平成 22 年 3 月 16 日
独立行政法人理化学研究所
播磨研究所　研究推進部

放射光システム生物学研究グループ　中間レビュー報告

放射光システム生物学研究グループ（倉光 成紀 グループディレクター）の中間レビューを下記のとおり実施いたしましたので報告いたします。

記

【日時】平成 21 年 11 月 7 日
【場所】独立行政法人理化学研究所　播磨研究所
【レビュアー】Prof. Masayoshi Nakasako / 中迫雅由（慶應義塾大学理工学部）
Prof. Mitsuaki Yoshida / 吉田光昭（東京大学大学院新領域創成科学研究科）
Dr. Midori Kamimura / 上村みどり（帝人ファーマ㈱創薬研究所　創薬開拓研究部）
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【評価結果の概要】

REVIEWER 1

1. Consistency of the SR System Biology Research Group's mission and the RSC's mission

The main mission of this research group is construction of the research field of "Whole-cell systems biology at an atomic level". Only if this group's mission is successfully completed fits this group's mission with that of RSC's of "Exploring, Promoting and leading the research utilizing advanced SR facilities at SPring-8", since the trial of the systems biology research with connection of structural biology research is the novel and top notch research area.

2. Research Object

The final goal of SR System Biology Research Group is the understanding of all fundamental biological phenomena in a cell based on three-dimensional structure and function of all molecules using a model organism of extremely thermophilic bacterium, Thermus thermophilus HB8. As a continuation of the "Structurome project (1999~2005), this group has three research objects.

i) Functomics Integration Research Team
- Structural genomics for whole-cell imaging
- Developing new platforms for functional genomics
- Bioimaging

ii) Functomics Biology I Research Team
- Structural and functional analysis of transcription factors

- Functional identification of functionally unknown proteins

iii) Functomics Biology II Research Team

- Structural and functional analysis of protein involved in DNA repair systems
- Functional discovery of functionally-unknown proteins involved in DNA repair systems
- In vitro reconstruction of DNA repair systems
- Construction of systems for the single-molecule imaging by using DNA repairing proteins
- Analysis of cell-wall construction system for cell imaging

Addition of structural information and the functional identification of proteome is significant contribution in the structural biology research filed. This traditional structural biology approach, however, is continuation of the structurome project. To have a novelty, this research group has to focus and elaborate more in systems biological research objects.

3. Research Results

This research group solved 111 structures in this term (2006~2009), succeed in the classification of the ~140 functionally unknown proteins, and published about 80 original papers. These research outputs are scientifically significance especially on the field of structural biology. In addition, this research group supported research communities by supplying resources (plasmids) and information (protein production, crystallization, structure, and functomics) obtained during the half-term of this research project. These public services obviously have high social impact to structural biology community.

4. Management of the Research Group

This group composed of three research team: Functomics Integration Research Team (FI), Functomics Biology I Research Team (B1) and Functomics Biology II Research Team (B2). Each research team is well equipped and has proper man power for the structural and functional research, but the connection or interaction between three research teams is somewhat weak point. Three research teams have generated a large amount of phenomics, transcriptomics, proteomics, and metabolomics data by gene disruption experiment in addition to the structural information. The effort for the integration of the already obtained massive data, however, seems to be insufficient. To complete the “Whole cell Systems Biology at atomic level” successfully, FI team with the strong connection of B1 and B2 research team should focuses more on the integration of the phenomics, transcriptomics, proteomics, and metabolomics data and the network analysis.

5. Future research plans

This research team proposed to develop the analytical methods for functomics and construct functomics resources in addition to the structural genomics data production including membrane proteins and multi-subunit proteins. In addition, this research team proposed to construct the database and collaboration with other researchers at RIKEN. For the successful systems biology research, however, the reviewer suggests to build a core system not only for the functional database construction and management but also for the integration of all the functomics data and network analysis within the research group as a core research team. Since the integration and the network analysis is the most important part of this project, out-sourcing for this core research area would not be recommended.

Although the original goal of the research group is the “whole-cell systems biology”, this research group may focus on the transcription and translation systems biology for the next half-period, because this research group has strong research background and output on this area. Otherwise, the given research period and fund may not be

sufficient to complete the whole-cell systems biology research.

REVIEWER 2

From industrial side, new technology is essential in this field. Especially I'm interesting in two different technologies of this group.

One is in vivo expression of membrane proteins. This group gave the data that twelve transmembrane proteins were tested for overproduction by the Mistic system and eight of them were successfully expressed. They said almost 70% success rate is enough for the future membrane-protein project for structural and functional analysis. Of course the expression rate is high but we want to know how many protein is obtained for the crystallization. In this point of view, this technology should be developed as a general method that can be available for mammalian proteins with some original ideas.

REVIEWER 3

1. On the consistency of the Group's mission and the RSC's mission

The RSC has missions on the scientific researches for both material and biological science based on cutting-edge measurement techniques utilizing X-rays provided from the SPring-8 and the X-ray Free Electron Laser (XFEL). The Research Group utilized SPring-8 in their structure analyses of proteins, and shows their ideas or plans in utilizing XFEL in the future. However, they are still users. Although the group leader emphasized that they could be a powerful developer and heavy user of XFEL, it must be very difficult for the researchers, who had little experience in beam line design and construction. Thus, at the present stage, the Group's missions do not match with those of the RSC. In other word, the Group requires technical supports from the RSC and the SPring-8, but the researches carried out by the Group are not necessary in the missions of the RSC. It will be better to reorganize one of two teams to carry more SR and/or XFEL oriented science research, if the project still continues in the next phase at the Harima Campus.

