over many decades, and it may not be clear at the outset when and in what form these benefits may accrue. *Nevertheless*, one example of CLST achievements within the current-events horizon is the commercialisation of the SmartAmp technology. This has taken more than 9 years to develop, but by 2019 this technology will be available commercially as a diagnostic kit for two important sexually transmitted diseases, providing rapid clear point-of-care diagnosis with real impactful societal benefit. Moreover there should be some financial return to RIKEN and to the company, if this technology's commercialisation is successful. Societal benefits are thus clear.

Term of Reference 2. *Comprehensively re-evaluate Centres in operation for more than 10 years and in this context consider inter-centre research and suggest areas of focus as well as cross-disciplinary research.*

This second term of reference is complex to apply as the Centre was formed just 3 years ago. Moreover, the AC is only partly aware of the constituents of other RIKEN Centres that may impact or complement CLST activities. For instance, last year, components of the Centre for Developmental Biology (CDB) were integrated into the CLST as per a decision of the RIKEN executive. We have evaluated these components separately, in the context of the PIs evaluation in Appendix 1. Like the Divisional components of CLST, the former CDB components have been assessed as internationally competitive and/or world class. Despite this, their scientific fit and relevance to the CLST is less apparent than their former relevance to the research themes of the CDB. Therefore, one area of focus would be to consider amalgamating these recently added components to research groups with more aligned scientific interests – including first and foremost those of CDB.

Term of Reference 3-1. *Pioneer a research management model for maximizing research development and results.*

The CLST is a new centre with a number of newly appointed PIs. In their presentations and the white paper, they each articulated their laboratory and personnel management styles. This was refreshingly thoughtful and also rather diverse, indicating that a number of styles had been actively and independently developed that were well suited to particular mixes of personnel with different cultural and technical backgrounds. We felt that all PIs were not only aware of the need to actively develop an optimal research management model, but they were embracing it.

This academic and intellectual independence of PIs, is an area that will need to continuously be encouraged and monitored, particularly in cases where the PIs have been locally appointed. One aspect the AC could evaluate was papers' authorship, particularly senior authorship. Although shared authorship is expected due to the collaborative nature of many projects, it is important that the authorships reflect

international principles and standards. In this regard the policies of ascribing individual senior authorship (e.g., corresponding authorship) did not always appear clear to the PIs –particularly the younger PIs.

The AC was impressed by the high degree of fund-raising competitiveness of all PIs, particularly the junior ones. At the same time budgetary management, including the pressing need of all PIs to seek external funding in view of declining core Centre budgets, could result in a loss of focus. This is a worrying issue in times of declining budget scenarios; see *Recommendations* for further details.

Term of Reference 3-2. *Lead the World in achieving new research and development results*

Most team and unit PIs of the Centre are well-recognized, world-class researchers in their own right (see *Appendix* for individual PI evaluations). The CLST has also started a number of new cross disciplinary initiatives that are expected to yield important results, exploiting platforms which stretch from genomic analysis to molecular structure and *in vivo* imaging. Many of these projects target all aspects of Life Sciences, ranging from atomic macromolecular descriptions to whole organism characterizations. The Centre has ambitions that, by working together and with other RIKEN Centres, they can discover drug targets and perhaps discover/develop new drugs. Near term, the development of the SmartAmp for STD testing will become a reality in 2019. These are all good examples of successful inter-academic and academic-commercial partnerships.

Term of Reference 3-3. *Help to facilitate the transformation of RIKEN into a hub for science and technology*

CLST and its component divisions were already in 2014 important hubs for science and technology. The following serve as examples:

- Leading international collaborative research – FANTOM V
- Providing assistance for imaging drug distribution
- A global centre for structural biology, particularly NMR and cryoEM

Although the capacities of the various Divisions are different and unique, their roles and interactions have been further strengthened over the last two years. The attractiveness and international competiveness of CLST as a technology base will only endure and develop with continuous financial support.

One aspect of becoming a hub is to enhance global awareness of the RIKEN-CLST activities. One way this can be achieved is to bring relevant international meetings into the proximity of the Centre in Yokohama and Kobe. The 29th Mammalian Genetics meeting held in Yokohama and co-organized by DGT's director Piero Carnici is a good example of this. Such activities are deemed essential to raise the Centre's profile

Term of Reference 3-4*. Serve as a focal point for global brain circulation*

CLST overall has a healthy ratio of international scientists: 20% of PIs and 25% of all scientists. It also benefits from a female Divisional Head, who should serve as a role model for other female scientists. These ratios however are not uniform in the three divisions. The DGT has a particularly impressive international/domestic ratio and serves as an example to the whole of RIKEN. Other Divisions and the Centre should emulate this.

