The RIKEN Center for Sustainable Resource Science (CSRS) Advisory Council meeting was held from August 8 to 10, 2023 at the RIKEN Yokohama Campus. The 2023 Advisory Council report is based on the comprehensive report and discussions of CSRS current activities and future goals (White Paper), presentations of six Flagship Projects, and research presentations by the Principal Investigators. The report summarizes the evaluation and recommendations of the CSRS Advisory Council.

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Executive Summary

Since the evaluation in 2019, the RIKEN Center for Sustainable Resource Science (CSRS) has continued to perform at an excellent level and cemented its international leadership in plant biology, chemistry, and chemical biology. The five flagship projects and Advanced Technology Platforms are well established and produce pioneering results from basic and applied research that are consistently published in high-ranking international journals. CSRS has made great strides in establishing transparent administrative processes and involving young scientists in strategic planning. Going forward, CSRS will integrate the flagship projects under the theme Sustainable Resource Science to focus on Sustainable Bio-production, Material Circulation and Catalysis, and Symbiosis and Environment, with clean renewable energy and food security at its center. These will be aligned with the Transformative Research Innovation Platform (TRIP) of RIKEN to accelerate research of national and international impact for the benefit of society. In this context and with new hires in the near-term, CSRS also has important opportunities of evaluating its research portfolio to expand strategic directions and strengthen the critical mass of research groups, as well as achieving gender balance and international diversity among its research leaders and staff. With this, CSRS and RIKEN will continue as critical technology hubs that drive disruptive research and development in Japan and beyond.

Comments and Recommendations

CSRS was started in 2013 by merging the RIKEN plant science, chemical biology, catalysis, and polymer research programs. Since then, CSRS has established itself as a unique and internationally leading research center by combining plant and microbial research with chemical biology, chemical catalysis and polymer science to drive excellent frontier research and innovative interactions between these disciplines. During the four years since the 2019 CSRSAC evaluation, Director Kazuki Saito has made tremendous efforts in keeping CSRS research performance and innovation at the highest level especially during the arduous COVID-19 pandemic period and adoption of new employment regulations that required difficult human resources decisions, while working with an essentially flat budget for the institute. The AC was impressed that despite these challenges CSRS researchers continued to produce new and pioneering research results that have been published in high-ranking journals. The number of excellent publications remains high, which has cemented the international visibility of CSRS as a leading research institute at the interface between chemistry and biology. Director Saito has also made impressive progress in charting the future direction of the institute to focus on Sustainable Resource Science and strategically integrating CSRS research activities with the Transformative Research Innovation Platform (TRIP) of RIKEN that is being developed under the leadership of President Makoto Gonokami.

Generally, the response to the 2019 AC recommendations have been comprehensive, excellent, and very useful. CSRS has increased translational research and interactions with industry. Spinning off three start-up companies from CSRS research by entrepreneurial young scientists is also a commendable achievement. Director Saito is increasingly involving young PIs in decision-making processes, which is a welcome cultural change because it gives the young PIs opportunities to take ownership not only for their own research but also for strategic planning and implementation of new research directions in CSRS. The AC noted that this has visibly improved collegiality and social interactions in the institute. The AC also noted increased efforts among the scientists to build synergies and collaborations between
flagship projects, which is a positive development that can be facilitated even more vigorously. CSRS has now established a strong record of dialogues with society, which is key to keeping the public informed and supportive of research to achieve a sustainable society. The AC also acknowledges the continuing efforts of recruiting female scientists into leadership positions and facilitating their careers, but as already recommended in previous AC reports, additional innovative approaches as well as institutional and social support structure adjustments are needed towards achieving a reasonable gender balance in the medium term. CSRS has launched a successful philanthropic fundraising effort that was recommended by the AC. Although donations to support research projects and career development are still few and small, the AC encourages CSRS (and RIKEN in general) to continue philanthropic outreach efforts and cultivating donors, especially in the context of Sustainable Resource Science for the benefit of society.

Director Saito had asked the AC to evaluate the CSRS flagship projects and whether their research contributes to establishing “Sustainable Resource Science” and will eventually lead to the realization of a sustainable society (TOR 4). In the following the AC summarizes its impressions of the flagship projects and provides recommendations when appropriate.

