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Report from the Advisory Council On Cluster for Science, Technology and Innovation Hub (CSTI)

Meeting was held on June 7-8, 2023

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1. Introduction

The current 2023 RIKEN Cluster for Science, Technology and Innovation Hub (RCSTI) Advisory Council (AC) comes after the global pandemic of COVID-19 and the resulting international situation, and after major internal changes at RIKEN like the appointment of a new RIKEN President and the subsequent announcement of the 5th Mid- to Long-term Plan, which all took place since the last AC (held in 2019). What remains unchanged is RIKEN's dedication to giving back to society with its research results, and the importance it places on cooperation with industry and society. The evaluation was undertaken based on the recognition that RCSTI is working to fulfil these immutable missions.

As this AC was held at an important time, before the full-scale implementation of the 5th Medium- to Long-term Plan, the AC is aware that it asked more questions about the significance and uniqueness of RCSTI, its functions as a frame that runs parallel to those of RIKEN as a whole, and the strategies that support these functions, compared to previous ACs. The AC was also more focused on the significance and uniqueness of the Science and Technology Hub Headquarters, its functions as a frame that runs parallel to RIKEN as a whole, and the strategies that support them.

From the beginning, RCSTI's support for returning value from RIKEN's research results to society has involved creating a mechanism to promote collaboration across research fields, organizations, national borders, and other such frameworks, and the implementation of measures towards that collaboration. Moreover, as a model institution for training researchers in Japan, RIKEN expressed in its 4th Mid-Term Plan that it will be proactive in taking action towards the functional strengthening of Japan's innovation ecosystem. RCSTI is responsible for putting this into practice.

As such, RCSTI compared with RIKEN as whole has several axes: a horizontal axis that cuts across centers, an axis that extends beyond the internal affairs of centers towards RIKEN-external collaboration, and a vertical axis that ranks the same as a center (Drug Discovery and Medical Technology Platforms (DMP)), meaning that the work under its jurisdiction is multilateral. Moving these multiple axes also amounts to substantial and constant breaking of new ground, and the planning, operation, and improvement of wide-ranging programs requires an experimental and agile approach that differs from the operation of a typical research and development project.

Taking the above recognition as a starting point, the RCSTI AC offers the following advice from its Sectional Committees 1 and 2 based on the materials provided by the RCSTI secretariat and the AC hearings and discussions held on June 7-8, 2023.

2. Report on Sectional Committee 1

2-1. General Comments/ Recommendations

[General comments]

While the response to some proposals made by the 2019 RCSTI AC is still in progress, and the response cannot be clearly understood for some cases, overall response is generally proper.

RCSTI pioneers new techniques and works hands-on to invest capital and human resources in different initiatives. This work is commended for proceeding in a conscientious manner. However, various cases that produced results were not shared much internally or externally, and how these initiatives will raise awareness of RCSTI and set forth its uniqueness, in addition to the logic model for how they will factor into RCSTI strategy, have still not been made visible. With a frame-like construction to support external collaboration at the center, the AC would like to see constructive reform that strengthens the advantages of past initiatives and re-examines them.

Though it is said to be based around the Transformative Research Innovation Platform of RIKEN platforms (TRIP) set forth by RIKEN as a whole, at the same time, the RCSTI's frame must be reorganized at this ideal timing, during the construction of the next Mid- to Long-term Plan.

[Recommendations / Future directions]

At this opportunity, the AC offers the following five proposals based on the efforts of RCSTI until this point, with hopes of it developing a greater sense of presence.

- Achieve constructive change – do not just scrap and build
- Construct (external) collaboration strategy – do not stop at domain mapping
- Formulate “Go Global” strategy and reinforce RIKEN’s global presence
- Communicate RCSTI success stories within and outside RIKEN
- Develop “RIKEN family” brand that will add higher value to collaboration

2-2. AC Report on TORs

2-2-1. TOR1: Response to proposals from 2019 AC

While the responses to some proposals made by the 2019 RCSTI AC are still in progress, and responses cannot be clearly understood for some cases, overall response is generally proper.

