Date: March, 2018
Institute Laboratories' Research Promotion Office RIKEN

Research Project Final Evaluation Result

The following research project underwent a final evaluation in accordance to Clause 10 and 11, Chapter 2 of the *Regulations for Research and Development Evaluations* (Regulation No. 74, October 1, 2003.)

Evaluation system:
Out of five reviewers, two experts from outside of RIKEN and tree RIKEN Science Council Research Programs Committee members were appointed as reviewers for the following research project. The reviewers evaluated the project based on the reporting session held on January 30, 2018.
***In this evaluation, it was agreed by the review committee to disclose their names and make clear who made report comments.**

Reviewers list:

External experts (alphabetical order)

1) Kaoru YAMANOUCHI , Professor, School of Science, the University of Tokyo
2)Yoshihito WATANABE, Trustee, Vice President, Nagoya University

RIKEN Science Council Research Program committee member (alphabetical order)

3) Yukishige ITO, Chief Scientist, Synthetic Cellular Chemistry Laboratory
4) Hideki UENO, Chief Scientist, Nuclear Spectroscopy Laboratory
5) Zhaomin HOU, Chief Scientist, Organometallic Chemistry Laboratory

Research project brief overview

Project name: Molecular Systems Research
Project Leader： Tahei TAHARA
Project duration： April, 2012～March, 2017（5 years）
Budget allocated： Total of 990,216 thousand Yen（5 years）
Research overview：

As materials become more complex, they contain more molecules or more molecular parts and start showing amazing functions that cannot be realized by a simple molecule. The study of the properties and functions of such complex molecular systems is critically important in materials science today. We gather researchers having high activities in chemistry, physics, biology and engineering, and carry out interdisciplinary research for elucidating, controlling and creating highly efficient molecular systems. This project consists of four teams: (1) Team for analyzing molecular systems, (2) Team for controlling molecular systems, (3) Team for biological molecular systems, and (4) Team for engineering molecular systems.

1. Comprehensive Evaluation (To be disclosed)

1) Evaluation on five-grade scale	S	A	B	C	D
(1) Research objective:	1	4	0	0	0
(2) Implementation of research plan:	1	4	0	0	0
(3) Research achievement:	3	2	0	0	0

S Outstanding / A Excellent / B Good / C Acceptable / D Not acceptable

2) Evaluation details

(*In this evaluation, it was agreed by the review committee to disclose their names and make clear who made report comments)

＜Kaoru YAMANOUCHI＞

(1) Research objective

A huge number of plants and animals are flourishing on the surface of the earth, and their bodies are composed of a huge number of living cells. We know that each one of the cells is an inhomogeneous complex system composed of biomolecules and molecular aggregates. Even though we have deepen our understanding of nature thanks to the development of modern science, we have to admit that we still do not understand well how the inhomogeneous complex systems could exhibit such a variety of characteristic structures, properties, and functionalities. We find with wonder that these systems are so ideally designed, and sometimes, we are obsessed incorrectly by the idea that someone purposefully designed the complex biological systems long ago. In Dr. Tahara's project entitled as "Molecular Systems research," the complex biological systems were defined as "molecular systems," which literally mean the systems composed of molecules, and the origin of the high-dimensional functionalities was explored on the molecular level by the interdisciplinary cooperation among the world-leading research groups in RIKEN. This objective of the research project is indeed appealing and can be regarded as that originating from our instinctive desire, which can be shared not only by researchers in scientific communities but also by common people.

(2) Implementation of research plan

We know that interdisciplinary interactions among researchers having different research expertise and experience are stimulating and that new ideas and projects can come out from interdisciplinary research cooperation. However, we have to realize that new research fields could not emerge promptly only through the interdisciplinary interactions. Because the objective of Dr. Tahara's research project is so general, it is possible that the member researchers wondered how they could contribute to achieving practically the objective. During the first phase of this is type of interdisciplinary project, the member researchers need to become familiar with the guiding principles in other research fields while concentrating on conducting their own research projects. By the time when the project enters into the next phase, the member researchers understand well the roles and actions they should take towards the achievement of the objective. From the oral presentations at the symposium for the final evaluation, I learned that the respective research groups were able to concentrate on their own research projects during the period of the Molecular Systems research project with the sufficient financial support, and that the member researchers frequently held joint scientific meetings in order to learn the research activities of other research groups. Therefore, I judge that the research plan was implemented properly in the first phase. I hope that the member researchers will continue making an effort to achieve the objective on the basis of their achievements during the first phase even though the period of the "Molecular Systems research" project was finished one year ago.