The ratio of female PIs is however less impressive overall. The Centre is aware of these issues and the PIs are all sensitive to the need to develop female scientists and foreign staff. The low ratio of female PIs is also apparent in other countries, although it is more extreme in Japan. In other countries there are programmes of activities and awareness exercises to promote female scientists. The Centre should look at emulating some of these programmes, as these are now well developed.

Term of Reference 3-5 *Foster the development of world-class leaders in scientific research. Contribute to brain circulation globally and provide researches in industry and academic opportunities to develop their skills*.

Fostering a research community is not achieved with a single initiative; it is a cultural, societal challenge that can takes decades to achieve. Engagement with the younger generation and full involvement of its female population in science, engineering and technology, is an investment that will pay-off many decades later. Perhaps it will be un-noticed by the Institute where a young child, high school or university student first saw a 1.2 GHz NMR scanner, a mass spectrometer with sub-milliDalton resolution or was able to spool DNA for the first time. The engagement of CLST staff in these outreach programmes is to be highly commended and should continue to be pursued, particularly with the students in elementary and high school, even if immediate results are not apparent.

CLST has trained a number of scientists who have moved to take up senior research positions in Japan, Australia, Belgium and Singapore. CLST has also accepted students or trainees from companies such as JEOL and FANCL to conduct collaborative research. While these are laudable examples more could be done in terms of initiatives, and of exploiting the Centre's resources to contribute to international brain circulation *see Recommendation for further details*.

Term of Reference 4 *How effective are the Centres activities towards maximizing RIKENs achievements as a whole, including collaborations between Centres.*

CLST has established numerous active initiatives with other RIKEN centres. These include the Single Cell Project, a collaboration with 6 centres headed by Carninci. Other examples include close collaboration between the DSSB and synchrotron, computational, optical and free electron RIKEN centers. The Epigenome and Aging projects also form firm links between CLST and the Quantitative Biology and the Brain

Sciences Centres. These projects are examples of how the technology foci in the CLST are being made available to enhance RIKENs achievements generally. Despite these examples, there may be some areas where there are additional opportunities; *see Recommendations for further details*

5.0 Recommendations from the 2nd meeting of the AC

Overall, the site visit team was deeply impressed with the level of preparation for the meeting, the extensive documentation provided, the energised atmosphere of the Center, as well as the leadership demonstrated by the Division Directors and particularly the Centre Director, Dr. Yasuyoshi Watanabe. Based on all this material and feedback, we offer the following recommendations for further consideration by RIKEN and the CLST.

5.a Budget management, see Term of Reference 3-1

As a result of an annual declining budget, a greater proportion of the CLST budget has been taken up by fixed costs – particularly personnel. To fill budget gaps the Centre PI and the Division directors are actively seeking for external funds. While this has the positive impact of making them eager to collaborate, the negative aspect to this is that more and more projects need to be managed with corresponding dilution of effort. For instance the lack of a budget to replace the aging Illumina sequencers, which are core technological requirements for DGT, is a symptom of the current situation. A core funded Institute should manage its budget strategically so that operational flexibility and focus is achieved and retained. We therefore suggest that CLST operate its core budget strategically, allocating 45-50% on salaries, 15-20% on capital instrumentation, and 30-35% on reagents/consumables.

5.b Recruitment, see Terms of Reference 3-1, 3-4 and 3-5

The productivity and progress of the Centre will depend entirely on the quality of the PIs who are recruited into vacant positions. While recruitment is open and transparent, we didn't get the impression that proactive head hunting of a previously identified top scientist of either local or international origin for key positions, was the preferred adopted style. We recommend a more proactive posture, particularly in an effort to internationalize the PIs in DSSB and DBDI. One strategy to achieve this is to bring researchers to Japan at an earlier time point in their career development, with the view that the best among the group may develop to become CLST PIs. For instance, if a critical mass of non-domestic postdoctoral staff becomes established, this could become a magnet for attracting others. Rapid promotion of one or two stars out of such a cadre to junior PI status will send a signal that the CLST might be an attractive option for a postdoctoral period, further stimulating the Centre's international and national appeal.