The following four points were included in the advice from the last AC (2019).

- Synergy among drivers
- Data management strategy
- RIKEN Innovation Company
- Matrix-type management

The following points were included in the proposal for action by RCSTI based on the above points.

- Modeling of successful cases
- Creation of a hub within RIKEN that will serve as a unit for collaboration with other organizations
- Pursue synergy with cross-sectional drivers
- Strategically promote activities with sights on international expansion while using the internal resource that is the International Affairs Division

Below is the AC's evaluation of the response to this proposal for action, and of the relationship and conflicts of interest between RIKEN Innovation Co., Ltd. (referred to as Riken Innovation Support Company in the previous AC) and RIKEN itself proposed in the previous AC. (The latter does not fall under the scope of this AC, but must be considered in order to evaluate industry-academia collaboration.)

[Response to proposals for modeling of successful cases / creation of a hub within RIKEN that will serve as a unit for collaboration with other organizations]

Regarding the response to proposals for the modeling of successful cases and good practices regarding the different initiatives formed from RCSTI's new techniques, a plan was presented to aggregate different initiatives using the TRIP Program presented in the 5th Mid- to Long-term Plan as a mechanism. This plan is thought to have its merits and demerits, and as the modeling of good practices will become strategically necessary in due course, on the contrary, it may be better to present RCSTI's unique strategy in accordance with the TRIP Program. This unique strategy will be discussed in the below section about RCSTI's policy regarding the 5th Mid- to Long-term Plan.

RCSTI is continuing to work on structuralizing expertise by implementing and modifying different drivers using new techniques. Pilot studies and trial schemes within RIKEN have led to successful cases. The Engineering Network's forging of connections within RIKEN that form the basis of collaborations with other institutions is a key concept for RIKEN. The implementation of the Engineering Network has taken much capital and administrative effort, but when conducting reviews, rather than simply listing initiatives implemented heretofore, RCSTI should continue considering how the mechanisms that have been built will carry on during the next Mid- to Long-term Plan, and what form future operations will take.

[Response to proposal to pursue synergy with cross-sectional drivers]

The various initiatives and tools (collectively referred to as “drivers” in the previous AC) at RCSTI give the impression of being promoted individually. Moreover, whether these drivers functioned complementarily with universities and led to them building on their individual strengths couldn’t be judged from the materials provided (white papers). While a sort of “chemical reaction” may lead to synergy amidst individual promotion, simply waiting for this to occur will likely not lead to anything. When creating new tools from here on, rather than just looking at the purposes and functions of individual tools, it would be best to create a cross-sectional outline of existing initiatives and tools, to consider functional synergy that allows them to work together, and moreover to consider synergy in the chronological order for implementing them in the next phase.

[Response to proposal to strategically promote activities with sights on international expansion while using the internal resource that is the International Affairs Division]

There were not many statements from an international point of view in the materials or hearings of the current AC. For RIKEN, which is a research institution on an international level, the research and academic institutions of other countries can be seen as both competitors and partners. Amidst major changes to the international situation due to the global pandemic, it is becoming essential from a worldwide perspective for RIKEN to break onto the international stage.

[Response to proposals regarding the relationship and conflicts of interest between RIKEN Innovation Co., Ltd. and RIKEN itself]

In 2019 at the time of the previous AC, RIKEN Innovation Co., Ltd. didn’t have a name settled on, much less a structure, but the AC congratulates the re-checking of its relationship with RIKEN three years after its establishment. RCSTI should continue its efforts towards building an even better relationship, aiming towards its systematic implementation.

