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The University of Osaka

Abstract of Thesis

Name （LEE Michelle Sue Jann）	
Title	*Plasmodium* products persist in the bone marrow and promote chronic bone loss （骨髄に残存するマラリア原虫生成物による慢性的骨量減少）

Abstract of Thesis

Although malaria is a life threatening disease with severe complications, most people develop partial immunity and suffer from mild symptoms. However, incomplete recovery from infection causes chronic illness, and little is known of the potential outcomes of this chronicity. Here, I found that malaria infection causes bone loss and growth retardation in mouse models as a result of chronic bone inflammation induced by *Plasmodium* products. Acute malaria infection severely suppresses bone homeostasis, but sustained accumulation of *Plasmodium* products in the bone marrow niche induces MyD88-dependent inflammatory responses in osteoclast and osteoblast precursors, leading to increased RANKL expression and over-stimulation of osteoclastogenesis favoring bone resorption. Infection with a mutant parasite with impaired hemoglobin digestion that produces little hemozoin, a major *Plasmodium* by-product, did not cause bone loss. Importantly, supplementation of alfacalcidol, a vitamin D3 analog, could prevent the bone loss. These results highlight the risk of bone loss in malaria-infected patients and the potential benefits of coupling bone therapy with anti-malarial treatment.

様式７

論文審査の結果の要旨及び担当者

氏　名	（　　LEE Michelle Sue Jann　　）		
		(職)	氏　　名
論文審査担当者	主 査	Professor	Cevayir COBAN
	副 査	Professor	NAGASAWA, Takashi
	副 査	Professor	YAMAMOTO, Nobuhiko
	副 査	Professor	ISHII, Ken

論文審査の結果の要旨

Title of thesis: Plasmodium products persist in the bone marrow and promote chronic bone loss

Ms. Michelle LEE has joined my laboratory as a MEXT Scholar at FBS, Osaka University to pursue MSc-PhD course and successfully completed her studies in 4,5 years. She has studied a very challenging subject, an interaction of Plasmodium parasites, causative agent of malaria disease, and bone cell interactions. Malaria is still an important disease in most of the world, causing acute as well as chronic complications, continuing its deleterious effects life time. In her study, Ms. Lee used mouse malaria models and immunological, biochemical, biological and imaging technologies to study the effects of malaria infection on bone. She found that malaria causes chronic bone loss. Even though infection is treated, malarial by-products including hemozoin accumulates in the bone marrow, captured by bone cells osteoclasts, stay long time and cause chronic inflammation in the bone, which leads a chronic activation of osteoclasts, skewing well-balanced bone remodeling in the favor of osteoclast activation. She has detailed underlying mechanisms of this phenomenon which is first time noticed by using immunological techniques and several lines of KO mice.

She has been very responsible for her project from the day of arrival to the Lab. She has developed many techniques first time and has worked independently. She has improved her knowledge and understanding enormously. She has gained ability to perform, think and present independently. She presented her findings several times in domestic as well as international meetings. We published her work in Science Immunology in June 2017. I believe she will continue to do a good science in future.

She has prepared her Defense with a great responsibility and enthusiasm, She presented her work in front of committee members very well and answered the questions. The committee members have judged her skills to prepare presentation, oral presentation, and the ability to answering questions. They were all satisfied for the amount of research she has performed and her deep involvement and thinking into the project. She performed well with the scientific questions and showed higher ability to give insights. Overall, she has obtained good comments and positive remarks from the all committee members.

I strongly believe that she well deserves to obtain a PhD degree.

Thank you for positive consideration.

Cevayir COBAN

August 29, 2017