Innovative Plant Biotechnology

Most of the excellent basic research in this flagship project focuses on Arabidopsis as the model plant organism, which is not unexpected because it includes many of the scientists from the former RIKEN Plant Science Center. The emphasis on crop plants that are key to global food production remains under-represented, with few exceptions. The AC is convinced that the Innovative Plant Biotechnology Flagship Project has the creative potential and scientific rigor to create economic and societal value nationally and internationally by translating basic research more quickly and effectively into crops. RIKEN is the premier basic research institution of Japan, and CSRS plant scientists may be constraint by political mandates (i.e., applied crop research is the domain of agricultural departments and national institutes in Japan). Therefore, CSRS plant scientists must continue and expand their efforts of building strategic alliances with agricultural institutions and scientists in Japan and internationally to accelerate research and application in crops. The AC also encourages CSRS plant scientists to intensify their interactions and collaborations with the other CSRS flagship projects to explore opportunities how translational research can be accelerated to benefit crop plants.

Integrative Symbiological Solutions

This important new flagship project focuses on fungi and bacteria that interact with plants, mostly associated with roots in the rhizosphere, which still reflects largely unchartered territory. The discovery that the bacterium *Streptosporangium* sp. AEG048 produces sporoburone when interacting with Brassicaceae roots (e.g., cabbage) but not roots of other tested plants, is an excellent example. Sporoburone is a novel type of antibiotic effective against multi-resistant pathogenic bacteria, which is urgently needed for the clinical treatment of patients who become infected with multi-resistant gram-positive or gram-negative bacterial. Sporoburone can now be handed over to the Drug Discovery Platforms Cooperation Division for development and clinical trials, which is a good example of synergistic interactions between CSRS flagship projects. The recent application of long-read PacBio DNA sequencing technologies for the rice phyllosphere microbiome metagenome has revealed that
80% of the bacterial species that are associated with the rice leaf represent novel species. The AC encourages the scientists of this flagship project to further expand their strategic collaborations and synergistic interactions with the other CSRS flagship projects to exploit the immense discovery potential of the plant microbiome to accelerate applications for use in clinical and agricultural research.

**Metabolic Genome Engineering**

RIKEN has strong platforms and analytical capabilities for genome engineering of microbes, but comparable bioengineering efforts in plants remain challenging because of the greater complexity of plant metabolism. The AC was impressed with artificial intelligence (AI)-assisted construction of novel synthetic metabolic pathways in bacteria. The production of maleate, which could be increased manyfold by designing novel enzymes, is a good example of the potential metabolic genome engineering. Similar AI-assisted construction of a synthetic metabolic pathway for butadiene production, which is a global multibillion dollar market, shows great promise. But it is now important to demonstrate that the bacterial production of value-added chemicals can be sufficiently scaled up and become cost-effective compared to existing conventional production methods to become an integral part of Sustainable Resource Science. Production of known or novel plant specialized metabolites such as camptothecin or verticillactame in bacteria are equally promising, but in certain cases also require optimization of primary metabolism for intermediates required for synthesis of specialized metabolites. The AC encourages CSRS to partner with companies that already have engineered bacterial metabolism to accelerate large-scale production of value-added compounds. Rapid advances in engineering existing and synthetic plant metabolic pathways for specialized metabolites and lipids will also be feasible with existing and emerging genome editing technologies. The AC is convinced that metabolic genome engineering will make substantial contributions to the use of sustainable resources in the future.

**Innovative Catalysts**

Efficient, robust, and cost-effective catalysts for synthesis of chemicals from renewable natural resources are key to reducing reliance on fossil fuels for their production. The AC was impressed with the breakthroughs that this flagship project has made in developing innovative catalysts for nitrogen and carbon dioxide chemistries at ambient temperatures. But the usefulness of the resultant molecules was not immediately obvious, although industry may have interesting compounds already for which the novel catalysts could be commercially valuable in their production chains. Similarly, CSRS is currently a global leader in the effective catalysis for green hydrogen production, which has been published in top journals of the field. But it was not clear if the innovative catalysts are ready for large-scale industrial hydrogen production as alternative fuel. The flagship project has developed several other catalysts for synthesis of novel reagents, fine chemicals, and functional materials, some of which have already been commercialized. Together, CSRS is among the leaders in developing novel catalysts that are key to realizing a carbon-neutral society.
Leading-edge Polymers