Regarding the relationship between RIKEN and RIKEN Innovation Co., Ltd., it should be made clear whether RIKEN Innovation Co., Ltd. will be a purely contracted party, both parties will equal partners in decision making, or RIKEN Innovation Co., Ltd. is hoped to take the initiative. Because RIKEN Innovation Co., Ltd. is still in the start-up phase, it is expected that constructive consideration will be given on how to craft the unique story of these two entities while negotiating and delineating whether it will become more powerful or not, and how much room RIKEN will give the company to take its own initiative.

Moreover, though RIKEN Innovation Co., Ltd., is still formulating its business model, the company must lead the way in pioneering in order to establish itself. Although RIKEN Innovation Co., Ltd., is a spin-off corporation of RIKEN, there are no past examples for a National Research and Development Agency at RIKEN’s level, and only the National Institute

of Advanced Industrial Science and Technology (AIST) has been established domestically as a copy of RIKEN's model. RIKEN Innovation Co., Ltd. must study and reconsider which duties (such as IP patenting, licensing, contracts, and research collaboration) its operations will be involved in, and how. If it will only deal with duties equal to those of existing technology transfer companies, it is hard to see the necessity for a global research institute such as RIKEN to have created it. The AC advocates for RIKEN Innovation Co., Ltd. and RIKEN to consider together its business model, including which duties it will execute other than fundamental technology transfer tasks, and what kind of additional value will be created.

The conflicts of interest with RIKEN Innovation Co., Ltd. proposed in the previous AC are considered to have been dealt with.

Additionally, RIKEN Innovation Co., Ltd. is said to handle business in all scientific fields, but in the beginning stages of a company when there is no surplus power, this policy seems unsustainable. In the current situation, it is necessary to focus on prioritizing dealings with scientific fields which are more apt to produce successful cases. The AC advocates for consideration to start now regarding returns to RIKEN in times of growth. As these returns are to encourage growth for both RIKEN Innovation Co., Ltd. and RIKEN, it is necessary to anticipate not only financial benefits, but various ways in which value can be returned. RCSTI should consider the timing, channels, and methods for carrying out these returns.

At this AC, the relationship between RCSTI and RIKEN Innovation Co., Ltd. was explained in text, and though it was mentioned that the division of roles has changed, it is difficult to clearly grasp what this means. From the arrows showing the arrangement of and relationships with RIKEN Innovation Co., Ltd. in the "Research Structure of RIKEN" chart used throughout the presentations, it seems that RIKEN itself is still unclear about many points of this relationship. RCSTI should make improvements so that the relationship can be clearly expressed in a diagram.

2-2-2. TOR2: Based on the results of the Center's self-analysis, evaluate operations and R&D activities for the 4th Mid- to Long-Term Plan period (FY2018-2024)

[Results of the SWOT self-analysis]

RCSTI has conducted a systematic SWOT analysis. Doing the work of this analysis is a source of encouragement in itself, so its implementation was beneficial, but RCSTI must get to the core of what can be gained from its results. The AC was unable to surmise from the hearing presentations that those who performed the analysis will connect the results of the analysis to the next stage of action. This analysis should be thoroughly utilized, and RCSTI's should work to connect the SWOT chart it has made to its next moves and use it to create unique value.

[RCSTI as a whole]

RCSTI pioneers new techniques and works hands-on to invest capital and human resources in different initiatives. This work is commended for proceeding in a conscientious manner. However, various cases that produced results were not shared much internally or externally, and how these initiatives will raise awareness of RCSTI and set forth its uniqueness, in addition to the logic model for how they will factor into RCSTI strategy, have still not been made visible. With a frame-like construction to support external collaboration at the center, the AC would like to see constructive reform that strengthens the advantages of past initiatives and re-examines them.