5.c Global brain circulation, Term of Reference 3-5

While CLST is clearly contributing in terms of academic circulation, more could be done to engage with industry. CLST have stated an interest in developing drugs, but this is largely being done in a knowledge vacuum and underutilization of commercial knowhow

and intellectual resources. Japan has a number of successful drug companies that are well known internationally; indeed one of the recently approved immuno-oncology drugs, which is likely to become the largest selling drug of all time, can be traced back to pioneering research conducted in Japan. Effort should be made to reach out to these companies, and eventually to international pharmaceutical companies, to discuss potential interest in scientific exchanges.

5.d Enhancing the proportion of female researchers and PIs, Term of Reference 3-5
This problem is global but particularly acute in Japan, and which is keenly recognised by the CLST's leadership. In the UK there are some proactive programmes that CLST's management may wish to study and if appropriate emulate, see http://www.ecu.ac.uk/equality-charters/athena-swan/.

5.e Interactions with other RIKEN Centres, Term of Reference 4.
Our impression is that CLST is responding to such initiatives. The establishment of the single-cell-platform provides further opportunities for such collaborations. For example in Yokohama the single cell platform offers the opportunity for making major strides in molecular immunology, because T cells can be identified based on their unique TCR and cytokine profiles. But it was not clear to what degree do CLST PIs are responding to initiatives, rather than proactively driving them. Greater academic credit could accrue from collaborations driven by CLST PIs, something which they should be encouraged to consider.

The investment of personnel and resources in maintaining international competiveness in the CLST's technical platforms, means that there is less emphasis on biology and a weaker focus on specific biological questions. All technology based Institutes struggle with this issue. While one can argue that the platforms allow the Centres to become reasonably open with respect to the biological question being addressed, and therefore more open for opportunity-driven research, the disadvantage is that the platform provider can be viewed as a data generator. As such, CLST PIs may not be viewed as "in the driving seat". Moreover, it can be hard to discriminate and evaluate the potential impact and opportunity provided by the different platforms in the overall scientific endeavour. As mentioned above, one way this can be managed is through strategic collaborations. Another is to encourage CLST PIs to develop a more overt biological focus, yet not at the expense of compromises in the technological basis that is unique to the CLST.

6.0 Assessing the Division of Structural and Synthetic Biology

6.a Leadership
Dr. Shirouzu has provided strong scientific leadership and an ambitious vision for her Division. The platform technologies that she manages form a world-class foundation upon which her Division's units and teams collaborate and build their science. Under her leadership the Division has been very successful over the past two years, enabled to

a large extent by the excellent technology platforms that it features. The amalgamation of DSSB with the remaining CLST divisions also exerted a very positive influence on all of the Division's teams and units, by providing an important "omics", metabolic and cell biology complement to DSSB's structural biology platforms. We encourage the continuation of this melding of technologies and life science research, among the groups that currently make up the CLST.

Over the last two years, the DSSB has produced numerous impressive results. In particular the cell free expression platform, the new membrane protein expression and crystallization strategies, and the single particle cryo-EM facility, have yielded outstanding new crystal and cryo-EM structures of important and challenging proteins. These include integral membrane proteins, and large macromolecular complexes. The committee notes that Dr. Shirouzu has also kept abreast of the state-of-the-art, bringing in new technologies for crystallization of membrane proteins through collaborations with Spring8 (X-ray Free Electron Laser), and new methods for the microscopy of mesocrystals in collaboration with the RIKEN Center for Advanced Photonics. Furthermore, and in line with our 2014 AC recommendations, Dr. Shirouzu recruited Dr. Shigamatsu from Yale to lead an expanded cryo-EM facility that is now yielding significant new results. Dr. Shirouzu's plans for the future envision further strengthening and integrating these and other technologies together with computational methods and with the excellent NMR facilities, in the establishment of an unparalleled structural biology center. In addition to planning this outstanding infrastructure effort that we applaud and encourage, Dr. Shirouzu should also be commended for supporting and developing a group of scientific teams that have coalesced around her platform. Finally, Dr. Shirouzu has addressed budget deficits by bringing in additional income from the DMP drug discovery platform.