Polymers from fossil oil resources are currently produced at an unprecedented scale (300 million tons annually) and contribute to the pollutions of land and oceans, with impacts on animal and human lives. The synthesis of high-strength and biodegradable polymers is therefore key to Sustainable Resource Science. CSRS scientists have synthesized super-strong functional polyolefins with self-healing properties that could revolutionize the industry. Synthesis of biomass-based acrylic resins and semi-aromatic polyesters from the phenolic compound resorcinol are other examples of novel polymers with commercial potential. Industry is interested in these novel polymers, but often requires kilogram amounts for evaluation and testing before making investment decisions for their commercial development and production. The capacity for larger-scale synthesis of novel polymers is not available in RIKEN, which impedes the technology transfer to industry for commercial exploitation and reduction of non-renewable resources for their synthesis. The AC encourages RIKEN leadership to consider building pilot plant facilities that could bridge the technology transfer gap between the laboratory and industry. Or scientists should team up with companies that have pilot-scale facilities, for example as a collaborative effort of scaling-up synthesis of new polymers. The bacterial production of peptide polymers for the synthesis of silk-like protein polymers for the creation of silk-like materials is another important advance in which CSRS has a leading position. The AC encourages the CSRS to accelerate this research and better explain to the public how new polymers from renewable resources contribute to a sustainable society. The development of marine-degradable polymers is equally important and has been encouraged by the AC during the last meeting. But caution should be exercised in public communication because the future availability of novel biodegradable polymers does not solve the current problem of plastics impacting the environment in the longer term.

Advanced Research and Technology Platform

CSRS has built excellent instrument and technology platforms on the Yokohama and Wako campuses, as well as a cross-sectional information platform. The technology platforms facilitate research not only among scientists of the flagship projects, but also support other RIKEN researchers and laboratories in Japan. Instrumentation and state-of-the-art technologies are available for metabolomics research, plant hormone analysis, plant phenotyping, and microscopy. The impact of the CSRS instrument platforms have spurred several collaborations with industry, who value the technological expertise of the platform scientists. Although the instrument and technology platforms do not contribute directly to Sustainable Resource Science, the AC appreciates that they facilitate the necessary research to achieve a sustainable society.

Drug Discovery Platforms Cooperation Division

The Drug Discovery Platforms Cooperation Division is not part of the CSRS flagship projects and is funded directly by the RIKEN administration, but it is associated with CSRS. Research in the Drug Discovery Platforms Cooperation Division focuses on drug targets x modalities (drug discovery technologies) to meet medical needs beyond existing drugs and treatments. It was not clear to the AC who sets priorities for drug targets. RIKEN scientists propose potential targets to the Drug Discovery Platforms Cooperation Division that are often not sufficiently validated, which makes screening for hit compounds and subsequent validation a resource-intensive and risky effort. Drug Discovery Platforms
Cooperation Division scientists are now working with data scientists using AI-based identification of potential targets, which is closely aligned with the development and implementation of the Transformative Research Innovation Platform (TRIP) concept by the RIKEN leadership. Recent efforts of the scientists have successfully identified compounds that could potentially be developed into anticancer drugs, and for drugs to treat sickle cell disease and mitochondrial diseases in humans. As the result, scientists have established early collaborations with the pharmaceutical industry, although it was noted that licensing of existing RIKEN patents is becoming difficult. Clearly, the Drug Discovery Platforms Cooperation Division is an important asset to basic RIKEN research and development, but the AC wonders how it will contribute to the CSRS Sustainable Resource Science. The AC also encourages Drug Discovery Platforms Cooperation Division scientists to focus on rare diseases, for which drug development is neglected by the pharmaceutical industry. There is less competition in the field and perhaps a shorter path to the market.

The AC recommends that Chemical Biology, which is part of the Drug Discovery Platforms Cooperation Division, should increase its own research activities in addition to providing chemical library screening support to CSRS and RIKEN scientists. The future of the Chemical Biology platform is somewhat uncertain with upcoming retirements. The AC agrees that the recent hiring of a younger scientist will provide a certain level continuity and maintain the legacy of the chemical screening platform. But CSRS should decide how Chemical Biology can best be integrated into the Sustainable Resource Science concept to accelerate research and maximize benefits from this important platform.