The Engineering Network is an initiative that cuts across RIKEN's centers, and the worldview that includes this so-called horizontal axis, together with the axis extending outside of RIKEN that consists of relationships with companies, universities, and other institutions, is essential for RCSTI. This is because, in recent collaborations with universities and companies, there are more and more cases where collaboration with multiple labs within RIKEN is desired due to durability, maintenance of workflow, and exit strategies; this demand cannot be met without a horizontal emphasis within RIKEN. A horizontal emphasis within RIKEN will lead to suitable proposals for collaboration external to RIKEN. The goal of interaction between these two axes is recognized as a vital point for the activities during the 4th Mid- to Long-term Plan Period, but at present, the two axes have been implemented separately, and the interaction between them was not presented in the AC materials or hearing.

The AC understands DMP, which has focused on crossing the organizational boundaries of drug discovery research between RIKEN's centers, to have developed into a RIKEN organization within RCSTI equipped with unique research ability equivalent to a center, and to be an organization that includes the vertical axis of drug discovery research. Because of these properties, DMP is positioned as a forming member of TRIP in the 5th Mid- to Long-Term Plan, but the AC advocates for RCSTI's mapping of DMP, the Engineering Network, and external collaborations to be shared with RIKEN as a whole. There are many cases where research centers see external collaboration as one step to promote a project. RCSTI sharing its initiatives as an axis checked against RIKEN as a whole will lead to greater understanding of external collaborations.

It is interesting that this frame supporting such multi-axis interactions functions as a dwelling place for use cases of actual external requests and cross-disciplinary projects conceived of by RIKEN. There are few examples of actual domestic collaboration projects constructed by such a frame, needless to say international ones. RCSTI should disseminate information externally about this frame and projects promoted by it, since RCSTI is in charge of external collaborations at RIKEN, which is engaged in world-class science.

This frame should not just aim to be a space to create and dispatch projects; RIKEN researchers participating will expand the range of research through external collaboration, and RCSTI should disseminate information that conveys it as a space to have experiences outside of one's specialized field. As in the examples of joint research teams, collaboration centers, and co-creation projects given at the hearings, the AC believes that researchers' active participation will lead not only to response to external requests, but also to proposals for RIKEN-conceived industry-academia collaboration projects.

In addition to utilizing the frame of RCSTI, it will be effective for external collaborations at RIKEN to take a proactive stance rather than a passive one in all areas in order to expand researchers' perspectives through various chances for collaboration. RCSTI is congratulated on the deployment of a coordinator at RIKEN Innovation Co., Ltd. and their proactive work.

[Review of RIKEN venture certification system]

The total number of RIKEN ventures is expected to keep increasing. The RIKEN brand supports the growth of these ventures during their establishment, and the success of the ventures supports RIKEN's branding. Thus, it is necessary to consider these relationships in the mid to long term, and to take the handling, assignment of value, and support period for each venture into account.

[Current state of RIKEN Innovation Co., Ltd.]

As proposed at the last AC, the relationship between RIKEN and RIKEN Innovation Co., Ltd. should be clarified, and RCSTI should undertake the promotion of external collaborations with which RIKEN Innovation Co., Ltd. is involved as its own scheme. While an external expert (Mr. Yamamoto from the University of Tokyo) has been invited to RIKEN Innovation Co., Ltd., which is expected as one way to handle the current deadlock, it is hard to say that this alone will be enough to handle it entirely. It is essential to make intrinsically clear what

RCSTI and the centers want to accomplish through external collaboration and how, and doing so will make this expert's appointment more meaningful for RIKEN Innovation Co., Ltd.

[RCSTI's "RIKEN spirit," and RIKEN's strengths, achievements, and traditions]

The question of what makes RIKEN special is not to be answered just by RIKEN as a whole, but within RCSTI as well. This is a crucial question raised in RIKEN's Vision on the 2030 Horizon towards the adoption of the 5th Mid- to Long-term Plan, but if RCSTI or centers decide this independently, it will leave the ability to communicate the answer quite weak. RCSTI's SWOT analysis should be compared to several cases of external collaboration involving RIKEN centers and established as a realistic logic model that will then be communicated to the research centers to collect their responses. The centers can then collaborate to come up with an answer to what makes RIKEN special, so that this message can be spread both inside and outside of RIKEN.