6.b Division Achievements (2014-2016)

The AC notes the outstanding overall scientific progress of the Division in the past two years. Particular highlights of the DSSB include, among others,

- Solving X-ray structures of a Chloride ion channel and cryo-EM structures at atomic resolution of kinesin-14
- High impact structures of protein complexes, including eIF2B
- Achievement of 1.02GHz and the acquisition of protein NMR spectra on solids and solutions, using a new high temperature superconducting NMR magnet developed in collaboration with NIMS and with industry
- Advances in the incorporation of nonv natural amino acids into proteins and into drug discovery projects
- Advances in protein design algorithms resulting, in the first *de novo* design validation of a symmetric functional protein.
- Multiple advances in early stage drug discovery programs using structurev guided and computational techniques, that leverage Riken's unique computational potential.

6.c Challenges

The AC recognizes that this Division is newly formed, and derives in part from a previous Centre. This creates challenges for establishing independence from previous legacies, and poses complex integration challenges –both for establishing its own character, and when considering its integration with the other two Divisions of CLST. As explicitly noted in the AC-CLST 2014 report: "*Dr. Shirouzu probably faces the greatest challenge in her new role […in that…] she needs to distinguish her leadership and vision from that of the former Director. This may not be something that she can achieve alone: high level support may be needed to achieve an agreement on how to disengage her new initiatives and scientific projects from those that originated under the headship of the former Director, and support her to obtain international recognition*". Remarkably, upon exploring the publication record of team and unit leaders over the last two years, we noticed that this disengagement recommendation had not been yet adopted. We fear that this conspires against the sense of self respect and self confidence that PIs in the Division need, in order to achieve their own international stature. This applies also to Dr. Shirouzu in her role as Division leader, but also to teams and units that had been associated with the previous Yokohama campus Center. Once again, as in 2014, we urge the RIKEN management to find a satisfactory solution to this taxing problem.

An additional challenge may arise from the expectation (or necessity due to budget shortfalls) of DSSB members to participate in RIKEN's drug discovery program. This is a task that they must achieve in addition to excelling in their own areas of research, and to providing a RIKEN-wide research infrastructure resource. It is no small challenge to remain at the forefront of their respective technologies and disciplines while also having to fulfil this additional mandate; this is a challenge that the leaders of the Division and Centre have successfully confronted to date, but which may be unsustainable with further budget cuts.

Finally, the committee was advised that there have been discussions within RIKEN upper management about possibly moving the DSSB to the Spring8 site in Harima. The origin of this plan may be due to the perceived value of grouping all the protein crystallography and structure activities at the same site. *However, the AC feels that such a move would be significantly misguided.* First, the DSSB already collaborates very effectively with Spring8, and is achieving world-class impact in protein structure research. The committee would also like to stress that the impact of structural biology research is highly dependent on strong interactions with collaborating biologists who can provide functional contexts to the structural work. The DSSB has many such collaborations with Japan's outstanding biologists at Tokyo and Yokohama Universities; these collaborations would suffer greatly if the division were to be more isolated at Spring 8.

6.d Recommendations

1. The DSSB's outstanding NMR facilities and ambitious plans should be leveraged to recruit an international senior research who can effectively use these world class NMR

technologies. One or more strong scientific leaders in the application of solution and solid state super high field NMR, would be excellent complements to the existing expertise, and contribute to fulfilling the DSSB future goals in this area. We encourage the CLST management to complement the sizable investment they have already made in this area –and the additional ones planned for the future– by the addition of NMR structural biology expertise at the senior leader level. This can also be an opportunity to improve the division's diversity of personnel and international visibility.

2. We strongly recommend that the DSSB not be moved to the Spring8 site, because (i) this will be highly disruptive (and expensive) for a laboratory dependent on highly sophisticated instrumentation such as EM and NMR, (ii) many key personnel that would not wish to move would be lost, and (ii) most importantly, a move away from the biological groups inside and outside of RIKEN/CLST would compromise the science and international competitiveness of the DSSB.

3. We urge the division to seek collaborations with the pharmaceutical industry and/or prominent biomedical scientists with experience in drug discovery/biologics to ensure the optimal impact of their drug discovery and biologics programs.

4. As described above, the AC firmly endorses and affirms the leadership and authority of Dr. Shirouzu with respect to the scientific direction of the division and the maintenance of reagents and databases historical to the division and its predecessor.

7.0 Assessing the Division of Biofunction and Dynamic Imaging Science (DBDI)

7.a Leadership: Dr. Watanabe provides inspirational leadership of DBDI as well as CLST, and is clearly respected by the divisional heads and the associated PIs. One challenge that he faced was to incorporate the Biosystem Dynamics group from the Center for Developmental Biology (CDB) in November 2014, which seems to have been achieved smoothly. He also established CLST-JEOL collaboration centre. As a result of his leadership, vision and a productive research management model, his research group is world leading. Dr. Watanabe's division serves also as a hub for science and technology innovation within molecular imaging.

