Approved by the Regents
May 15, 2008

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL
DEPARTMENT OF INTERNAL MEDICINE

John Wiley, M.D., Associate Professor of Internal Medicine, with tenure, Department of Internal Medicine, Medical School, is recommended for promotion to Professor of Internal Medicine, with tenure, Department of Internal Medicine, Medical School.

Academic Degrees:

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| M.D. | 1980 | Oregon Health Sciences University |
| | 1975 | Portland State University, completion of Pre-Med requirements and Post-Baccalaureate studies in Developmental Biology |
| B.A. | 1971 | Claremont-McKenna College |

Professional Record:

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| 1994-Present | Associate Professor of Internal Medicine, University of Michigan |
| 1989-1994 | Assistant Professor of Internal Medicine, University of Michigan, |
| 1987-1989 | Instructor, Department of Internal Medicine, University of Michigan |
| 1984-1987 | Fellowship in Gastroenterology, University of Michigan |
| 1984-1987 | NIH-NRSA Postdoctoral Training Fellow in Gastroenterology, University of Michigan |
| 1983-1984 | Instructor, Department of Internal Medicine, University of Michigan |

Summary of Evaluation:

Teaching: Dr. Wiley's teaching activities consist of classroom instruction, serving as a preceptor in gastroenterology clinics; administering the K-30, K-12 and Multidisciplinary Clinical Researchers in Training (MCRIT) training programs in clinical research; and fulfilling training, education and mentoring responsibilities associated with the position of Director, UM GCRC (General Clinical Research Center), which includes seminar presentations, mentoring of residents, fellows, and faculty to achieve their career development goals in clinical research and twice weekly clinical rounds with nursing staff. Dr. Wiley is a gifted and effective teacher. He is a hands-on instructor who gives his students the proper guidance and encouragement. He has an enthusiastic, friendly and approachable demeanor and also allows his students the freedom to see and interact with the patients and come up with a treatment plan. In 2006, Dr. Wiley received a unanimous evaluation score of 5.0 from the seven students who rotated with him in his GI clinic. In addition to teaching in the clinical setting, he also participates in classroom instruction, acting as a proctor to third- year medical students doing the physical examinations.

At the University level, Dr. Wiley has served in an exemplary manner on the Program and Executive Committees for the NIH K30, K12, and MCRIT (T32) Training Grants in clinical and translational sciences research since their inception. He actively participates in curriculum development and seminar series and co-directs the K30 and K12 courses in translational research. These programs have been considered most successful in training our future clinical translation investigators.

At the national and international levels, Dr. Wiley has trained multiple investigators interested in neurophysiology research. Many of them have completed their research training under his guidance and are now independent investigators in their own rights.

Research: Over the years, Dr. Wiley has made important contributions to the field of gastrointestinal neurophysiology with emphasis on visceral afferent (sensory) pathways in health and disease. His laboratory focuses particularly on improving our understanding of the pathophysiology of diabetic sensory neuropathy and was among the first to report elevated calcium levels in sensory (dorsal root ganglia) neurons obtained from diabetic rats. In a related series of studies, Dr. Wiley's laboratory went on to report the novel and provocative observation that sera from patients with Type 2 diabetes contain autoantibodies that bind to the surface of neurons and promote calcium influx and activations of programmed cell death. Parallel studies demonstrated similar results in diabetic BB/W rat. Dr. Wiley further showed that exposure of sensory neurons to increased titers of IgM or IgG autoimmune immunoglobulins induces oxidative stress and mitochondrial dysfunction leading to autophagy. This is the first demonstration that the presence of autophagosomes is increased by serum factor, likely autoantibody(ies) in a pathological condition. Stimulation of autophagy by an autoantibody-mediated pathway can provide a critical link between the immune system and the loss of function and eventual demise of neuronal tissue in diabetes.

Dr. Wiley's laboratory is also interested in the molecular mechanisms of chronic neuropathic pain in diabetes. His recent studies demonstrate that early painful diabetic neuropathy is associated with differential changes in tetrodotoxin-sensitive and -resistant sodium channels in dorsal root ganglion neurons of diabetic rats. In a separate study, Dr. Wiley showed that early diabetic neuropathy is also associated with differential changes in the expression and function of the capsaicin-sensitive vanilloid receptor 1. DRG neurons from diabetic rats demonstrated significant increases in capsaicin- and proton-activated inward currents. This appears to be related to increased expression of the tetrameric form of TRPV1 mediated through PKC-induced phosphorylation, oligomerization, and targeted expression of the receptor on the cell surface membrane.

Throughout the last 15 years, Dr. Wiley's research has received continued support from the NIH. He has made several important observations regarding the biochemical and molecular mechanisms underlying the pathophysiology of diabetic neuropathy. These groundbreaking discoveries are highly regarded by other neurophysiologists working in the diabetic field.