The components of the "RIKEN spirit" and the initiatives that can be called strengths, achievements, and traditions are seen not just as simple words to be noted, but components that occupy various activities. Moreover, amidst rising expectations for scientific research due to recent experiences with infectious disease, RCSTI is expected to take on the role of responding to the public's expectations by communicating RIKEN's role, including its overhead view of the relationship between technology and society.

2-2-3. TOR3: Evaluate the policies of the 5th Mid- to Long-Term Plan period (FY2025-2031) and recommend new directions for operations and R&D that should be implemented and promoted

[RCSTI's policy regarding the 5th Mid- to Long-term Plan]

During the implementation of the 4th Mid- to Long-term Plan, initiatives such as the horizontal, vertical, and external axes were carried out, but RCSTI's construction of a frame to encompass these efforts was missing. Each initiative was carried out independently, and although each has produced suitable results, they are entirely individual efforts, and could not be seen as forming a full picture of RCSTI.

Towards the 5th Mid- to Long-term Plan, it is necessary to closely investigate past initiatives using SWOT analysis, and in order to construct a frame within RCSTI that supports external collaboration and fosters RIKEN-conceived collaborations, not only RCSTI, but RIKEN as a whole must be involved. More consideration for and implementation of this matter are expected.

The approach to and preparations for the 5th Mid- to Long-term Plan have begun, and the concept of TRIP (a challenging project) presented therein was cited in RCSTI's policy. However, in actuality, a concrete plan for how this concept is related to RCSTI's mission was not made clear.

There are limits to the extent to which the concept of the challenging project known as TRIP can be positioned as a main axis of RCSTI. There will be cases where it is difficult to embed TRIP into external collaborations. Keeping the all-RIKEN concept of TRIP in mind, RCSTI's frame must be reorganized at this ideal timing, during the construction of this Mid- to Long-term Plan.

This reorganization should include consideration for the following directions, based on RCSTI's past experiences and SWOT analysis.

- Connecting the results of the SWOT analysis to RCSTI's next steps
- Establishment of a realistic logic model based on the SWOT analysis compared with cases of external collaboration, and communication of this model outside of RCSTI to obtain reactions.

[Proposals for new operations to implement and promote, and for R&D directions]

Because the current AC is being held during the final stages of the 4th Mid- to Long-term Plan, now is a good opportunity to add new matters for RCSTI to implement and promote while participating in construction of the 5th Mid- to Long-term plan. The timing is right. With the appointment of a new President, administrative ranks have reformed, policies made new, and moreover, even if implementation is not entirely smooth, it is easy for this to be understood externally as a transition period.

At this opportunity, the AC offers the following five proposals based on the efforts of RCSTI until this point, with hopes of it developing a greater sense of presence.

-- Achieve constructive change – do not just scrap and build

After close investigation, rather than “scrapping” what is marked for improvement (in other words, completely throwing out an initiative), RCSTI should engage in constructive reform that strengthens the advantages of past initiatives and re-examines them.

-- Construct (external) collaboration strategy – do not stop at domain mapping

External collaboration is necessary, but rather than setting an unambiguous goal like a certain number of cases, RCSTI should make its goal to collaborate in a strategic manner. In order to achieve this, it is essential for RCSTI to first formulate a strategy based on its experiences. This strategy should include not simply information mapping regarding coverage of academic fields and plans to build on existing strengths, but consideration for what will be necessary for RIKEN in the next 5-10 years, and what kinds of contributions can be made through external collaboration to meet those needs.

RIKEN Innovation Co., Ltd. will be a key for this strategy, and because it is in its post-startup phase, its ability to run well on its own should be utilized considerably.