7.b Summary: The AC is of the opinion that the DBDI has a proven track record of performing *in vivo* imaging analysis at multiple levels using molecular imaging such as PET and other multimodality techniques. DBDI has a world-class potential to image a large series of different potent compounds for highly interested targets with radioisotopes suitable for PET. Both the Labelling Chemistry Team and Chemical Biology Team are developing novel molecular imaging probes with a high efficiency. But these two teams may be combined into one in order to more efficiently meet the demands for new projects.

There exists a strong capability in radiochemistry and biology, which enables the development of chemical and biochemical methodologies to insert short-lived radionuclides into key molecules for further examination within a translational approach from animal to human. The AC recommends the development of an even more advanced radiochemistry platform, enabling the labelling of new potential novel tracers so as to take full advantage of all new compounds that can be supplied internally as well as from pharma companies. This can be accomplished by introducing ^{11}C-CO carbonylation radiochemistry, and even further developed by introducing the concept with microfluidic radiochemistry.

DBDI has already high level equipment needed to fulfil most of its major tasks, including cyclotrons, hot-cells, radiolabeling synthetic modules and a GMP lab for clinical production. A variety of PET cameras needed for translational research exist, but the AC recommends the introduction of a state-of-the-art combined human PET-MRI camera, which will benefit a series of on-going human projects.

Basic systems for drug discovery and medical sciences well developed at DBDI, enable 1) kinetic analyses of biological molecules in diseases, 2) time-course analyses of functional changes in biomolecules and cells, and 3) next-generation imaging for visualising more than one molecule simultaneously. The Bio-Function Imaging Team is developing additional imaging biomarkers and novel molecular imaging methods, and has clearly the ability to perform translational research at a high international level. However, a rearrangement of the Division by merging the Imaging Chemistry Group, the Imaging Function Group and the Imaging Function Group into a single combined Imaging Group, would be even more productive.

The existence of a preclinical facility with animal models of rodents and non-human primates, is considered a strength by the AC. The imaging application group is certainly performing world-class development of the next-generation molecular imaging, such as molecular and neurofunctional imaging for health science focusing on fatigue. Additional examples of achievements include innovative developments of the next generation simultaneous multi-imaging, molecular dynamics imaging, and micro-signaling regulation technology. We strongly support DBDI's promotion of molecular imaging applications all the way to clinical set-ups, including their work on neuronal networks and neuronal diseases (Alzheimer's disease, Parkinson's disease, autism), on fatigue, regenerative medicine, cancer stem cells and hepatitis.

In summary, this AC meeting re-affirmed our confidence in DBDI. We anticipate that this will continue to promote the high-level molecular imaging that is needed in a world-class centre such as CLST.

8.0 Division of Genomic Technologies (DGT)

8.a Leadership

DGT is directed by Dr. Piero Carninci, an internationally highly recognized scientist in the field of genomics, in particular RNA research. The leadership of the previous Director, Dr. Yoshihide Hayashizaki, created a legacy that has become one of the trademarks of RIKEN, the FANTOM projects. That DGT is an internationally leading research center in the fields of transcriptomics, gene regulation and understanding of RNA functions, is broadly recognized and beyond any doubt. The evaluation period 2014-2016 is characterized by the harvesting time for the FANTOM5 project, with cornerstone papers published in *Nature* and *Science* and tens of important and highly original satellite reports being published in other leading journals.

Dr. Carninci has taken over this jewel of RIKEN in a worthy manner, with his visionary leadership of FANTOM6. In addition to the FANTOM projects, DGT and Dr. Carninci are broadly involved in a diverse range of national and international collaboration projects, further adding to the international visibility of RIKEN and leading to significant scientific observations. DGT boasts an exceptionally international staff structure, with a majority (63%) of non-Japanese nationals, far exceeding the RIKEN goal (20%).

Additional initiatives of DGT (besides FANTOM6) include several forward-leaning programs:

- Developing technologies to enhance Nucleic Acid RNA therapeutics, expanding SINEUPs
- Single-cell project
- Advanced cell reprogramming with epigenetic manipulation
- RIKEN Aging Project

Each of these initiatives is significant, tackles a worthy line of research or development, and is likely to yield important scientific results. The CLST-AC wish, however, to make specific recommendations in some respects toward these projects, as detailed below in Challenges and Recommendations.