**Integration of CSRS flagship projects with Sustainable Resource Science and TRIP**

The AC noted that except for Integrative Symbiological Solutions, none of the flagship projects referred to or integrated the TRIP concept developed by the RIKEN leadership into their future plans, milestones and goals. This is also the case for the Sustainable Resource Science concept that has been developed by the CSRS leadership scientists. It is now key for CSRS to articulate the central mission of Sustainable Resource Science in the context of the TRIP concept and delineate how this new mission is different from the original mission of CSRS. The AC recommends defining research fields in which CSRS is internationally leading, such as plant hormones and stress biology, or catalysis, and research fields in which CSRS can be a global player with the appropriate financial and infrastructure support. It is also important to explain how the TRIP concept can make CSRS research internationally unique in making contributions to sustainability. The strategic program outlined by Director Saito for the next mid-to-long-term plan integrates Sustainable Resource Science with TRIP for the benefit of “global commons—one earth”. This new strategic program combines the current flagship projects to focus on Sustainable Bio-production, Material Circulation and Catalysis, and Symbiosis and Environment, with clean renewable energy and food security at its center. It is less clear to the AC how the Drug Discovery Cooperative Division will fit into the new CSRS strategic program, although the AC agrees that this a valuable research platform for RIKEN. The TRIP concept and Advanced Technology Platform are integral parts of Sustainable Resource Science. The AC is convinced that this new strategic program is well positioned to develop the necessary scientific principles and technologies to achieve the reduction of environmental impact by industry and agriculture while securing sufficient and useful production for a sustainable society based on the SDGs. It should be noted that recently the United Nations has warned that the SDGs are in peril, including the SDGs that are the focus of CSRS research, and that the world risks big misses across the SDGs unless measures are taken to accelerate their implementation.
The new and refocused CSRS strategic program therefore is timely but also needs to reflect on why SDGs will likely not be met by 2030 as originally envisioned. Historically, research at RIKEN was bottom-up, but with the TRIP concept RIKEN is now moving towards integration of different fields to accelerate pioneering research in Sustainable Resource Science for global impact. The AC is convinced that if such integration can be achieved for the benefit of society, it can only be done successfully in Japan. CSRS is in an excellent position to accelerate integrated synergistic frontier research to produce high-impact results that will help to achieve the SDGs.

In discussions with CSRS scientists the AC noted that TRIP is still an emerging concept. Success of TRIP will partially depend on funding that can be made available by the Ministry of Education, Culture, Sports, Science and Technology (MEXT). A well-developed innovative strategic program such as TRIP can explain how integration of large data from different scientific fields can eventually become predictive for scientific solutions to global problems. The AC is convinced that the TRIP concept will persuade government officials and ministries to increase the funding for RIKEN and Sustainable Resource Science, because finding scientific solutions to global problems is at the center of their political decision-making. The rationale behind the TRIP concept is comparable to ChatGPT, whose artificial intelligence (AI) algorithms are based on a large amount of information. AI can predict but not explain, which in addition to large datasets requires simulation and modeling to developed new theories that accelerate research, especially for understanding and managing environmental complexity. CSRS scientists understand the value of data integration and the role of ecology in their research projects, which also require the acquisition of more information on microbes, chemicals, metabolic pathways, environmental factors, etc., to integrate this information with their fundamental and applied research.

**Future CSRS research plan and management of the Center**

Dr. Saito had asked the AC for comments and advice to a future research plan and management of the Center (TOR 6). As discussed above, the strategic program outlined by Director Saito for the next CSRS mid- to long-term plan integrates the existing flagship projects into the Sustainable Resource Science that is aligned with TRIP. The AC strongly endorses this new strategic program and encourages the RIKEN leadership and all CSRS scientists to support it and actively participate in its realization.