-- Formulate “Go Global” strategy and reinforce RIKEN’s global presence

At present, RIKEN’s activities play an important role as part of Japan’s national strategy. As such, it is not sufficient to do research in a steady and dispassionate manner; RCSTI should consider RIKEN’s position on the world stage, including external collaborations, as its competitors change.

-- Communicate RCSTI success stories within and outside RIKEN

RCSTI has many successful cases, and has built up external collaboration experiences that allow for rich learning, but these successful and enriched results have only been communicated to those actually involved. Rather than keeping these successes and rich experiences within RIKEN, they should be communicated externally as well. Communicating both the TRIP concept from the 5th Mid- to Long-term Plan and examples of success and enriching experiences together should raise the level of understanding.

-- Develop “RIKEN family” brand that will add higher value to collaboration

RCSTI should acknowledge the “RIKEN family” (consisting of RIKEN as a whole, its centers, RIKEN Innovation Co., Ltd., and RIKEN ventures), and use this family and its members to reinforce the “RIKEN spirit” and RIKEN’s strengths, achievements, and traditions. For RCSTI-led external collaborations in particular, while the RIKEN brand is distinct from the high level of research, it offers significant added value to collaborative partners and is thus quite attractive.

3. Report on Sectional Committee 2

3-1. General Comments/ Recommendations

[Achievement and progress of DMP drug discovery activities]

- The Advisory Council (AC) evaluated that DMP continued drug discovery activities successfully utilizing its matrix organizational structure. DMP also successfully expanded its matrix organizational structure through the establishment of a new research platform (aAVC Drug Translational Unit).
- DMP is to be congratulated on making a smooth transition to a renewed organization directed by new program director Dr. Okazaki since 2021.
- The AC also congratulates DMP on significant advances in its societal implementation of technology transfer to industry and commencement of clinical trials on promising projects generated from DMP discovery efforts, including four Exit3, one Exit2/3, and six Exit2 achievements since 2018. These achievements far exceeded the 4th mid-term goals.
- It was also acknowledged that DMP successfully promoted newer projects (e.g., aAVC-SARS, aAVC-HPV, G9a inhibitor) and generated new research themes, which are both considered to be promising seeds to be conveyed to the society in the future.

[Future directions]

- Given the SWOT analysis on external factors, including a general trend in decrease of druggable targets and difficulties for pharmaceutical companies to identify drug targets by their own efforts, and a thorough review of internal successes/failures, RIKEN should dedicate efforts to identify innovative drug targets, and DMP should be a key player for such activities. To this aim, the AC recommends that DMP should be re-organized to become an organization which will have autonomous research capability to identify and validate drug targets to generate innovative discovery themes and to coordinate TRIP-driven collaborations within RIKEN for this purpose. To achieve the goal, scientists with expertise of dry science and wet biology need to be recruited and allocated to DMP. Sufficient budget also needs to be allocated to the new research function of DMP. Income related to technology transfer from DMP to industry should be re-invested to this new DMP research function. Through these efforts, DMP is expected to create innovative science and collect innovative drug targets/seeds and modality technologies within RIKEN, and to translate them to promising drug discovery themes.
- Moreover, shifting business development activities from late-stage projects to early-stage drug discovery is very important, and DMP is recommended to communicate more with pharmaceutical companies and bio-ventures, presenting DMP's early-stage discovery efforts and platform technologies.
- Dynamic rotations and exchanges of research members and managers should be seriously considered within RIKEN to reform DMP. Recruitment of necessary talent from other

RIKEN research centers and also external organizations will be important for sustained growth of DMP activities.

- Speed and mobility will be key issues when considering future DMP organization.

3-2. AC Report on TORs

3-2-1. TOR1 (Evaluate the responses to the 2019 AC recommendations)

[DMP organizational structure]

- DMP's continuation of successful drug discovery activities through maintenance of its matrix organizational structure is evaluated highly.
- DMP has also successfully expanded its matrix structure by establishing a new research platform (aAVC Drug Translational Unit).

