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:

Analysis of mechanistic actions of novel natural compounds and their derivatives that inhibit mast cell activation and allergy

2. Term of Research: From July 1, 2010 To June 30, 2012

3. Total Budget

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

1st Year 1,200 thousand yen 2nd Year 1,200 thousand yen

3rd Year 0 thousand yen

b. Other Financial Support : Total amount: 5,000 thousand yen

4. Project Organization

a. Japanese Principal Researcher	
Name	**Makoto Murakami**
Institution / Department	**Tokyo Metropolitan Institute of Medical Science/ Lipid Metabolism Project**
Position	**Project Leader**
b. Korean Principal Researcher	
Name	**Hyeun Wook Chang**
Institution / Department	**Yeungnam University/ College of Pharmacy**
Position	**Professor**

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

Name	Institution/Department	Position
Yoshitaka Taketomi	Tokyo Metropolitan Institute of Medical Science/ Lipid Metabolism Project	Research Staff
Hiroyasu Sato	Tokyo Metropolitan Institute of Medical Science/ Lipid Metabolism Project	Post-doctoral fellow

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

Name	Institution/Department	Position
Jong Keun Son	Yeungnam University/College of Pharmacy	Professor
Meihua Jin	Yeungnam University/College of Pharmacy	Professor
Seung Lark Hwang	Yeungnam University/College of Pharmacy	Post-doctoral fellow
Yue Lu	Yeungnam University/College of Pharmacy	Graduate student
Li Xian	Yeungnam University/College of Pharmacy	Graduate student

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
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 3 persons FY2010: Total 3 persons			

b. from Korea to Japan

Name	Home Institution	Duration	Host Institution
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 1 persons			

6. Objective of Research

Mast cells play important roles in allergy and other diseases such as autoimmune and metabolic diseases. Mast cells are derived from hematopoietic progenitors in bone marrow, and after residing in extravascular tissues, they differentiate into mature mast cells in a tissue-specific manner. There, mast cells release a wide variety of inflammatory mediators such as histamine, lipid mediators and cytokines in response to FcεRI crosslinking or to other microenvironmental stimuli. Because numerous people in both countries suffer from allergic diseases, understanding of the regulatory mechanisms for maturation and activation of mast cells is of particular importance. In this joint project, we aim to look for new low-molecular-weight compounds that are capable of inhibiting mast cell functions. The Korean team performs screening of a library for a wide array of natural compounds (from oriental herbal medicines traditionally used in Korea) and their derivatives to evaluate their effects on mast cells *in vitro*. Subsequently, the Japanese team identifies their molecular targets by means of transcriptome and metabolome approaches, and also examines their efficacies to inhibit mast cell-associated allergic diseases *in vivo*. These approaches lead to the discovery of novel cellular factors that are involved in mast cell-related biological events and to the development of novel drugs for allergy or other mast cell-associated diseases.

7. Methodology

An advantage of the Korean team is that this group has a library of a number of low-molecular-weight natural compounds (originated from oriental herbal medicines) and their lead derivatives. Interestingly, the Korean team has recently found that some of these compounds have the ability to potently inhibit mast cell activation. This suggests that the library represents a nice resource to search for novel classes of anti-allergic agents.

In this joint project, the Korean team carries out global screening of a library of natural products and their lead derivatives to select particular classes of compounds that could attenuate mast cell maturation or activation *in vitro*. Positive compounds screened as such may include those inhibiting mast cell degranulation, lipid mediator synthesis, and cytokine expression. Parameters to evaluate the inhibition of mast cells include their effects on 1) granule exocytosis (degranulation), 2) synthesis of lipid mediators (PGD_2 and LTC_4), 3) cytokine/chemokine production, and 4) signal transduction molecules involved in the receptor proximal events, such as activation of *Src* family kinases and *syk* kinase, PLCγ-mediated phosphoinositide signaling and Ca^{2+} influx, as well as downstream signaling pathways, including phosphorylation and activation of the components in the PI3K pathway, Ras/MAPK pathway, NFκB pathway, NFAT pathway, and so on. These analyses underscore the specific target pathways affected by the compounds at a cellular level.

The positive compounds from this screening are supplied from the Korean team to the Japanese team. Then, the Japanese team perform (i) transcriptome analysis (DNA microarray) to unveil the global effects of the compounds on gene transcription in mast cells (1^{st} year), (ii) lipid metabolome analysis (mass spectrometry) to comprehensively understand the effects of the compounds on lipid metabolism in mast cells; and (iii) animal studies to address the effects of the compounds on various models for mast cell-associated diseases. All information from these approaches are returned to the Korean team for further analyses of molecular interactions between the compounds and the specific cellular targets, which may lead to identification of novel cellular factors that control mast cell maturation and functions. The Korean team also synthesizes additional lead compounds with more potent and specific activity toward mast cells, and their effects are re-evaluated by the Japanese team through the same strategies.