BIOGRAPHICAL SKETCH

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NAME: Takeshi Utsunomiya, M.D., Ph.D.

eRA COMMONS USER NAME: TAKESHI UTSUNOMIYA

POSITION TITLE: Postdoctoral Research Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Nagasaki University, School of Medicine (Nagasaki, Japan)	M.D.	03/2009	Primary medicine
Department of Orthopaedic Surgery, Kyushu University, School of Medicine (Fukuoka, Japan)	Residency	03/2015	Orthopaedic surgery
Graduate school of Kyushu University, School of Medicine (Fukuoka, Japan)	Ph.D.	03/2019	Biomechanics of hip joint
Department of Orthopaedic Surgery, Goodman laboratory, Stanford University, School of Medicine (CA)	Postdoctoral Research Fellow	Present	Orthopaedic tissue engineering

A. Personal Statement

In my time in the United States, I have learned to collaborate with and manage people of many different professional and cultural backgrounds. Thus, I am prepared to make the connections necessary to help this project succeed. I have also worked on projects from the initial, *in vitro* cell stages to *in vivo* animal models, not only to investigate their mechanisms and confirm their reproducibility, but also to ensure their ability to translate into human models. I have the expertise, training, leadership and motivation necessary to successfully carry out the proposed research project. I have a broad background in the field of Orthopaedic surgery, with specific expertise in the biomechanics of the hip joint. In addition, I am doing basic research at Stanford University to treat chronic inflammation and bone loss (periprosthetic osteolysis), which is one of the most serious and unsolved problem in the field of total hip arthroplasty (THA). My research combines perspectives in osteoimmunology, bone microstructure, histopathology and genetic modifications of mesenchymal stem cells (MSCs). As Collaborator on a NIH-funded grant, I have already laid the groundwork for the proposed research by clarifying the pathophysiology of osteolysis and developing effective and innovative treatments for osteolysis using genetically modified MSCs that sense Nuclear Factor kappa B (NF-kB) and secrete Interleukin-4, leading to mitigate chronic inflammation in our established murine continuous polyethylene particle femoral intramedullary infusion model. Platelet-Derived Growth Factor-BB (PDGF-BB) is an anti-inflammatory cytokine and chemokine that enhances endothelial progenitor cell and MSC migration and differentiation, leading to enhanced angiogenesis and osteogenesis. Recently, we have developed genetically modified MSCs that sense NF-kB signaling and overexpress PDGF-BB (PDGF-BB MSCs). In the context of these recent experiences, I am strongly motivated to address the unsolved issues of osteolysis from the aspects of basic research using our PDGF-BB MSCs, with frequent communication among project members and constructing a realistic research plan, timeline, and budget.

B.Positions and Honors

Positions and Employment

2009 Passed the Examination of National Board (M.D.) in Japan
2009-2010 Resident in Nagasaki University Hospital (Nagasaki, Japan)
2010-2011 Resident in Kitakyushu General Hospital (Fukuoka, Japan)
2011-2012 Resident of Orthopaedic surgery in Miyazaki Prefecture Miyazaki Hospital (Miyazaki, Japan)
2012-2013 Medical Staff of Orthopaedic surgery in Shimonoseki City Hospital (Yamaguchi, Japan)

2013 Medical Staff of Orthopaedic surgery in Kasuya Shinko-en Children's hospital (Fukuoka, Japan)
2013-2014 Medical Staff of Orthopaedic surgery in Kyushu University Hospital (Fukuoka, Japan)
2014-2015 Medical Staff of Orthopaedic surgery in Kyushu Rosai Hospital (Fukuoka, Japan)
2015-2019 Graduate school in Dept. of Orthopaedic Surgery (Ph.D.) in Kyushu University (Fukuoka, Japan)
2019- Postdoctoral research fellow in Dept. of Orthopaedic Surgery, Goodman laboratory at Stanford University (CA)

Other Experience and Professional Memberships

2011- Member, Japanese Orthopaedic Association
2014- Member, Japanese Hip Society
2016- Member, American Academy of Orthopaedic Surgeons
2016- Member, Orthopaedic Research Society

C. Contributions to Science

1. Clarification of the mechanism of femoral head collapse in patients with osteonecrosis:

My early research focused on elucidating the mechanism of hip osteonecrosis, with particular focus on the collapse of the femoral head. Femoral head collapse is challenging to predict, due to the asymptomatic nature of the preceding states, and is a high cause of morbidity amongst osteonecrosis patients. Based on MicroCT data of patients after femoral head collapse, I was able to characterize the fact that collapse always involved the lateral necrotic boundary and create a hypothesis that stress concentration around the lateral necrotic boundary caused femoral head collapse. I then tested this hypothesis by generating a computational model that incorporated stress concentration on various parts of the femoral head before collapse, and was able to prove that the sheer stress was concentrated around the lateral necrotic boundary with sclerotic changes, leading to femoral head collapse in patients with osteonecrosis. I also complemented this with histological data of collapsed femoral heads that proved that the disruption of the subchondral bone plate corresponded to the area where the shear stress was concentrated as demonstrated by the model. This research culminated in several papers and presentations, and has allowed prediction of femoral head collapse in osteonecrosis patients, and to therapeutic recommendations in a previously unpredictable pathology.

Publications:

1.1. **Utsunomiya T**, Motomura G, Ikemura S, Kubo Y, Sonoda K, Hatanaka H, Baba S, Kawano K, Yamamoto T, Nakashima Y. Effects of Sclerotic changes on stress concentration in early-stage osteonecrosis: A patient-specific, 3D finite element analysis. J Orthop Res. 2018; 36(12):3169-3177.

