Approved by the Regents
May 17, 2012

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

Akira Ono, Ph.D., assistant professor of microbiology and immunology, Department of Microbiology and Immunology, Medical School, is recommended for promotion to associate professor of microbiology and immunology, with tenure, Department of Microbiology and Immunology, Medical School.

Academic Degrees:

Ph.D.	1994	University of Tokyo
M.S.	1991	University of Tokyo
B.S.	1989	Waseda University

Professional Record:

2005–present	Assistant Professor of Microbiology and Immunology, University of Michigan

Summary of Evaluation:

Teaching: Dr. Ono is a dedicated and capable teacher of department courses for medical and graduate students. He teaches Microbiology 615, a literature-based graduate level course which focuses on cellular and molecular mechanisms of viral pathogenesis. He has also served as a small group leader in the Medical School course in infectious diseases (ID/Microbiology 500). He consistently receives strong evaluations from his students, who gave him good scores in their evaluations for his knowledge of the material and his level of preparation in the classroom. Written comments from students applauded his strengths in explaining material. His talent and commitment to teaching follows through in his training of students both in the department and around campus as well. He has attracted five graduate students, two undergraduate students and two postdoctoral fellows to train with him since he joined the faculty at Michigan. These students and fellows have successfully published their work in good journals and obtained honors, awards and opportunities for presenting their work at international meetings in the field. The students who graduated from his lab were each first author of two publications and second author of two more; and they obtained post-doctoral positions in prestigious institutions. Dr. Ono is sought after by students in other labs to serve on their thesis committees, having served on 14 of these, in addition to those of his students, since 2005. He serves on numerous student preliminary examination committees in several graduate programs. In addition to the graduate program in microbiology and immunology, he is a member of the training faculty for four interdepartmental graduate programs or training programs. He serves on advisory committees for two of those programs. Dr. Ono's commitment to the educational mission of the Medical School is exemplary.

Research: Dr. Ono's research has made significant contributions in retrovirus biology and pathogenesis. In the last 15 years, he has made major discoveries that have elucidated fundamental aspects of human immunodeficiency virus (HIV) particle assembly inside infected cells. As a staff scientist at the National Cancer Institute of the NIH, he studied HIV-1 Gag protein function and its interactions with membranes. One of his significant studies, published in *PNAS* in 2001, describes the importance of lipid rafts in HIV-1 assembly and virus infectivity. This research was the subject of press releases by NIH and the National Academy of Sciences and of numerous articles in the popular press around the world. While at the NCI, he published another *PNAS* paper which identified a role for the plasma membrane lipid phosphatidylinositol (4,5) bisphosphate ($PI(4,5)P_2$) as a specific cofactor for HIV-1 assembly. This was also heralded as a landmark study, which set the stage for his independent research career at the University of Michigan. In his laboratory in the Department of Microbiology and Immunology, Dr. Ono continued his studies of the mechanism of Gag-dependent targeting of replicating viruses to cellular membranes in infected cells. He secured funding for these projects in grants from the NIH and other agencies. The studies conducted in his laboratory have been published in high quality journals, including the *Journal of Virology, PNAS* and *PLoS Pathogens.* His laboratory first characterized the specificity of the interactions between the HIV-1 structural protein Gag and $PI(4,5)P_2$, excluding non-specific electrostatic charge interactions. From this molecular starting point, his research team discovered a previously unsuspected, complex mechanism by which lipids and RNA regulate specific localization of HIV-1 Gag to the plasma membrane. This introduced a new concept to the field of retrovirus assembly mechanisms in which RNA bound to a highly basic region of Gag limits $PI(4,5)P_2$-independent binding to cell membranes. Dr. Ono's group also discovered a key step leading to formation of virological synapses that facilitate cell-to-cell spread of HIV-1, namely that Gag targets HIV-1 assembly to T-cell uropods - tail-like cell protrusions of crawling cells - which interact preferentially with neighboring, uninfected T-cells. Here again, Dr. Ono's distinct, big-picture view of HIV biology introduced a new concept to retrovirus research. These and other ongoing studies will further the understanding of the replication of HIV-1 and other retroviruses at the cellular and molecular level, and will likely suggest new strategies for antiviral therapy.