(3) Research achievement

I learned from the presentations made at the symposium for the final evaluation that the following impressive research results were obtained during the period of the Molecular Systems research project:

(i) The two-dimensional fluorescence correlation spectroscopy was developed and the folding and unfolding dynamics of proteins proceeding in the microsecond time domain was investigated.

(ii) The electronic excitation dynamics of molecules on the surface was investigated by scanning tunneling microscope combined with optical detections.

(iii) The dynamical behavior of proteins was investigated by the large-scale molecular dynamics calculations combination with machine learning.

(iv) The Block-Lanczos density-matrix renormalization group method was developed and was applied to the investigation of the Kondo effect in graphene

(v) The molecular conductors, molecular metals, and molecular superconductors were designed and synthesized.

(vi) The crystallization of the NOR(nitric oxide reductase)-NiR(nitrite reductase) complex was achieved for the investigation of the denitrification mechanism in microorganisms.
(vii) The membrane proteins were investigated by X-ray crystallography and electron crystallography combined with the information obtained from single particle cryo-electron-microscopy.
(viii) The photoactive gold nanoparticles and gold nanorod functionalized by double-stranded DNA were synthesized.
(ix) The efficient labelling method through a rapid 6π-azaelectrocyclization of conjugated imines called the RIKEN CLICK reaction was discovered and developed for clinical applications.

As listed above, the individual groups in the Molecular Systems research project conducted highly original studies and their achievements are now recognized well internationally. There is no doubt that the Molecular Systems research project concluded with great success. However, the research result (iv) may not fit in well with the objective of this project because the Kondo effect could not be used for the analysis of molecular systems. It could have been better if such solid-state oriented research projects were incorporated and presented in a more consistent manner with the research objective.

＜Yoshihito WATANABE＞

(1) Research objective

This reviewer was very impressed with the results presented by the nine members of this project. They have been engaged in some very challenging work, such as the single molecule FRET experiments by Dr. Tahara. His research group has also applied their set-up to folding/unfolding dynamics of some proteins. Moreover, Dr. Tanaka's work on organic synthesis in living tissues seems to me to be very original and pioneering research. The other members are also employing their own unique tools in their research. For example, Dr. Kim's team utilized STM for manipulating single molecules at a metal surface; fabricating molecular assemblies; and energy transfer. These techniques allow them to visualize very detailed chemical processes as well as dynamic motion of complicated molecular systems. The research objectives are very novel and the results they presented at the symposium ought to be appreciated as pioneering and world-class research.

(2) Results

As mentioned above, the results presented at the symposium are really amazing. The main focus of the five groups has been on protein dynamics, reactions and imaging. Dr. Tahara has visualized microsecond protein dynamics through his group's unique single molecule FRET approach. The molecular dynamics approach by Dr. Sugita, including the modeling of macromolecular structures and their dynamics, is very much complementary to the experimental work being done by the other members. The ability to carry out detailed analysis of hemoproteins responsible for nitrogen transformation in biological systems is a great advantage that researchers in RIKEN-SPring8 have. While Dr. Shiro did not mentioned their SACLA experiments on the conversion of two molecules of NO to N_2O and H_2O catalyzed by an NO synthase, snapshot type analysis of enzymatic reaction processes is only available at SPring8/SACLA and is one of the leading edge topics in the field. Dr. Yonekura has demonstrated his group's cryo-EM techniques to solving the structures of protein assemblies and his approach is also leading edge. Dr. Maeda presented unique properties of DNA-functionalized nano-materials such as Au nano-particle and Au nano-rod assembly. Dr. Tanaka's presentation shocked me because of his quite unique approach to drug delivery systems (DDS). *In situ* synthesis of drug molecules by utilizing carbohydrates (sugar)-linked metal catalysts is quite likely to be at the forefront of the next generation of DDS. This reviewer is quite sure that these research results are highly pioneering work and will stimulate researchers in related fields as well.

