

May 17, 2007

PROMOTION RECOMMENDATION  
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL  
DEPARTMENT OF PHARMACOLOGY

Yoichi Osawa, Ph.D., Associate Professor of Pharmacology, with tenure, Department of Pharmacology, Medical School, is recommended for promotion to Professor of Pharmacology, with tenure, Department of Pharmacology, Medical School.

Academic Degrees:

Ph.D.	1987	University of Michigan
B.S.	1982	Massachusetts Institute of Technology

Professional Record:

2001-Present	Associate Professor of Pharmacology, University of Michigan
1995-2001	Assistant Professor of Pharmacology, University of Michigan

Summary of Evaluation:

Teaching: Dr. Osawa has made major contributions to teaching in the department and Medical School. He has participated in Pharmacology 500 (Principles of Pharmacology), Pharmacology 501 (Cardiovascular Pharmacology), Pharmacology 525, (Medical Pharmacology), Pharmacology 646 (Student Seminar Course), Senior Therapeutics, Pharmacology 659 (Pharmacology for Pharmacy and Nursing Program), and has been co-director of Pharmacology 611 (Principles of Pharmacology) since 2000. He has also taught in both the second- and fourth-year medical student courses and, in the first-year Pharmacology course, Dr. Osawa has given three hours of formal lecture each year, covering the topics of drug disposition and metabolism. Dr. Osawa has earned high marks in terms of his organization; his ability to make the material interesting; his enhancing student understanding; the provision of useful handouts; and the respect and professional behavior he exhibits to students. In all of the courses he has taught, Dr. Osawa has proven to be a superior teacher. He has also excelled in graduate student mentoring of pre- and postdoctoral fellows. He has supervised seven Ph.D. candidates and six postdoctoral fellows. His students have been highly productive with numerous publications in high quality journals.

Research: Dr. Osawa has been studying chemical mechanisms of inactivation of P450 enzymes since his undergraduate work at MIT. He has made significant contributions to the fields of cardiovascular pharmacology, drug metabolism, and gene regulation by addressing important scientific questions with an innovative and rigorous approach. His studies have resulted in the discovery that the cross-linking of the heme moiety of myoglobin to its apoprotein leads to the conversion of myoglobin from an oxygen-carrying molecule to that of an oxidase. He has also shown for the first time that some drugs may irreversibly inactivate nitric oxide synthase, which could be responsible for many of the side effects of these drugs. During his years at the University of Michigan, he has continued his work on mechanisms of chemical inactivation of

the neuronal nitric oxide synthase (nNOS-a P450 enzyme), but has also published seminal studies on the formation and degradation of the enzyme. His observations on the roles of the hsp90 chaperone system in formation of nNOS and the demonstration of ubiquitin-mediated proteolysis of nNOS are novel and have opened new directions for his work. In addition, Dr. Osawa has linked the heat shock proteins, Hsp 70 and 90, to heme-binding, activation, and regulation of nNOS and the oxidation state of tetrahydrobiopterin to nNOS ubiquitylation. He has been very productive since his arrival in the Department of Pharmacology with 34 peer reviewed publications. The great majority of these are in rigorous, high quality publications such as the *Journal of Biological Chemistry*. Dr. Osawa has also been highly successful in obtaining research grants. He currently has an RO1 from the NIGMS and another from NIDA. He previously received a Pharmaceutical Manufacturers Research Starter Grant, an established Investigator Award from the American Heart Association, and an award from the Burroughs Wellcome Fund.

#### Recent and Significant Publications:

Lee AJ, Noon KR, Jianmongkol S, Lau M, Jenkins GJ, Osawa Y: Metabolism of aminoguanidine, diaminoguanidine, and  $N^G$ -amino-L-arginine by neuronal NO-synthase and covalent alteration of the heme prosthetic group. *Chemical Research in Toxicology* 18:1927-1933, 2005.

Lowe ER, Everett AC, Lee AJ, Lau M, Dunbar AY, Berka V, Tsai A-I, Osawa Y: Time-dependent inhibition and tetrahydrobiopterin depletion of endothelial nitric-oxide synthase caused by cigarettes. *Drug Metabolism and Disposition* 33:131-138, 2005.

Peng H-M, Morishima Y, Jenkins GJ, Dunbar AY, Lau M, Patterson C, Pratt WB, Osawa Y: Ubiquitylation of neuronal nitric-oxide synthase by CHIP, a chaperone-dependent E3 ligase. *The Journal of Biological Chemistry* 279:52970-52977, 2004.

