

**JSPS Core-to-Core Program**  
**FY2007 Implementation Plan (Project No. : 1 6 0 0 3 )**

**Research Theme** Advanced Molecular Pathophysiology of Bone and Cartilage Diseases  
**Duration of Project** 2006 / 4 / 1 - 2009 / 3 / 3 1 ( 36 months)  
**Core Institution in Japan (Co-Chair)** Tokyo Medical and Dental University  
( Pro . Masaki Noda )

**Implementing Organizations**

**Japan**

Japan	Core Institution	Tokyo Medical and Dental University	
	Co-Chair (name and title)	Masaki Noda,MD . Ph.D,Professor	
	Cooperating Institutions	The University of Tokyo	Number of Cooperating Institutions 1

**Partner Countries**

USA	Core Institution	Harvard University	
	Co-Chair (name and title)	Henry M.Kronenberg,M.D.,Professor	
	Cooperating Institutions	Harvard Medical School Stanford University University of Dayton	Number of Cooperating Institutions 3

Canada	Core Institution	University of Toronto	
	Co-Chair (name and title)	Jane E. Aubin ,Ph.D.,Professor	
	Cooperating Institutions		Number of Cooperating Institutions 0

Austria	Core Institution	Institute of Molecular Pathology, University of Vienna	
	Co-Chair (name and title)	Erwin F. Wagner,Ph.D.,Professor	
	Cooperating Institutions		Number of Cooperating Institutions 0

## Objectives of Research Exchange (including the five years after the project finishes)

Bone and joint diseases are major issues in advanced countries. Quality of life of the individuals is dependent on the locomotor function. Although the longevity of life has been prolonged in many advanced countries, question is how the individuals are active during the full period of life. Our objectives are to focus on the development of research activities to tackle these problems of locomotor function in aged population. First, osteoporosis would be targeted by working on the possible anabolic function of parathyroid hormone (PTH) and to elucidate the mechanisms of action of this hormone in order to identify new therapeutic measures to increase bone mass after the patients lose bone mass significantly. The part research regarding PTH and its action would be established by the collaboration between Japan and the United States. The second issue of bone and joint research disease area is how to regenerate bone mass from the mesenchymal stem cells. In order to address this point stem cell research would be developed as a joint research program between Japan and Canada especially with respect to identify the molecules which form niche to provide environments to harness stem cells. The PTH studies will also touch on the stem cell parts especially with respect to the niche formation by osteoblastic cells which are regulated by PTH receptors. Thirdly, osteoblastic differentiation will be studied by analyzing the function of transcription factors including AP1 family members and this part would be conducted based on the collaboration between Austria and Japan. In addition, we will be working on the possible collaboration on the osteoblastic and osteoclastic research with respect to nuclear receptor function in Japan between Tokyo Medical and Dental University and University of Tokyo. For the future, after the current program is completed, these basis of the research on the new measures to resume bone and cartilage will be continued to further enlarge the research scopes as well as to raise the young generations in bone and joint research communities.

## Results to the present

Up to this point, we have a strong tie in terms of the research on parathyroid hormone actions. This part of the study has been under the collaboration between Harvard University and Tokyo Medical and Dental University especially with respect to the function of PTH receptor in osteoblastic cells. Since osteoblastic cells are responding to mechanical stress and loss of such physical environment strongly disturb the function of these cells, we have focused on the signaling of PTH in terms of the regulation of osteoblastic function under the loss of mechanical stress. We found that unloading condition should reduce bone mass in wild type mice while such reduction was blocked by the presence of constitutively active receptor for PTH. Analysis of bone formation and bone resorption to sort out the reason for this mechanism revealed that suppression of bone formation was observed regard of the presence the constitutively active PTH receptor. On the other hand, bone resorption unloading was paradoxically increased by the presence of constitutively active PTH receptor. This reversal appears to be contributing to the preservation of bone under the unloading condition. Extracellular matrix biology research has also been carried out as collaboration between Canada and Japan. Osteopontin protein function has been known to vary depending on the micro environment. We examined the function of OPN in the background of anabolic signaling and found that this RGD containing molecule appears to be a negative regulator for the function of osteoblastic cells or stem cell population. With respect to the transcriptional regulation of osteoblastic differentiation, we have established that one of the AP1 transcription factors exerts unforeseen regulatory function in the network of the AP1 family members. This work has been done in collaboration with Austria group and exchange of the research resources has been successfully promoted. We have published an abstract in the American Society for Bone and Mineral Research. In summary, in the last couple of years of Core-to-Core Program we developed efficient collaboration among the four countries including Japan, United States, Canada and Austria. The research teams in each of the countries collaborated together and we established the significant progress in terms of understanding bone and cartilage physiology which would lead to the development of new ideas and measures for the diseases in this field.

## Summary of FY 2007 Exchange Plan

### **Joint Research**

Based on the discoveries that PTH receptor modulates important function of osteoblastic cells such as the response to mechanical stress (collaborative research was published in Journal of Biological Chemistry 2007). We will expand the research on the PTH actions in formation of the niche which is also possibly the target of the mechanical stress as matrix molecules and osteoblastic cells are considered to be sensitive to such physical stimuli. We will proceed how the stem cells and their micro environment would be regulated by the physical forces. This research aspect would be conducted in collaboration with the stem cell research group in Canada and cell fate determination research group in Austria. In 2007, research projects would be promoted as conversion of these four advanced countries to concentrate their research actions on the cell biology of osteoblastic and chondrogenic stem cells.

### **Seminar**

We will be organizing an international symposium where the representatives of the United States, Japan, Austria and Canada will get together. We will have a strong interaction between bone research activities in these four countries. The Senior and Young researchers of American, Canadian and Austrian Society for Bone and Mineral Research will interact each other. We will also contemplate a joint research between Japanese groups and Canadian group as part of the advanced bone and joint research program. We will have joint seminars where the representatives of both countries will present their data in Tokyo. In addition, we will have another joint seminar in Canada (Halifax) where The Canadian and Japanese representative will discuss the science and the future development of the international tie to expand our Core-to-Core Program for the future. These seminars will be conducted so that senior researchers and young researchers in Canada and Japan will have more close interaction. Between Japan and the United States we will have a senior investigator conference and young investigator network. In Japan we will have a workshop for the young investigators and in addition we will organize a young investigator net discussion in the United States to let the individual young Japanese students to meet the top United States scientists at the conference style in the United States.

### **Researcher Exchanges**

In 2007, Japanese scientists and Canadian scientists will send their young investigators to each other. Canadian research society will invite Japanese senior scientists to their meeting to exchange knowledge and establish relationship between their researchers of these two countries. Austrian bone research society members and Japanese researchers will get together in Bone and Mineral Research Society Meeting to make a strong interaction between the Austrian young scientists and Japanese research scientists. American bone research group members will participate in the Japanese conference and young American scientists will be supported by the American fund to establish this researcher exchange. Japanese young scientists will be sent to the partner countries to exchange their research experience in the United States. More than handful of the Japanese young researchers will be sent based on the funding of Core-to-Core Program to interact with researchers in the United States.