The research members have organized scientific meetings regularly to share and discuss their idea and results. This reviewer believes that the meetings stimulated each researcher.

(3) Research structure

The research project entitled "Molecular Systems" has been carried out by 4 team leaders: Dr.

Tahara (chemistry); Dr. Kato (physics); Dr. Maeda (engineering) and Dr. Shiro (Biochemistry). There are many collaborators (RIKEN researchers) working with each research team. Also, there are several third party researchers who are top scientists in the related fields. According to the list of publications, it is quite apparent that the project is very successful and has provided high impact results. The contribution by younger researchers was the key to the project's success. In fact, a number of the young researchers in this project have received international as well as domestic awards, and have received promotions both within RIKEN and in external organizations such as universities, research institutions and industry. This reviewer believes those young talents will be leaders of novel scientific activities in the future.

More importantly, Dr. Tahara has been leading the "Grant-in-Aid for Scientific Research on Innovative Areas" project supported by JSPS, and two key scientists of this JSPS project are also external members of the Molecular Systems Research team. The JSPS project has been providing a great opportunity for many young scientists to conduct their research.

The greatest advantage of research at RIKEN is the facilities the institute provides, such as SPring8/SACLA. In addition, ultra-fast laser systems, STM, high field NMR, and the super computer "KYO" are readily available to RIKEN researchers. The members of the "Molecular Systems" group have fully utilized these advantages to further their research.

(4) Collaboration with universities and other institutions

Dr. Tahara officially organized the Molecular Systems program by inviting scientists from institutes outside RIKEN to participate, including Tohoku University, Tokyo Tech., Osaka University, KEK and IMS in Japan. Besides these collaborations, members of the Molecular Systems group organized international collaboration (see pp.7-8, "Research Activity Report," Jan. 30, 2018) and have published joint papers. As a world-class research institution, RIKEN should emphasize the promotion of international collaboration, as well as domestic collaboration. It is clear that the "Molecular Systems" project is a good example of this.

＜Yukishige ITO＞

(1) Research objective

Importance of knowing about molecules in understanding the Nature is obvious. Exploitation of knowledges on molecules has brought tremendous impact to human societies, for instance through creation and production of novel materials, development of diagnosis and therapeutics, and bioengineering technologies. Clearly, this country has strong history in molecular sciences, turning out 7 Novel laureates in chemistry, the number compares favorably with physiology or medicine. Traditionally, however, studies on molecules have been conducted mainly by individual laboratories and collaboration among molecular scientists or chemists has been rather rare. Molecular scientists, especially organic chemists, tend to feel urged (even if not interested in) to make good use of their expertise in collaborating with researchers in other fields, especially biology. In other words, molecular science or chemistry is considered highly valuable in providing materials or analytical techniques to "users". Under these circumstances, identity of molecular science is becoming somehow obscure. Now, it is clear that the pioneering project "Molecular Systems" aims to promote studies on molecules and to ignite collaboration between researchers in various disciplines both inside and outside RIKEN. Accordingly, there is no reason to be skeptic about value of this project. It has indeed addressed a number of fundamental problems valuable for deepening understanding of molecules. It deserves to be considered as a good example of project research in which researchers think and work together in order for driving specific fields (in this case molecular science) into new direction and solidifies its position as a central player in science.

(2) Implementation of research plan / (3) Research achievements

Selection of research subjects is mostly appropriate. A number of excellent research outputs, many in high-impact journals, have been made. In terms of both quality and quantity, level of achievements is outstanding. This project is characterized by breadth of research subjects that can be included. By that, highly ambitious research subjects have been promoted without worrying too much about their suitability to conventional funding systems like Kakenhi. In addition, the project has been able to support laboratories whose financial basis was not strong enough.

On the other hand, this reviewer felt that the breadth of research subjects would be a “double-edged sword”. Whereas this character has given research opportunities to heterogeneous group of researchers, it might have obscured big goal of the project. Apparently, some collaborative studies between member’s laboratories and subprojects have been conducted, progress report as well as presentations gave an impression that the project is mostly a mixture of focused studies conducted by individual members.