[Change in DMP management]

- DMP is to be congratulated on making a smooth transition to a renewed organization directed by new program director Dr. Okazaki since 2021.

[Collaboration with other RIKEN research centers and groups]

- DMP has continued its close collaborations with relevant research centers within RIKEN in a number of contexts including cell therapy programs and AI-driven drug discovery, even after MIH and PMI were closed and consolidated to other research centers within RIKEN.
- Collaborations with other internal and external institutes are a vital process for DMP's drug discovery research and are expected to be further strengthened by TRIP activities as fundamental framework.

[Organizational change in business development function]

- While we had concerns relating to the transfer of business development function to RIKEN Innovation Co. in 2019, the AC acknowledges that DMP has actively collaborated with the relevant team of RIKEN Innovation Co., resulting in outstanding achievements such as Exit 2/3 of DMP pipeline projects (e.g., aAVC-WT1, iPS-NKT cells).

3-2-2. TOR2 (Based on the results of the Center's self-analysis, evaluate operations and R&D activities for the 4th Mid- to Long-Term Plan period (FY2018-2024)).

[Contribution to society]

- DMP is to be congratulated on making significant advances in social implementation, including four Exit3, one Exit2/3, and six Exit2 achievements since 2018.
- Achievement far exceeded the expected 4th mid-term goal (transfer of 4 projects to pharmaceutical companies and medical institutions) which is consistent with RIKEN's 7-year plan regarding medical innovations.

[Projects in development]

- The AC congratulates DMP on the progress in development of the artificial adjuvant vector cells (aAVC) project. Clinical efficacy of aAVC-WT1 for solid tumors is expected. Application of aAVC technology to other cancers and infectious diseases also looks promising. It will be important to strengthen patent strategy, and to make a concrete plan for clinical development of these aAVC-based technologies through discussions with pharmaceutical companies.
- The G9a inhibitor project is an excellent example of success in small molecule development through application of different global-standard technologies at RIKEN (including X-ray crystallography, computational chemistry and medicinal chemistry). Switch of therapeutic indication from oncology to β -globin disorders is highly evaluated, and there are high expectations for clinical development of RK-701 for sickle cell disease.

[Discovery research]

- The AC congratulates DMP on the progress in development in retinal degeneration of iPS-derived retinal cells. Differentiation from other similar technologies and manufacturing costs should be seriously considered.
- It was good that protein degradation approach was applied successfully on Sirt2 (which will become a model case for future PROTAC drug discovery), although lack of its efficacy on cancer cells was disappointing. The compound can be used as a chemical probe to better understand the physiological role of Sirt2, and the AC recommends that DMP explore other therapeutic indications. Additionally, the AC recommends that DMP learn from this experience about the importance of target selection and validation.
- mPTP inhibitor project is interesting in terms of manipulation of mitochondria function, but the validity of Protein X as a target for the treatment of bipolar disorder should be further clarified. It will also be important to better understand the validity of Polg1 transgenic mice as animal model of bipolar disorder or mitochondrial diseases.

- Given the DMP response to COVID-19 (namely the COVID-19 Special Project), it is important for DMP to contribute to combating future outbreak of infectious diseases using RIKEN's competitive technologies/seeds.

[DMP capability]

- It is important to differentiate DMP's infrastructure and support style from other systems supporting drug discovery in Japan, like multiple initiatives sponsored by AMED, and to let RIKEN scientists know the significant role of DMP.
- The AC recommends that DMP reinforce the platform to validate drug targets and molecular mechanisms of targets of interest.
- It is important for DMP to focus on drug discovery research to provide ground-breaking solutions in untapped disease areas with unmet needs, and to have a unique strategy for differentiation from other technologies in the competitive landscape.

