JSPS Core-to-Core Program
FY2008 Implementation Plan (Project No. : 16003)

Research Theme Advanced Molecular Pathophysiology of Bone and Cartilage Diseases
Duration of Project 2006／4／1 － 2009／3／31 (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)

In our modern aging society, bone and joint diseases are becoming more critical issues. Skeletal tissues are under the control of remodeling and modeling and could be lost due to the impairment in the balance between bone formation and bone resorption in the aged population. Bone mass decreases along with age, especially in women after menopause. At the same, osteoarthritis is coming to be another major issue because of its pain and disability for the locomotion. Our objective is to understand the molecular mechanisms underlying the bone loss, osteoarthritic changes, and repair of the injuries. In the first place, bone loss due to the imbalance between bone formation and bone resorption should be corrected by the intervention with drugs. One of the popular drugs used currently is the inhibit one for bone resorption. However, the efficacy of these inhibitors for bone resorption still is limited to prevent the fracture and reduce the fracture rate by 50 % at most. Therefore, parathyroid hormone and other bone formation stimulators are needed in the future treatment. In this program, we are focusing the action of parathyroid hormone as part of the collaboration studies among the countries including Japan, United States, Canada and Austria. The mechanisms of the function of anabolic agents are to enhance the bone formation through the activation of the mature cells but also promote the differentiation from the mesenchymal stem cell pool. Therefore, stemness of the cells in bone is also an issue of our focus. Most importantly, the mechanisms of differentiation of both bone forming osteoblasts as well as bone resorbing osteoclasts are controlled by the interaction among the cytokines and transcription factors. Our will focuses on the understanding of the function of transcription factors which are operating in these cells. These three major targets are the bases of our internationally collaborative studies in this program now and in the future.

Results to the present

Anabolic actions of PTH have been well understood. However, the mechanisms of such action have not yet been fully understood. Our collaborative studies between Japan, United States, Canada and Austria as well as the institutes in Tokyo Medical and Dental University and University of Tokyo have been focusing in the action of such anabolic agents including PTH and cytokines. Osteoblasts and osteoclasts are the main cells to participate in the regulation of bone mass. With respect to osteoblasts, our collaborative studies indicated that constitutively active parathyroid hormone receptor mutant has shown to enhance the bone formation as well as bone resorption with a positive balance for bone formation. In terms of the bed-ridden patients, loss of mechanical stress reduces bone mass. Presence of constitutively active parathyroid hormone receptor signaling surprisingly suppresses bone resorption rather than activate it. This was the first indication that reversal of such signal could be under the control of mechanical stress. Furthermore, the mechanical stress could be mediated through the action or the properties in extracellular matrix proteins. Our collaborative studies between United States and Japan elucidated that one of the bone matrix protein, osteopontin, is not only the

target of osteogenic action of PTH, but also inhibitory against bone formation action, forming a negative feedback loop. With respect to the activation of the bone formation, JunD, one of the AP-1 proteins, is also playing the role for the negative signal and determining the basal levels of bone mass. Deletion of estrogen induces the bone mass through the activation of bone resorption and then also activation of bone formation. This is less than the activation for osteoclasts. The presence of JunD would suppress the levels of the bone mass through the reduction of in vivo function of osteoblasts. This was revealed by the decrease in formation rate. This transcription factor, JunD, also suppresses the levels of bone resorption through its action on osteoclasts. Therefore, ovariectomy induced loss of bone is under the control of such suppressive activity of this transcription factors for both bone formation and bone resorption. Control of such action identified through these studies can be pursued under the collaboration between Japan, United States, Canada and Austria. We have published these works as abstracts as well as journals, as a main part of the establishment of our work through this core-to-core program.

Summary of FY 2008 Exchange Plan

Joint Research

We will be conducting the analysis further on the action of the anabolic agents (parathyroid hormone) to understand the nature of its action in terms of the maintenance of bone. As we have already seen that PTH activities and signaling appear to interact with the mechanical stress as well as matrix protein (osteopontin), we will further pursue whether such interaction could be translated into the recovery of the bone after the injury. This will be pursued by the joint action between Harvard, United States and Tokyo Medical and Dental University, Japan. With respect to the stem cells and niche, we will be pursuing the activities of the matrix proteins to hold the stem cells onto its surface and deliver the signal of OPN to bone cells under the control of the systemic activities such as nervous system. We will be conducting the manipulation studies of the nervous system and examine its effects on the properties of stem cells and osteoblasts in bone through the collaboration between Japan and Canada. With respect to the transcriptional regulations, we will be conducting the studies on the interplay between the AP-1 transcription factors and attachment dependent transcriptional signals and will focus on the activities of interaction in the maintenance of bone mass. These parts of studies will be conducted through the collaboration between Japan and Austria.

Seminar

In this fiscal year, we will be conducting the international symposium to be held in Tokyo, Japan as collaborative activities between Japan, United States, Canada and Austria. For this symposium, all the main coordinators in each of the countries including Harvard University (Professor Kronenberg), University of Toronto (Professor Aubin) and Institute for Molecular Pathology, Vienna (Professor Wagner) will be participating in the discussion and presentation of forefront knowledge and discoveries in the area of bone and cartilage research. We will also conduct the collaboration between the senior researchers as well as the trainees in our activities between the senior and young generations. Young investigator network will be conducted to put together the activities of the young generations in Japan, United States, Canada and Austria to have the interaction for the mutual exchanges of knowledge as well as the sorts and technologies.

Researcher Exchanges

For the midterm, as a part of the exchange program, we will be sending our young investigators to the collaborative countries. They will train themselves in their international setting to learn further the specific expertise in the partner countries and to develop ties among young researchers.