Dr. Ono's lab has also adapted and improved technically advanced methods of quantitative microscopy. In collaboration with investigators at the Center for Live Cell Imaging in the Department of Microbiology and Immunology, his team used state-of-the-art methods for Förster resonance energy transfer (FRET) microscopy to quantify Gag assembly inside living cells. This allowed them to determine essential and auxiliary domains of Gag essential for virus assembly at cell membranes. His lab continues to develop new ways to visualize virus assembly quantitatively and at high resolution. His widely appreciated expertise has led to invitations to chair sessions or to speak at important meetings in the field of retrovirology, as well as to write review articles covering recent literature in the field of virus assembly mechanisms.

Recent and Significant Publications:

Inlora J, Chukkapalli V, Derse D, Ono A: Gag localization and virus-like particle release mediated by the matrix domain of human T-lymphotropic virus type 1 Gag are less dependent on phosphatidylinositol-(4,5)-bisphosphate than those mediated by the matrix domain of HIV-1 Gag. *Journal of Virology* 85:3802-3810, 2011.

Chukkapalli V, Oh SJ, Ono A: Opposing mechanisms involving RNA and lipids regulate HIV-1 Gag membrane binding through the highly basic region of the matrix domain. *Proc Natl Acad Sci USA* 107:1600-1605, 2010.

Llewellyn GN, Hogue IB, Grover JR, Ono A: Nucleocapsid promotes localization of HIV-1 gag to uropods that participate in virological synapses between T cells. *PLoS Pathogens* 6:e1001167, 2010.

Hogue IB, Hoppe A, Ono A: Quantitative fluorescence resonance energy transfer microscopy analysis of the human immunodeficiency virus type 1 Gag-Gag interaction: relative contributions of the CA and NC domains and membrane binding. *Journal of Virology* 83:7322-7336, 2009.

Chukkapalli V, Hogue IB, Boyko V, Hu WS, Ono A: Interaction between the human immunodeficiency virus type 1 Gag matrix domain and phosphatidylinositol-(4,5)-bisphosphate is essential for efficient gag membrane binding. *Journal of Virology* 82:2405-2417, 2008.

Service: Dr. Ono serves ably on faculty committees, bringing the same focus and insight to these activities as he does to his research and teaching. In the Department of Microbiology and Immunology, he has served on the Graduate Studies Committee, the Departmental Appointments, Promotions and Awards Committee and on the Faculty Search Committee for Cluster Hiring (Multi-scale Cell Mechanics hire). At the institutional level, Dr. Ono served on admissions committees, advisory committees and as *ad hoc* reviewer for the Michigan Institute for Clinical and Health Research. At the national and international levels, he served as a reviewer for several high-profile journals and as a guest editor or editorial board member for several other journals. He reviewed grant applications for several international research funding agencies. Thus, Dr. Ono's efforts are contributing in key ways to the future excellence of our mission.

External Reviewers:

Reviewer A: "Dr. Ono's contributions in the past and as an independent investigator at your institution have provided important insights into several aspects of retrovirus assembly and membrane interaction....I have no doubt that Akira will continue to be highly productive and contribute novel ideas to the field."

Reviewer B: "He is an established player in the field of membrane association of the HIV Gag proteins and virus budding; he has made a name for himself with defining the role of PIP2 in Gag associating with rafts and mediating budding..."

Reviewer C: "Given that retroviral assembly has been studied by highly competitive laboratories for many years, I am impressed by Dr. Ono's ability to consistently push the field further through significant new observations."

Reviewer D: "Dr. Ono is an internationally recognized retrovirologist with specific expertise in virus assembly. He is a leader in this field....Dr. Ono is an innovative leader in the area of

retroviral assembly who is internationally recognized for his accomplishments. He is productive, well published, and well supported by competitive research grants. His teaching and university service appear excellent."

Reviewer E: "...Dr. Ono has been one of the most influential and productive contributors to understanding the role of lipids in HIV budding."

Reviewer F: "Since starting his own lab at the University of Michigan in 2005, Akira has firmly established himself as a leading independent investigator in our field....In short I think Akira is well over the tenure bar, even at an outstanding institution like the University of Michigan."

Summary of Recommendation:

Dr. Ono has distinguished himself as an outstanding researcher who has earned the respect of his peers in the field and the admiration of his Michigan colleagues. He is a leader in a competitive and important field of research. He is clearly on a trajectory to make continued important observations in his research. He has made outstanding contributions in research, teaching and service, and he shows great promise for continued growth as a scholar and colleague. I am pleased, therefore, to recommend Akira Ono, Ph.D. for promotion to associate professor of microbiology and immunology, with tenure, Department of Microbiology and Immunology, Medical School.

James O. Woolliscroft, M.D.
Dean
Lyle C. Roll Professor of Medicine

May 2012