Despite these minor concerns, there are enough reasons to believe that this project has been implemented successfully. In addition to its excellence in research outputs, it is impressive to see that extensive effort has been made among project members to seek common theme in a huge area on molecular science. It is clearly seen that the project has helped younger researchers to find higher positions through opportunities to work with influential PIs. Hopefully, many of them will be next leaders in molecular science.

At the end, it should be emphasized that maintaining Pioneering Project or similar funding system which promote bottom-up type research is essential in order for keeping RIKEN’s identity that distinguishes it from other research institute or universities in Japan.

＜Hideki UENO＞

(1) Research objective

The aim of the project was to understand properties and functions of molecular systems, caused as many-body effects through, e.g., the concerted action, synergistic action, and interaction among them, which cannot be understood simply by observing an isolated molecule. To achieve this purpose, molecular systems of interest should be multilaterally analyzed from various points of view. In this regard, it is necessary for each research group not only to utilize their special experimental techniques for their own studies, but also to mutually utilize them. Development of a new technology was also necessary for some of the challenging programs proposed. The project was designed to achieve the purpose by building a new research framework beyond the layer of the laboratory and research field, by adopting an organic collaboration such as technical collaboration between cross-disciplinary groups, and research collaboration between experiment and theory, among the others. The project objective is suitable for the Pioneering Project as a bottom-up style research program by the cross-disciplinary and experiment/theory collaboration of the research groups.

(2) Implementation of research plan

The project was carried out by the four teams consisting of the ten RIKEN research groups. Although the research field of the project as a whole is widely spreading, the experimental techniques concentrates mainly on chemical and physics techniques. This structural feature made it easy to create new cooperation. For instance, several research programs in the project were conducted by the collaboration of theoretical and experimental research groups. Moreover, the cooperative researchers were not limited to the inside of RIKEN, but extended to many institutes/universities outside RIKEN. The allocation of the research groups inside and outside RIKEN to each team was well balanced, and the research programs progressed smoothly in all four teams.

Characteristically in promoting the project, plenary workshops were held twice a year continuously so that the participants can share information on the research progress of each team and can take opinions from the other teams actively. Here, in addition to the summary progress report by PIs, oral and poster presentations by young researchers were also set up for their active opinion exchanges. This effort was quite effective in the promotion of various cooperation in the project. The project provides a successful example that newly created collaboration among interdisciplinary research fields, experimental/theoretical groups, and institutes inside/outside RIKEN. It should be also mentioned that many young researchers have been promoted from this project.

(3) Research achievement

Although my expertise is different from the research subjects treated in the project, many research results from all four teams have been published in high-impact journals and selected for invited talks of international conferences. It is clear, by objectively judging, that the project created

world-leading research outputs. Not all of these researches were conducted in the collaboration scheme, and some of them were achieved by individual research groups. However, improvement of individual research capability is indispensable for a new interdisciplinary collaboration, and thereby several technical breakthrough were successfully achieved in the project. I highly appreciate that many outputs have been obtained as results achieved in this new research framework.

＜Zaomin HOU＞

(1) Research objective

This is an ambitious research program, aiming to elucidate, control, and utilize the properties and functions originating from synergistic molecular interactions in materials with structural hierarchy. The possible outcome of this research may show strong impact in various areas.

(2) Implementation of research plan

The four research teams with focuses on molecular interaction characterization and control, biological function, and molecular integration are well organized. The team members contain experimental and theoretical researchers in areas ranging from physics, chemistry, metalloproteins and bioengineering. Considerable attention has been paid to collaborations between teams and with researchers outside of RIKEN.

(3) Research achievement

The research achievement of each team is excellent. Collaborations between experimental and theoretical groups are very successful and impressive. Research highlights include the development of two-dimensional fluorescence lifetime correlation spectroscopy, real-space investigation of energy transfer between two molecules by STM, discovery of pressure-induced metallic conductivity in a single-component molecular crystal and light-induced superconductivity using a photoactive electric double layer, crystal structure determination of a mega-complex of nitrite reductase (NiR) and nitric oxide reductase (NOR), and DNA dangling-end-induced colloidal stabilization of gold nanoparticles.

RIKEN Science Council Research Programs Committee