The AC agrees that science in CSRS is excellent, which is also reflected by the impressive number of highly cited CSRS researchers for many years. But the AC recommends also considering what can be done to build more critical mass in individual research groups. Often research groups are small and constrained by the flat RIKEN budget and the limited external funding sources that are available in Japan. The AC recommends merging smaller groups with related research into larger groups in the longer term. Upcoming retirements and open scientific leadership positions create opportunities to strengthen and shape the directions of the Sustainable Bio-Production, Symbiosis and Environment, and Material Circulation and Catalysis programs within the context of Sustainable Resource Science and TRIP. Strategic hirings in the next 2-3 years need to be well planned because they will have considerable implications for the future of science in CSRS. Generally, research in CSRS is bottom-up, but strategic funding should be available as well for collaborative mission-oriented and applied
research projects. The ongoing CSRS research projects on nitrogen catalysis and fixation are good examples of how new strategic interdisciplinary alliances could be built among individual groups to accelerate pioneering high-impact research for solving environmental challenges.

The established CSRS Advanced Technology Platforms are excellent and support high-impact basic research both within RIKEN and nationally. The AC recommends maintaining the strengths of the Advanced Technology Platforms with state-of-the-art instruments and expert technical support personnel. Certain shortcomings in infrastructure, however, such as the shortage of greenhouse space on the Yokohama campus or the ability of scaling up new biopolymer production for industrial testing, continue to plague CSRS in rapidly translating basic research results into promising applications within the context of Sustainable Resource Science and TRIP. The AC recommends that CSRS develops a comprehensive infrastructure plan that will provide optimal research support for discussion with the RIKEN leadership and government officials.

The AC notes that CSRS lacks sufficient computational biology expertise, especially considering the large amount of data that is produced by the Advanced Technology Platforms. RIKEN has an excellent computational infrastructure, and more intensive networking of CSRS scientists with RIKEN computational experts could strengthen CSRS data analysis capabilities. But this alone is not sufficient because in the future AI-driven data integration among different fields and disciplines as envisioned by the TRIP concept will key to accelerate research within the context of Sustainable Resource Science. The AC recommends that CSRS develops a strategic plan that articulates how its research can be better aligned with the RIKEN computational infrastructure, for example by hiring experts that can build bridges between biological and AI-driven research.

The rapid emergence of genome editing capabilities based on CRISPR-Cas and other site-directed nucleases provide unprecedented opportunities for developing new crop varieties that are more resilient to environmental stresses, higher yielding, or more nutritious for human health and food security, which are key challenges for a sustainable society. The AC noted that compared to other plant and crop research institutions, genome-editing approaches are still underrepresented in the CSRS plant research portfolio. The AC encourages CSRS scientists to consider how their excellent research in Arabidopsis can be translated more quickly into crop improvement by clever design of site-directed nuclease 1 (SDN1) events that are already deregulated (i.e., they are not considered GMO) in Japan and many other countries, or even SDN2 events that will likely become deregulated in the near-future.

As discussed above, the AC commends Director Saito for involving CSRS scientists, and especially younger scientists, into decision-making processes. The AC recommends maintaining transparency in all administrative and fiscal processes and continuing to strengthen collaborative and social interactions among the scientists. The AC is convinced that the new culture implemented by Director Saito is the best recipe for excellent science and international leadership. As already recommended in previous AC reports, CSRS should increase its efforts of promoting international activities and exchanges of scientists between Japan, Europe and USA, as well as hiring foreign scientists to expand the current small group of international researchers in CSRS and RIKEN. The AC is convinced that promoting international activities will also help with raising international funding to complement the continuing flat CSRS and RIKEN budgets.
TOR1: Evaluate the response to the 2019 AC recommendations.

The response of CSRS to the 2019 AC recommendations has been comprehensive, excellent and very useful in further strengthening the integration of interdisciplinary R&D despite continuing physical distance challenges. CSRS increased translational research, established more collaborations and interactions with industry, and started companies resulting from pioneering research efforts. This is a very good start and important for accelerating Sustainable Resource Science. The effective and productive engagement of young PIs in strategic planning and decision-making processes is a very positive cultural change that has established transparency and facilitated community building. The increased efforts of building synergies within and between flagship projects is a positive and welcome development. CSRS has established a strong dialogue with society about the progress and benefits of their research activities for the sustainable use of global resources, which is helping to sustain public acceptance of R&D efforts. Achieving gender balance and recruiting female scientists into leadership positions remains challenging, and further efforts are needed to reach this goal. CSRS successfully implemented philanthropic fundraising, which is critically needed to supplement dwindling funds, especially for the training of next-generation scientists.

