

Project No. : 16003
Core Institution in Japan: Tokyo Medical and Dental University

**JSPS Core-to-Core Program -Strategic Research Networks-
FY2007 Research Report**

Project No.	16003
Research Theme	Advanced Molecular Pathophysiology of Bone and Cartilage Diseases
Duration of Project	3
Core Institution in Japan	Tokyo Medical and Dental University

Implementing Organizations

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

Country	United State of America
Core Institution	Harvard University
Co-Chair (name and title)	Henry Kronenberg, Professor
Number of Cooperating Institutions	3
Cooperating Institutions	Harvard Medical School Stanford University University of Dayton
Matching Fund	NIH

Country	Canada
Core Institution	Tronto University
Co-Chair (name and title)	Jane E Aubin, Professor
Number of Cooperating Institutions	0
Cooperating Institutions	
Matching Fund	Canadian Arthritis Network

Country	Austria
Core Institution	Institute of Molecular Pathology
Co-Chair (name and title)	Erwin Wagner, Deputy Director
Number of Cooperating Institutions	0
Cooperating Institutions	
Matching Fund	Austrian Academy of Science

Result of Program Implementation

In the fiscal year of 2007, we carried out our research on the mechanisms underlying the bone and cartilage diseases. This was done as pursued in the collaboration studies between Japan, United States, Canada and Austria. In these collaborative studies, we were focusing on bone anabolic agents especially parathyroid hormone using transgenic mice harboring the gene which was mutated to form constitutively active receptor. Analysis of the signaling being given by such constitutively active receptor, unraveled important mechanisms underlying the bone loss due to unloading as well as the interaction between the hormonal signaling and matrix signaling. As to the collaboration with respect to matrix proteins, knockout mouse studies using the matrix protein deficient animals and the analysis of the stem less of the cells have been proceed. AP (Activator Protein)-1 was also another target of the studies and the collaboration studies were established among the participating countries to discover the new roles of the transcription factors in the maintenance of the bone mass as well as its role in the pathological situations such as the model of postmenopausal osteoporosis.

In addition to the collaborative studies, symposiums and seminars have been also held and these contributed to the dissemination of the world top class scientific information regarding the research achievements on bone and cartilage diseases. Furthermore, educational programs for the young generations including young investigator net and the structures to raise young scientists being led by senior investigator collaborations were efficiently implemented during the period of 2007.

Achievements in FY2007 (Self Review)

We have established main 3 streams of the activities of core-to-core program in 2007. First of all, with respect to the collaborative studies, we have discovered brand new phenomena of bone in the case of disuse osteoporosis model. It has been known that the patients who have been bed ridden for a long term lose bone quickly. The number of patients of such bed ridden situation in Japan has been these days due to the increase in the aged population as well as the associated increases in the diseases of heart and brain. Due to the loss of mechanical stress, bone is usually lost based on the increase in bone resorption and decrease in bone formation. However, in collaborative studies between participating countries in this core-to-core program, we have first discovered the fact that the constitutive activation of the signaling of PTH could reverse the events due to the unloading to increase the bone mass. This is a surprising observation and also is one of the great steps to set up a target molecule for the future treatment of the bone and joint diseases. We have also discovered in the collaborative studies a new central nervous system-related molecules which are governing the bone mass in the whole body system.

Secondly, we have successfully set up a series of seminars based on international collaboration among Japan, United States, Canada and Austria. These seminars have been conducted by the senior researchers from each of the countries and importantly, the expenses of these seminars or the transportation were funded by the agencies of the partner countries. Most importantly, we held a major collaborative symposium between Japan and Canada, where Canadian senior researchers as well as young researchers participated based on Canadian funding. Moreover, the program of this joint symposium was also supported by the participation of the administrative officers from Canada, as well as the representatives of the association of patients who are suffering from bone and joint diseases. Young investigators in Japan as well as United States and whole world including Europe participated in this symposium and workshop and presenting the cutting edge research results. The information presented in the meeting were not only stimulatory to the seminar research scientists but also educational for the young scientists in Japan who came from almost all over Japan. Thirdly, the young generation was highly educated through the interaction between the senior and young scientists and also through the participation of the seminars and symposium. Moreover, the mid-term program for two months stay was conducted to send young talented Japanese scientist to stay in Harvard in the United States to work together with the researchers from two countries. This was highly successful to have a strong tie between the countries and also to promote the research collaboration in the new area based on the fusion of our expertise.

Future Plan (Measures toward Achieving Research Objectives)

To tackle the problems of the bone and joint diseases, one way is to polish up our collaborative studies between Japan, United States, Canada and Austria, with respect to the enhancement of bone mass, and analysis of the mechanism for the degenerative diseases of the joints, and basic science underneath the development and the differentiation of bone cells. For the year of 2008, we will be concentrating our efforts on the aspects of the transgenic mice of the PTH signaling how the intra cellular signaling could lead to the enhancement of bone mass through activation of the cells, in association with the signals from the extra cellular matrix. This would be also examined with respect to the upstream a regulatory molecules such as transcription factors, and all of these levels of research on the regulation including hormone, extracellular matrix and transcription factor would not be possible without our collaboration among these four countries and participation of our university as well as the collaborative universities such as University of Tokyo Medical School and Molecular and Cellular Biology Institute. We will be exchanging our resources including new types of transgenic mice or knockout mice and crossing out our mice to specifically manipulate the gene activities in osteoblasts or osteoclasts and pursue the mechanisms which would be involved in establishing diseases. We will most focus on the origin of the diseases being driven by the cells which are coming from niche in the bone and will try to utilize our discoveries and knowledge on the function of the molecules to eventually regenerate the tissues of bone cartilage. For this part, our collaboration will be further expanded not only including the currently involved members but also the people who are closely associated within this field of bone and cartilage research. With respect to the symposium and the seminars, we will hold a third workshop for the young investigators in bone and joints, and also we will have a symposium on the diseases of joint and bone in more clinical point of view this year, again in collaboration among Japan and the western partner countries, especially Canada, the U.S and Austria. For the sake of the generation of the system to raise the young scientists, we will have seminars and a symposium to be a place for the young generation to learn and to be trained. We will also continue our endeavors to individually train young people by the senior investigators from Japan and the partner countries. This has been proven to be very effective measures not only based on the scientific training and education but also expanding the personal ties between the young generations of the partner countries but also beyond the walls of ages between seniors and young scientists. We will have a midterm long training program, if it is possible, to continue that tie between Japan and United States or Canada. Through these three activities including the collaborative scientific studies on bone and joints as well as symposium seminars and the training programs for the young generations, we will fully pursue the goal of the core-to-core program for bone and joint diseases.