1.2. Baba S, Motomura G, Ikemura S, Kubo Y, **Utsunomiya T**, Hatanaka H, Kawano K, Nakashima Y. Quantitative evaluation of bone-resorptive lesion volume in osteonecrosis of the femoral head using micro-computed tomography. Joint Bone Spine. 2019 Sep 12. pii: S1297-319X(19)30123-X.

1.3. Kubo Y, Motomura G, Ikemura S, Sonoda K, Hatanaka H, **Utsunomiya T**, Baba S, Nakashima Y. The effect of the anterior boundary of necrotic lesion on the occurrence of collapse in osteonecrosis of the femoral head. Int Orthop. 2018; 42(7):1449-1455.

1.4. Hatanaka H, Motomura G, Ikemura S, Kubo Y, **Utsunomiya T**, Baba S, Kawano K, Nakashima Y. Differences in magnetic resonance findings between symptomatic and asymptomatic pre-collapse osteonecrosis of the femoral head. Eur J Radiol. 2019. 112:1-6.

2. Clinical and radiologic research in patients with osteonecrosis and other hip diseases:

My later research was clinically focused on the proceeding steps of osteonecrosis and on the diseases that required differential diagnosis, such as subchondral insufficiency fractures of the femoral head (SIF). Patients with osteonecrosis often progress to femoral head collapse, while some of the patients with SIF heal through conservative treatment. Thus, it is important to accurately diagnose and determine the desirable treatments in each patient. Patients with post-collapsed osteonecrosis are usually treated with total hip arthroplasty (THA) and/or joint osteotomy. A common joint preserving procedure in Japan after collapsed osteonecrosis of the hip joint is femoral osteotomy--however, due to the changed biomechanics of the joint after the procedure, a THA is sometimes necessary as well. There have been concerns about the success of a THA after osteotomy; by studying patient outcomes and radiological data, I was able to characterize the effectiveness of THAs directly after femoral head collapse versus after joint preserving surgery. As there was no appreciable difference found in the final patient outcomes, combined with the benefits of a prolonged native joint and delayed the timing of THA after osteotomy, this study allowed osteotomy to continue to be recommended as a treatment for

osteonecrosis. In addition, I was able to provide practical tips to ensure the success of a THA post-osteotomy, which was presented internationally as a set of formal recommendations.

Publications:

2.1. **Utsunomiya T**, Motomura G, Ikemura S, Hamai S, Fukushi JI, Nakashima Y. The Results of Total Hip Arthroplasty After Sugioka Transtrochanteric Anterior Rotational Osteotomy for Osteonecrosis. J Arthroplasty. 2017 Sep; 32(9):2768-2773.

2.2. **Utsunomiya T**, Yamamoto T, Motomura G, Hamai S, Iwamoto Y. The clinicopathologic findings of a subchondral insufficiency fracture of the femoral head in a male patient: a case report. Skeletal Radiol. 2016; 45:1425-1429.

2.3. **Utsunomiya T**, Yamamoto T, Motomura G, Karasuyama K, Sonoda K, Kubo Y, Hatanaka H, Iwamoto Y. The choice of locking plate in the treatment of peri-implant femoral fracture eight years after trans-trochanteric rotational osteotomy: A case report. Int J Surg Case Rep. 2016; 26:101-103.

2.4. Xu M, Motomura G, **Utsunomiya T**, Ikemura S, Yamaguchi R, Hatanaka H, Baba S, Kawano K, Nakashima Y. Traumatic subchondral fracture of the femoral head occurring concurrently with contralateral acetabular fracture. J Orthop Sci. 2019 Jun 14. pii: S0949-2658(19)30151-4.

Both of these research endeavors have successfully provided treatment recommendations for patients at different stages of osteonecrosis (a prevalent and yet poorly characterized and managed pathology) --prediction before femoral head collapse, and surgical intervention throughout the progression of osteonecrosis. I was able to centralize this research and increase its impact in my role as a co-investigator for the executive office of nationwide interdisciplinary research, which prioritized the development of an established treatment and innovative prophylaxis for osteonecrosis of the femoral head in Japan from 2015 to 2017. This nationwide, multi-center study strove to prevent the occurrence of osteonecrosis of the femoral head, and required me to collaborate with many people from different professional backgrounds. I was able to progress the project successfully while also managing other research projects at my home institution, and learned the importance of time management, collaboration, and how to logically progress a large research project. Colleagues have since been able to take this research, obtain new grants, and complete clinical trials regarding prophylaxis of osteonecrosis. All of these experiences have equipped me to pursue further investigations into related unsolved problems, such as osteolysis. These have also informed my current research into the pathologies that follow a THA, where wear particle generation from the implant causes chronic inflammation, leading to failure of the THA.

D. Research Support

Current Research Support

2R01AR06371706 (PI: Stuart Goodman) 08/01/2017 – 07/31/2022
NIH/NIAMS
Enhanced Bone Healing Around Implants by Transplanted NF-kB Driven Immunomodulating MSCs
Role: Collaborator
Overlap: None

Completed Research Support

16ek0109024h0003 (PI: Takuaki Yamamoto) 04/01/2014 – 03/31/2017
Practical Research Project for Rare / Intractable Diseases
Nationwide interdisciplinary research for the development of established treatment and innovative prophylaxis for osteonecrosis of the femoral head
Role: Collaborator
Overlap: None

16K10906 (PI: Goro Motomura) 04/01/2016 – 03/31/2019
Grants-in-Aid for Scientific Research
Pathophysiology for the prevention of femoral head collapse in osteonecrosis
Role: Collaborator
Overlap: None

16H07057 (PI: Satoshi Ikemura) 08/26/2016 – 03/31/2018
Grants-in-Aid for Scientific Research

The Role of vasospasm of the development of osteonecrosis of the femoral head
Role: Collaborator
Overlap: None