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

[Strengths (internal/positive)]
CSRS is a unique and well-functioning RIKEN Center that has made impressive scientific progress, with pioneering research output on solutions for a sustainable world that is internationally recognized. But the self-perceived strengths that focus primarily on commendable administrative achievements are too modest and do not fully reflect the ongoing excellent research accomplishment. The CSRS leadership has made considerable advances in building a more inclusive and integrated research community, recruited talented PIs, and accelerated translational activities.

[Weaknesses (internal/negative)]
The focus on the physical separation of CSRS research laboratories on two campuses and other operational issues addresses important and continuing challenges, but it does not help to understand how research in CSRS could be strategically strengthened even further. Going forward, gaps in CSRS scientific research activities must be identified that are critical to achieve Sustainable Resource Science goals through strategic hirings of the best young scientists.

[Opportunities (external/positive)]
The focus on the external appreciation of the Sustainable Development Goals is important. However, the internal scientific, technology and interdisciplinary strengths of CSRS also offer tremendous opportunities, especially when combined with other disciplinary and technology capabilities in RIKEN. This could be more favorably articulated.
CSRS is facing increasing international competition as science is recognizing and addressing global challenges that need to be solved to make the world sustainable. Stability of research funding is a concern for achieving the goals of Sustainable Resource Science. But it is also necessary to develop ambitious and high-priority research directions that are of critical concern to society and government.

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.

CSRS is recognizing the TRIP concept as a timely, important and useful framework for accelerating research and interactions between different disciplines. The CSRS flagship projects have made impressive advances and have been highly effective in preparing the ground for the even greater integration of CSRS interdisciplinary research into three important programmatic areas that are supported by advanced technologies: 1. Sustainable Bio-Production, 2. Symbiosis and Environment, 3. Material Circulation and Catalysis. These new programmatic areas should be implemented and promoted in the TRIP framework to accelerate Sustainable Resource Science. RIKEN is among the world-leading research institutions in Sustainable Resource Science, which is exemplified by the excellent scientific output, impact and potential of CSRS research. This will be further strengthened by aligning Sustainable Resource Science with the opportunities presented by TRIP to foster pioneering research in RIKEN for society and global sustainability. Japan has the potential of becoming a global hub in this critical endeavor.

TOR4: Evaluate the Center’s six flagship projects and whether their research contributes to establishing “Sustainable Resource Science,” and will eventually lead to the realization of a sustainable society.

The five flagship projects and Advanced Technology Platforms are well established and produce pioneering results from basic and applied research that are consistently published in high-ranking international journals. Going forward, CSRS will integrate the flagship projects under the theme Sustainable Resource Science to focus on Sustainable Bio-production, Material Circulation and Catalysis, and Symbiosis and Environment, with clean renewable energy and food security at its center. These will be aligned with the Transformative Research Innovation Platform (TRIP) of RIKEN to accelerate research of national and international impact for the benefit of society. This new strategic program is well positioned to develop the necessary scientific principles and technologies to achieve the reduction of environmental impact by industry and agriculture while securing sufficient and useful production for a sustainable society.
TOR5: Evaluate whether each PI’s research activities meet high international standards.
See separate report. All CSRS group leaders perform at an excellent level of productivity and international visibility that meet high international standards.

TOR6: Provide comments and advice regarding research plans and management of the Center.
Science in CSRS is excellent, which is also reflected by the impressive number of highly cited CSRS researchers for many years. Upcoming retirements and open scientific leadership positions create opportunities to strengthen and shape the directions of the Sustainable Bio-Production, Symbiosis and Environment, and Material Circulation and Catalysis programs within the context of Sustainable Resource Science and TRIP. Strategic hirings in the next 2-3 years need to be well planned because they will have considerable implications for the future of science in CSRS. The established CSRS Advanced Technology Platforms are excellent and support high-impact basic research both within RIKEN and nationally. More intensive networking of CSRS scientists with RIKEN computational experts could strengthen CSRS data analysis capabilities. CSRS scientists should also consider how their excellent basic research can be translated more quickly into crop improvement for the benefit of society.