2. On the research objectives

At the present stage, the Research Group seems to contribute little to the system biology and whole-cell imaging of the bacteria. The major part of the research is simple structural analyses of soluble proteins crystallized easily by the commercially available crystallization buffers. The research project contribute little on the methodologies and techniques in utilizing synchrotron X-rays from the SPring-8. If this group will continue in the next phase, the scientific objectives must be more discussed and clearly shown. The research group should have their own tactics and strategies for the system biological approach, because the research group seems to work as an outstation of the RIKEN Yokohama at the present time.

3. On the research results

The group has published 68 peer-reviewed research papers in collaboration with the research groups in universities or the RIKEN Yokohama institute. The level of each research is at a standard level. Through the last 10 years including the Structurome project, the Group obtained a set of large data on the structures and functions of proteins from the thermophilic bacteria. The results are well organized in a database through the efforts of young scientists. However, the Group seems to have little idea to use effectively the database. The data may be better handled by bioinformatics groups in Tsukuba and/or Yokohama campus. This may be clever choice to

utilize effectively the research results.

4. Management of the Research group

Group member composition

In the last four years, 87 researchers from the fields of structural biology and molecular biology, including the visiting researchers and trainees, joined to this research project. On the other hand, little physicochemists, theoretical biologists and biophysicists joined to the research group. Thus, the composition of the researches seems to be inappropriate for the missions targeting the system biology.

Researchers' interaction

Young scientists seem to interact with each other or the team leaders within the Campus. The opportunities to interact with scientists outside the RIKEN may be limited in the meetings of Japanese Protein Society and the group meeting in every summer at the Campus.

Facilities and equipments

Although the set of equipments is suitable to carry out crystal structure analyses of proteins, from 2007, the number of group members is insufficient for the set. At that time, the leader should decide to reduce the size of the research group or to get external budget to maintain the activity.

5. Future research plans

The future research plans of the Group are presented both in the report and the talks in the review session. In my impression, the project leader showed little about future research plan. He still stands within the protein science field. If the Research Project will be continued, a project leader, who is more professionals in the system biology field, may be better choice for RIKEN. In addition, the group is expected to show their scientific activities independent from the RIKEN Yokohama institute.

6. Possibility of cooperation with related fields

Dr. Mochiduki, a young PI and a theoretical biologist of the WAKO main campus of the RIKEN, may help researches the molecular interactions in small cell systems.

7. RIKEN's management

Why does the RIKEN approve closely similar or redundant research projects in Yokohama and Harima? The RIKEN spent about 721 million yen for this basic science research project at the Harima Campus. About this point, the group leader spoke that their researches are complementary with those at Yokohama institute. However, the research results seem to be redundant or simple collaborations between them. The RIKEN must explain clearly the necessity to the government and the tax payers. This mid-term evaluation may provide a good chance to merge the research group or to terminate one of the two.

REVIEWER 4

- Mission: The SR System Biology Research Group aims at understanding the whole-cell phenomena in the cell at an atomic-resolution. This sounds logically, but certainly requires very long period to be achieved and could be almost end-less. The initial phase of the project has started from structural and functional analysis of all protein components of thermo-stable bacterium. This trial fits in a scope of RIKEN SPring-8 Center's mission, which contributes to life science providing a powerful tool for protein structural analysis. Targeting the thermo-stable bacterium for whole-cell system biology sounds reasonable in view of its genome size and

stable properties of the components. However, such logical target selection has a weakness in other hand in less availability of biological information and collaboration due to extremely small research community when compared with others such as E. coli.

- Objectives: The objective of the program overlaps with an ultimate goal of the life science in general in full understanding the whole-cell biology as a system. It is too high to challenge even for a huge research group, therefore should be arranged into stepwise composition. In fact, the group has proposed a long term strategy in stepwise propulsion such as structural genomics, functional genomics, and interpretation of global biological phenomena; however, each goal, even at initial step, is obscure in its scale and timing. For example, the term “all proteins” in structural analysis of all proteins in thermophilus should be practically defined. It would not be clear probably even to the group, therefore, it would be hard for any one to make decision or assess the program.

- Research results: The group has determined crystal structure of over 300 proteins of thermophilus and published the results. The results were all original and contributed to understanding function of each protein at atomic levels, and also contributed to the National Project so called “Protein 3,000” through depository of the results into the Protein Data Base. So far in the world, about 400 proteins of thermophilus were structurally analyzed and the group contributed to 75%of those, thus their contribution is predominant. On the other hand, proteins so far success fully analyzed stays at the level of 20% of whole proteins of thermophilus. Driving further the structural analysis would require new technologies, thus require more efforts than to date, since proteins which are technically difficult to be analyzed have been postponed.

- Management of the research group and future: Despite of their efforts on structural analysis, the selection of target proteins was random-based. As result, most of their own data are left as alone without integration into any significant arrangement or system. Unfortunately, the efforts in developing system biology were very limited. Development of system biology in conjunction with this project might provide any better strategy for the project. The group’s skill is so focused on structural analysis and may not retain any capacity to challenge bioinformatics, therefore, close collaboration with other groups focusing on the system biology is strongly suggested.

- The basic and long term programs are critically important for RIKEN in a point of view different from the university, however, the goal should be set clearly for understanding the progress and also for making decision at any stages.

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