(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 O 6. Medical Science 7. Humanities & Social Sciences

1. Research Title:

Use of a new polymyositis model for development of specific treatment

2. Term of Research: From 7/1/2009 To 6/30/2011

3. Total Budget

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

1st Year 800 thousand yen 2nd Year 1,200 thousand yen

3rd Year 400 thousand yen

b. Other Financial Support : Total amount: 0 thousand yen

4. Project Organization

a. Japanese Principal Researcher	
Name	**Hitoshi Kohsaka**
Institution / Department	Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences, Department of Medicine and Rheumatology,
Position	Associate professor,
b. Korean Principal Researcher	
Name	**Yeong Wook Song**
Institution / Department	Seoul National University, Department of Internal Medicine Division of Rheumatology
Position	Professor

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

Name	Institution/Department	Position
Naoko Okiyama, M.D.	Tokyo Medical and Dental University	Postdoctoral fellow
Shinya Hirata, M.D., Ph.D.	Tokyo Medical and Dental University	Assistant professor

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

Name	Institution/Department	Position
Eun Bong Lee, MD, PhD	Department of Internal Medicine, Seoul National University College of Medicine	Associate Professor
Eun Young Lee, MD, PhD	Department of Internal Medicine, Seoul National University College of Medicine	Assistant Professor
Jinhyun Kim, MD	Department of Internal Medicine, Seoul National University College of Medicine	Fellow in Rheumatology

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
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 3 persons FY2010: Total 3 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 4 persons FY2010: Total 3 persons			

6. Objective of Research

C-protein-induced myositis (CIM) mouse model of polymyositis we developed has following advantage:

1) Muscle damage is mediated by CD8 cytotoxic T lymphocytes (CTL) just like human PM.
2) Myositis can be induced in C56BL6 mice, which are the background strain of numerous gene mutant mice (knock-outs and transgenics).
3) It can be induced by single immunization of recombinant C protein fragment, which is readily prepared with E coli. expression system.
4) Disease activity can be assessed with histology (figure) as well as with MRI scan.
5) Its responses to therapeutic interventions appeared similar to that of human PM; High-dose intravenous immunoglobulin infusion is effective both in PM and CIM. (Arthritis Rheum 2007)

Another unique feature we will make use of in the present studies lies in the fact that adoptive transfer of lymph node CD8 T lymphocytes from CIM mice to naïve mice can transfer myositis. In this adoptive transfer model, therapeutic intervention can be applied to

A) Donor mice to suppress development of autoreactive CTL that damage the muscles.
B) Recipient mice to suppress recruitment and cytotoxicity of CTL to the muscle tissues.

Our previous observation demonstrated that PM patients treated successfully with conventional treatment still had expansion of muscle-damaging CTL in the peripheral blood (Nishio et al. J Immunol 2001). This suggests that suppression of the autoreactive CTL recruitment can be the essential goal of the treatment.

Objective of the present study is to elucidate the differential roles of cytokines and chemokines in development and recruitment of the autoaggressive CTL. First, we will transfer techniques to induce and evaluate CIM to Dr. Song's laboratory. Next, using specific antibodies and knock-out mice, cytokines and chemokines will be evaluated. Attraction of CTL by IP-10 and fractalkine is of particular interest. Expression of these cytokines in human PM/DM will be also evaluated.

7. Methodology

The first phase

1) Following techniques will be transferred to Dr. Song's laboratory
   I. Preparation of immunogen: recombinant C protein fragments and complete Freund's adjuvant should be emulsified carefully to induce CIM.
   II. Immunization: the footpads and limb base should be the site of injection to avoid artifact in muscle pathology.
   III. Evaluation of pathology: muscle tissues should be fixed properly for microscopic studies.

The second phase

2) Antibodies reactive to chemokines and cytokines will be administered to CIM mice.
   I. Inflammatory cytokines will be focused in Japanese side.
   II. Chemokines including IP-10 and fractalkine will be focused in Korean side.
3) Cytokine/chemokine knock-out mice will be evaluated for susceptibility to CIM.
4) Techniques relating to the adoptive transfer model will be shared with both sides.
5) IP-10 and fractalkine expression in serum and muscles from PM/DM patients will be evaluated.

Related techniques will be transferred to each other.

The third phase:

6) Antibodies to chemokines and cytokines will be administered to naïve mice to prevent adoptive transfer of CIM (Protocol I: Recipient treatment).
7) The same antibodies will be administered to donor mice to inhibit autoagressive CTL (Protocol II: Donor treatment).

Treatment effective in Protocol I but not in II should be the specific treatment that inhibits recruitment of CTL into the muscles and is superior to general immunosuppressive treatment currently employed in clinical settings.