3-2-3. TOR3 (Evaluate the policies of the 5th Mid- to Long-Term Plan period (FY2025-2031) and recommend new directions for operations and R&D that should be implemented and promoted)

[SWOT analysis and self-renovation plan of DMP]

- The AC acknowledges that DMP carried out SWOT analysis in appropriate manner, conducting a thorough review of internal successes/failures and weaknesses/strengths, and evaluates the proposed future directions of DMP including reform of strategy as agreeable and reasonable.
- Execution of the proposed "7 innovations" will be important to make DMP's evolution successful.
- DMP is expected to dedicate more efforts to translating innovative drug targets/seeds and modality technologies stemming from innovative science within and outside RIKEN to promising drug discovery themes.

[Identification and validation of drug targets as a future core function of DMP]

- Considering a general trend in decrease in druggable targets and difficulties for pharmaceutical companies to identify drug target by their own efforts, RIKEN should dedicate efforts to identify and validate innovative drug targets. DMP should be a key player for such activities.
- Reinforcement in identification of novel drug targets generated from genome research based on clinical big-data and target validation activity using clinical samples with single

cell level and multi-omics technologies will be very important as new core functions of DMP.

- DMP-initiated collaborations with a number of research centers within RIKEN based on the TRIP initiative will be a vital infrastructure in RIKEN for identification and validation of drug targets.
- Understanding human biology will be fundamental for future drug discovery, and solid science needs to be the basis of DMP activity. To promote target identification and validation, application of data science and AI to human biology will be of vital importance.
- RIKEN's research infrastructure and equipment should be also fully used for drug discovery research in DMP, which will impact successful collaborations with industry as well.

[Small molecule drug discovery]

- The AC agrees that small molecules will continue to be a core modality in DMP drug discovery. Rational approaches using small molecules on targets considered undruggable will be important and this methodology should be formulated by DMP (identification of cryptic pockets using MD, targeting RNA, development of small molecule-alternatives of biomedicines such as antibodies, proteins and nucleotides, AI-driven generation of seed molecules, etc.).
- The molecular dynamics and artificial intelligence approaches are at or near the global level, and practical applications to small molecule projects are expected.

[TRIP platform as drug discovery DX]

- The AC believes that DMP should play a key role within RIKEN to translate RIKEN basic science into original drug seeds as a hub of RIKEN TRIP organizational structure, consequently contributing to society and human health.
- It is important to integrate big data regarding disease biology in the public domain (GWAS, multi-omics data etc.) and internal data with data science technology, and to extract interesting disease targets for polygenic diseases.
- The AC agrees that patient-derived iPS cells will be one of the core resources for target identification and validation. For instance, phenotype analysis of patient-derived iPS cells stimulated by certain stress may lead to elucidating the causes of a number of sporadic diseases.
- The drug discovery DX platform is expected to contribute to improving the success rate of clinical development.

[Business development strategy]

- Shifting business development activities from later stage projects to early drug discovery is very important and DMP is recommended to communicate more with pharmaceutical companies and bio-ventures, presenting DMP's early discovery efforts and platform technologies.

[Future direction and DMP organizational restructuring]

- The AC recommends that DMP should be re-organized to become an organization which will have autonomous research capability to identify and validate drug targets to generate innovative discovery themes from its own research activities, and to coordinate TRIP-driven collaborations within RIKEN.
- The AC recommends that DMP not simply maintain its matrix structure, but also create an internal research team that is responsible for target validation and selection and proposal of discovery themes.
- To achieve this goal, scientists with expertise of dry science and wet biology need to be recruited and be allocated to DMP. Sufficient budget also needs to be allocated to the new research function of DMP. Income related to technology transfer from DMP to industry should be re-invested to this new research function of DMP.
- Dynamic rotations and exchanges of research members and managers should be seriously considered within RIKEN to reform DMP. Recruitment of necessary talent from other RIKEN research centers and also external organizations will be important for sustained growth of DMP activities. Team building will be important, as will providing continuous training opportunities.
- Speed and mobility will be key issues when considering future DMP organization.