8.b Division achievements 2014-2016

The publication record of DGT in the period between the AC visits is impeccable, obviously as the result of the FANTOM5 project being completed and now bearing fruit. Altogether 108 articles have been published, including 13 in some of the leading journals (Nature, Science, Nat Genetics, Nat Methods, Nat Communications, Genome Research, Molecular Cell). A full review of FANTOM5 scientific achievements would require excessive space, and therefore is omitted here.

Among the many achievements of DGT, the AC wishes to especially mention the successful planning of introducing the SmartAmp technology to the medical diagnostic

marketplace, now scheduled for 2019. The technology bears high potential for rapid and field-condition friendly application.

8.c Challenges and recommendations

The challenges ahead are both organizational, managerial and scientific. One of the most challenging organizational issues concerns the recruitment of a new senior-level PI to lead the Genome Information Analysis Team. Experienced leadership of this team will be key to the success of FANTOM6 and other DGT projects, and finding an appropriate individual has taken time and remains unsolved. For the time being, Dr. Carninci leads this team besides his other duties. The organizational problem is exacerbated by the limited period of appointment that can currently be offered to the recruit, at this point only up to two years. We recommend that the problem would be recognized at the highest level and possible solutions would be considered in the light of this specific example, as similar situations may arise also in the future in different Centres.

The next period will include the full roll-out of the FANTOM6 project. At the on-going pilot phase, 20 international research groups have signed up to participate, and the number of participating groups is expected to grow to 60. FANTOM6 management will be challenging due to the number of interactions and the magnitude of the consortium. Obviously, DGT can benefit from the tradition of successful management of FANTOM5 and previous projects, but nevertheless, careful attention need to be devoted to this task.

One weakness detected by the AC was a certain amount of biological naivety in some of the presentations. While the strong technology focus may defuse biological emphasis, this may result in the Division being viewed more as a data provider and less as an intellectually empowered collaborator. The DGT PI's are therefore encouraged to develop their biological knowledge and interest to the point where they can seek out and lead collaborative projects with PIs in other RIKEN centres.

9.0 Future plans

The CLST presented its developing plans for the next 5 year period, which will begin in approximately 2 years time. A central theme of these plans is to continue to develop the concepts that were articulated to the AC two years ago, namely to build up the base for what CLST terms "live" science. The vision is that analysis of molecular events –from the normal, through the pre-diseased state and onto the diseased state– will enable early intervention to correct perturbations. This vision is not realizable today, but the plan is to continue to invest in the foundations needed to deliver this vision through continued investment in the current platforms: structural/synthetic biology, functional genomics and multi-level molecular/functional imaging.

To be relevant to human health, CLST will need to conduct studies in healthy humans. In this regard clinical collaborations are essential. The future plans, although nascent, do articulate a desire to use its resources for studying human physiology. Special

emphasis is placed on the future plans for studies of normal rather than the diseased state, even if the prospect for a more in-depth analysis of aging and symptomatic processes was also raised.

The AC made a related recommendation in 2014, but at the time we suggested there should be a disease focus. We understand now that the Centre sees its role and activities slightly differently. These points were discussed and debated within the committee and with the CLST leadership team and, as the AC began to appreciate the strategy of the latter, we were convinced that gathering data on the normal (non-diseased) state would serve as a gateway into understanding the extremes of variation that cause disease at one end of the spectrum and super-healthy at the other.

This ambition does of course mean that the Centre will need to establish facilities and form relationships with the academic medical community for this to become a reality. But overall it is a positive, flexible and resourceful way of implementing our 2014 recommendation.

The future plans also include a re-statement of the desire to use CLSTs technologies to both develop and re-position drugs. While the CLST-AC support such laudable goals we also advise that this is not the CLST's main expertise, and that one should not embark on such a plan unless the medical need, the biology of the target, and the commercial opportunity (including competition), have been thoroughly evaluated. CLST should also acknowledge that pursuing such an agenda will detract it from pursuing other goals that lie at the core of the Centre's mission. The time taken to develop and market the SmartAmp diagnostic test is illustrative of what basic science centres like CLST can achieve in terms of innovation, but they also reveal the understandable lack of knowledge with respect to the unmet need and the commercial /competitive landscape. It also reveals just how long a diagnostic test can take to develop; medicines will take significantly longer. Therefore, we urge significant caution and expectation management about the potential outcome(s) of these mandated efforts.