(Form4-2)

JOINT RESEARCH PROJECT

FINAL REPORT
For Japan-Korea Joint Research Project

AREA	1. Mathematics & Physics 2. Chemistry & Material Science 3. Biology 4. Informatics & Mechatronics 5. Geo-Science & Space Science 6. Medical Science 7. Humanities & Social Sciences

1. Research Title:

Integrated study of nuclear receptor-mediated signaling pathway

2. Term of Research: From 1st July 2009 To 30th June 2011

3. Total Budget

a. Financial Support by JSPS: Total amount: 2,400 thousand yen

1st Year 800 thousand yen 2nd Year 800 thousand yen

3rd Year 800 thousand yen

b. Other Financial Support : Total amount: thousand yen

4. Project Organization

a. Japanese Principal Researcher	
Name	Shigeaki Kato
Institution / Department	Institute of Molecular and Cellular Biosciences, The University of Tokyo
Position	Professor
b. Korean Principal Researcher	
Name	Sung Hee Baek
Institution / Department	Seoul National University Department of Biological Science
Position	Associate professor

c. List of Japanese-side Participants (Except for Principal Researcher)

Name	Institution/Department	Position
Ken-ichi Takeyama	Institute of Molecular and Cellular Biosciences, The University of Tokyo	Associate professor
Yuuki Imai	Institute of Molecular and Cellular Biosciences, The University of Tokyo	Lecturer
Ryoji Fujiki	Institute of Molecular and Cellular Biosciences, The University of Tokyo	Research associate
Saya Ueda	Institute of Molecular and Cellular Biosciences, The University of Tokyo	Post doctoral fellow
Kazuki Inoue	Institute of Molecular and Cellular Biosciences, The University of Tokyo	Post doctoral fellow
Min-Young Youn	Institute of Molecular and Cellular Biosciences, The University of Tokyo	JSPS Foreign Research Fellowship
Jinseon Lim	Institute of Molecular and Cellular Biosciences, The University of Tokyo	JSPS Research Fellowship
Tomoko Asatsuma	Institute of Molecular and Cellular Biosciences, The University of Tokyo	Ph.D. candidate
Naoya Tsuji	Institute of Molecular and Cellular Biosciences, The University of Tokyo	Ph.D. candidate

d. List of Korean-side Participants (Except for Principal Researcher)

Name	Institution/Department	Position
Jason Lee	Seoul National University	Research Professor
Ji Min Lee	Seoul National University	Research Professor
Ik Soo Kim	Seoul National University	Ph. D candidate
Hye Jin Nam	Seoul National Universityx	Ph. D candidate
Zang Hee Lee	Seoul National University	Professor
Hueng Sik Choi	Connam National University	Professor
Ju Yeon Yoo	Pohang University of Science	Professor

5. Number of Exchanges during the Final Fiscal Year*

a. from Japan to Korea *Japanese fiscal year begins April 1.

Name	Home Institution	Duration	Host Institution
Shigeaki Kato	The University of Tokyo	April, 4 days	Seoul National University Chonnam National University
Yuuki Imai	The University of Tokyo	April, 5 days	Seoul National University Pohang University of Science and Technology
Min-Young Youn	The University of Tokyo	April, 5 days	Seoul National University Pohang University of Science and Technology
Kazuki Inoue	The University of Tokyo	April, 5 days	Seoul National University Pohang University of Science and Technology
Jinseon Lim	The University of Tokyo	April, 5 days	Seoul National University Chonnam National University
Saya Ueda	The University of Tokyo	April, 5 days	Seoul National University Chonnam National University
For Final Fiscal Year(FY2011) Total: 6 persons		For Final Fiscal Year(FY2011) Total: 29 man-days	
Numbers of Exchanges during the past fiscal years			
FY2009: Total 7 persons FY2010: Total 7 persons			

b. from Korea to Japan

Name	Home Institution	Duration	Host Institution
None			
For Final Fiscal Year(FY2011) Total: 0 persons		For Final Fiscal Year(FY2011) Total: 0 man-days	
Numbers of Exchanges during the past fiscal years			
FY2009: Total 0 persons FY2010: Total 0 persons			

6. Objective of Research

Nuclear receptor co-regulators are often formed complexes as functional units to conduct histone modifications and chromatin remodeling. Such complexes are in general shared with the other classes of transcription factors, therefore serving as a center for cross-talk with the other signaling pathways.

This field is expanding very quickly, however, the directions are quite diverse. Therefore, experimental and theoretical collaborations between to laboratories derived from the different school are no doubt essential to stimulate and develop new and original directions.

Thus we have planned to perform the study " Integrated study of nuclear receptor-mediated signaling pathway " with Korean partner Dr. Sung Hee Baek.

Though the study of these complexes is indispensable to support physiological events, their molecular link to cancer is not yet characterized. In this respect, possible cross-talk with Wnt signaling is quite interesting. Considering from these situations, we plan to discuss and collaborate with the group of Dr. Baek on the matters of the molecular link of the identified complexes to cancer and Wnt signaling.

At first, we have planned to characterize the role of histone methylase/ demethylase complexes in prostate cancer (Yr 2009).

Second, we have focused on the clarification of cross-talk of the nuclear receptor co-regulator-mediated signal with Wnt signaling at molecular levels.

Besides of such proposal, we have planned to organize an international meeting and symposium in connection with annual meetings of Japanese biochemistry and molecular biology societies. Within budget limitation, young scientists were encouraged to visit Korea to establish personal relationship to foster mutual relationship for future between two countries.

7. Methodology

1.Biochemical approach

To identify novel co-regulators associated with Nuclear receptors (NRs), we tried biochemical purification approach using cultured cells. For that, antibody columns will be established against each NR protein. And then, nuclear extracts prepared from several tissue cells applied to the established antibody column. Associating proteins with specific NR will be identified by using MALDI-TOF/MS or LC-MS/MS analysis. The effect of identified novel candidates to NR transactivation was confirmed by reporter assay using knock-down system.

To analyze molecular function of the identified factors, we further tried identification of associated factors with the NR interactants by biochemical purification. On the other hand, we checked expression pattern, screened target genes, and confirmed recruitment to the target gene (by quantitative PCR, micro array analysis and ChIP assay), which would lead to understand NR transcriptional mechanism regulated by the identified factors.

2.Genetic approach

To understand the epigenetic regulations through newly identified factors *in vivo*, we constructed KO mice of the factors. At first, we targeted genome locus of the identified factor using homologous recombination in ES cells and generate the flox mice of the factors. Then, the newly generated flox mice were crossed with generally Cre recombinase expressing mice to generate null mice.

After analyses of the phenotypes of the null mice, we will generate tissue specific KO mice to understand the biological function of epigenetic factors related to NR in several tissues, and clarify the molecular epigenetic function *in vivo*.