Recent and Significant Publications:

Towns R, Kabeya Y, Guo C, Shangsuan Y, Kaplan M, Yoshimori T, Klionsky D, Wiley JW: Sera from patients with type 2 diabetes and neuropathy induce autophagy and colocalization with mitochondria in SY5Y cells. *Autophagy* 1:163-170, 2005.

Shangguan Y, Hall K, Neubig R., Wiley JW: Diabetic neuropathy: Inhibitory G protein dysfunction involves PKC-dependent phosphorylation of $G_{o\alpha}$. *J Neurochemistry* 86:1006-1014, 2003.

Hall K, Liu J, Sima A, Wiley J: Impaired inhibitory G-protein function contributes to increased calcium currents in rats with diabetic neuropathy. *J Neurophysiol* 86:760-770, 2001.

Srinivasan S, Sheng H, Hall K, Stephens M, Wiley J: Serum from patients with type 2 diabetes with neuropathy induces complement-independent, calcium-dependent apoptosis in cultured neuronal cells. *J Clin Invest* 102:1454-1462, 1998.

Hall KE, Sima A, Wiley JW: Opiate-mediated inhibition of calcium signaling is decreased in dorsal root ganglion neurons from the diabetic BB/W rat. *J Clinical Invest* 97:1165-1172, 1996.

Service: Dr. Wiley has served as the Director of the General Clinical Research Center (GCRC) since 2000. Over the last seven years, Dr. Wiley has guided the GCRC through two successful competitive renewals. Through his unyielding efforts, he is largely responsible for making the UM GCRC one of the most successful centers in the country. From 2004 to 2006, Dr. Wiley was President-Elect and President of the GCRC Program Directors Association. During his tenure, he participated and contributed directly to the development of the NIH Clinical Translational Sciences Award (CTSA). The NIH launched the new national consortium which is designed to transform the ways clinical and translational research is done in the United States. As a result, the Clinical and Translational Science Awards (CTSAs) were created which would allow for local flexibility in terms of funding for clinical and translational science. Dr. Wiley played a key role in the recently approved UM CTSA application and the NIH has awarded the University $55 million for five years. He will serve on the Michigan Institute for Clinical and Health Sciences Research Executive Committee, which will serve as the administrative umbrella for this grant.

Since 2005, Dr. Wiley has been the director of the Functional Bowel Disorder (FBD) Clinic, which is supported by a UMHS Clinical Innovation Award. A key component of this clinic is to provide state-of-the-art training to healthcare personnel in the diagnosis and management of functional bowel disorders. Patients are also encouraged to attend the educational session in which our multi-disciplinary team of experts, including specialized gastroenterologists, registered dietician, and clinical psychologist, give them the most current facts about how to manage their illness. Data from patient questionnaires will also be compiled for a database to be used in future research protocols. The FBD clinic is the only such program in the State of Michigan and one of very few such programs in the United States.

Dr. Wiley has also served on a national and international level. He has chaired many committees including the Program and Scientific Committees for the 12$^{th}$ Biennial American Motility Society Meeting, Abstract Selection Committee for the American Gastroenterological Association, and chaired the Program and Scientific Committees for the 1$^{st}$ Joint International Neurogastroenterology and Motility Meeting.

Professional Work: Dr. Wiley's patient care responsibilities include: clinic one-half day per week at Taubman Health Center, one-half day every six weeks at East Ann Arbor Health Center devoted to the care of patients with functional bowel diseases, one day of endoscopy every two weeks at the Medical Procedures Center, and staffing fellows clinic one day every month. In recognition of his clinical skills, Dr. Wiley has been selected in "America's Top Physicians."

External Review:

Reviewer A: "Dr. Wiley's research on the effects of diabetes on central nervous system neurons is outstanding and always published in journals with a high impact factor....Dr. Wiley's

academic capabilities and performance are impeccable. His work is original, and it is NOT derivative."

Reviewer B: "I am absolutely certain that John Wiley, M.D. would be readily promoted to Professor in the Division of Gastroenterology, Department of Medicine [at my institution]. I believe that he is outstanding by all criteria that could be applied and that this promotion is long overdue."

Reviewer C: "I would place him in the top 10 percent of individual scientists working in his field of scholarly work."

Reviewer D: "...Dr. Wiley is a skilled scientist and gastroenterologist who has made outstanding contributions in the area of gastrointestinal physiology, and who has a strong national and international reputation in the field. He is a crucial player in your university's neurogastroenterology research efforts, which is one of the strongest in the world today."

Reviewer E: "John has always been a leader in our area of gastrointestinal motility. His ideas are on the cutting edge."

Summary of Recommendation:

Dr. John Wiley embodies the finest principles of academic medicine. He is a highly innovative investigator who has achieved national and international recognition for his contributions on the biochemical and molecular mechanism underlying the pathophysiology of diabetic neuropathy. He is an excellent teacher and an astute physician. In addition, he is a skillful administrator who has contributed enormously to the success of the UM GCRC. I am very pleased to recommend Dr. Wiley for promotion to the rank of Professor in the Department of Internal Medicine.

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

May 2008