Billecke SS, Draganov DI, Morishima Y, Murphy PJM, Dunbar AY, Pratt WB, Osawa Y: The role of hsp90 in heme-dependent activation of apo-neuronal nitric-oxide synthase. *The Journal of Biological Chemistry* 279:30252-30258, 2004.

Billecke SS, Bender AT, Kanelakis KC, Murphy PJM, Lowe ER, Kamada Y, Pratt WB, Osawa Y: Hsp90 is required for heme binding and activation of apo-neuronal nitric-oxide synthase. *The Journal of Biological Chemistry* 277:20504-20509, 2002.

Service: Dr. Osawa has contributed significantly in the area of departmental service. He has served on both the Departmental Advisory Committee and on the Graduate Programs Committee. He has also contributed to student activities including the Midwest Pharmacology Colloquium and the Charles Ross Summer Student Fellowship. He is on the Steering Committee of the new Chemical Biology Training Program and he is Director of Biomedical Mass Spectrometry Facility. Dr. Osawa has substantial national and international recognition as evidenced by his extramural invited presentations and his election to the Executive Committee of the Drug Metabolism and Distribution Division of ASPET; his appointment to the International Advisory Board of Okayama University Medical School; and in 2006, his election as co-chair of

the organizing committee of the Great Lakes Metabolism Discussion Group. He has also served as ad hoc reviewer for a number of highly respected journals (*JBC*, *JPET*, *Analytical Biochemistry*, *Chemical Research in Toxicology*, and *Biochemistry*).

External Review:

Reviewer A: “Dr. Osawa is an acknowledged national/international leader in the area of drug metabolism and toxicology....over the past 11 years, Dr. Osawa has clearly demonstrated his ability to excel in his research accomplishment of his academic career. Dr. Osawa is a highly intelligent, enthusiastic, insightful, creative and practical-minded researcher with great insight in the field of Pharmacology and Toxicology. He is an exceptionally gifted scientist, able to approach questions from the chemical and molecular level, and to translate data obtained into novel insights.”

Reviewer B: “As an illustration of his vision and drive to do cutting edge science, the Biomedical Mass Spectrometry Facility (BMSF) that Dr. Osawa created and now heads is a tremendous resource not only for his own research program, but also for his colleagues and University of Michigan students. This facility is matched in only a few other premier institutions....I frequently point my students and postdocs to his papers not only for information and concepts that have direct bearing on our own research, but also as models of careful, rigorous and inventive science.”

Reviewer C: “...I consider Dr. Osawa’s scientific contribution to be very original, well thought out and executed, elegantly presented and of great significance. His standard in his field is very high and he fully deserves the recognition that he enjoys both at the national and international levels.”

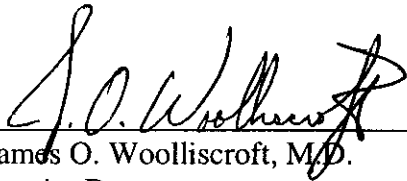
Reviewer D: “Overall these studies are novel, clearly presented, and make significant contributions to our understanding of NOS function....I would certainly wish to have him in my department.”

Reviewer E: “He is the type of individual who solidifies an academic community and makes it function more smoothly and harmoniously. I believe that his promotion to Full Professor with tenure is both appropriate and timely.”

Reviewer F: “...I am highly enthusiastic about Dr. Osawa’s promotion and would dearly like to have him as a permanent member of my own department....All individuals trained in his laboratory have responsible research positions in academia or industry....He is a highly productive, dedicated, and accomplished scientist, teacher, and faculty member who should continue to reflect very well on your University. From colleagues at [another university] I know how aggressively Dr. Osawa was being recruited a few years ago. I think you were very fortunate and skillful to retain him at the University of Michigan.”

Summary of Recommendation:

Dr. Osawa has demonstrated himself to be an innovative and outstanding scientist as well as a sincere, articulate, and well respected teacher. He is recognized both nationally and internationally by his success in obtaining grant support, invitations to speak, and publications in high caliber journals. He has made major contributions to his field in the understanding of hemoprotein function and nitric oxide synthesis (NOS) which translate to clinically relevant scenarios. He is respected by the faculty and students and is a dedicated member of the faculty. Dr. Osawa is heavily involved in the teaching in the department, provides a strong and successful research program, and participates fully in every facet as a faculty member in the department and school. He will, without a doubt, continue to be successful in research and teaching, and I enthusiastically support his promotion to Professor, with tenure.

A handwritten signature in black ink, appearing to read "J. O. Woolliscroft", written over a horizontal line.

James O. Woolliscroft, M.D.

Interim Dean

*Lyle C. Roll Professor of Medicine*

May 2007