

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF NEUROLOGY
DEPARTMENT OF MOLECULAR AND INTEGRATIVE PHYSIOLOGY

Michael M. Wang, M.D., Ph.D., assistant professor of neurology, Department of Neurology, and assistant professor of molecular and integrative physiology, Department of Molecular and Integrative Physiology, Medical School, is recommended for promotion to associate professor of neurology, with tenure, Department of Neurology, and associate professor of molecular and integrative physiology, without tenure, Department of Molecular and Integrative Physiology, Medical School.

Academic Degrees:

Ph.D.	1994	Johns Hopkins University
M.D.	1994	Johns Hopkins University
A.B.	1987	Harvard University

Professional Record:

2003-present	Assistant Professor of Neurology, University of Michigan
2003-present	Assistant Professor of Molecular and Integrative Physiology, University of Michigan
2002-2003	Assistant Professor of Neurology, Johns Hopkins University
2002-2003	Instructor of Anesthesiology/Critical Care Medicine, Johns Hopkins University
2000-2002	Instructor of Neurology, Johns Hopkins University

Summary of Evaluation:

Teaching: A major part of Dr. Wang's teaching is performed in the laboratory. Many of his fellows have attained excellent positions within academia. In addition, he actively participates in both basic science and clinical teaching. He is a regular group leader for the M1 physiology module. He plays a critical role in the department as the faculty organizer for the Basic Science Lecture Series, which is a required didactic course for neurology residents. He also leads the basic science education for The Stroke Program. Clinically, his teaching activities include ward and clinic staffing. As chief of neurology at the VA, he is responsible for a significant portion of the education of residents and students. Importantly, Dr. Wang enjoys and excels in teaching at all levels. The quality of his teaching is considered excellent by M1 and M3 students and by residents. Comments from students include superlatives such as, "Best small group leader ever" and "I wish Dr. Wang could lead all of our small groups."

Research: Dr. Wang has performed high quality research in multiple biomedical fields during his career. He has described studies of the molecular biology of the olfactory system, the circadian system, and regulation of neuronal hormone receptors (e.g. Estrogen receptors).

Work on estrogen served as the initial base for Dr. Wang's research program at the University of Michigan. Dr. Wang's studies have proven that estrogen receptors can be localized to the surface of neurons, providing a direct route for activation of protective signals such as MAPK activation. In addition, he has shown that estrogen receptors localized to the membrane can, in fact, translocate to the nucleus, providing intriguing support for a dynamic interplay between two pools of the receptor and further supporting estrogen-mediated rapid actions in neurons. Finally, Dr. Wang has uncovered several new gene activation modes mediated by estrogen, some of them activated by the motor protein p150, highly expressed in neurons and previously not known as a nuclear protein. Although his estrogen work progressed well and was supported by strong intramural and extramural sponsorship, key clinical trial data became available in 2003 suggesting that estrogen is not, in fact, beneficial for stroke. As a consequence, Dr. Wang made a bold decision to chart a new research direction. Rather than continue on a narrow line of research on estrogen, he decided to study a clinically important, but neglected field: the molecular basis of stroke susceptibility. Translational stroke researchers almost exclusively study the effects of stroke on neurons; however, few investigators are interested in what causes stroke. Dr. Wang's studies of the molecular pathways leading to vascular dysfunction in stroke promise to lead to improved knowledge on how stroke can be prevented. As a model system, he is studying the most common genetic form of stroke, CADASIL, which is caused by mutations in a single gene. What is most impressive about his studies is that because only a handful of researchers study CADASIL, Dr. Wang has essentially built his research program on CADASIL from the ground up based on sheer persistence, a number of insightful observations, and the recruitment of a cadre of collaborators here at the University of Michigan—this is somewhat of a homegrown Michigan operation.

The payoff is now becoming apparent. Dr. Wang has now shown that Notch3, the protein affected in CADASIL, binds to a series of novel proteins. Some of these proteins, such as thrombospondin2, stimulate the activation of Notch3. Meanwhile, other protein binding partners, such as LRP1, participate in the clearance of Notch3 protein. Other works have shown that the clearance of Notch3, which may be impaired in CADASIL, may be influenced by the leader sequence of the protein, which is a surprising finding and unique to this isoform of the Notch family. Also, in recently published work, Dr. Wang has shown that Notch3 is metabolized through the lysosomal pathway, which again distinguished it from other Notch proteins and forms from lower species. The work on Notch3 is part of a set of nine publications in the last 12 months; this volume of recent work confirms that Dr. Wang has reached a period of high productivity at this point in his career.

In other areas, Dr. Wang has begun new studies investigating the interrelations between stroke, circadian rhythms, and sleep. He has now shown that stroke can markedly affect the circadian clock, a surprising finding considering that the seat of the body clock has long been considered the hypothalamus, which is not affected by stroke. This work utilizes novel physiological measurement tools that have yet to be applied in stroke. The promise of this work is that it may lead to a better understanding of the reciprocal relationship between stroke, sleep, and circadian rhythms. The success of this direction of Dr. Wang's work is in part a result of his ability to seek out unique strength within our institution, which has long developed both stroke and sleep research.

Dr. Wang's outstanding funding record is a good measure of his scientific success. His grants have continuously supported 75% or more of his effort since 1998, when he was a fellow. He was awarded a highly selective Burroughs Wellcome Career Award which honors a select group of early stage investigators. Throughout his faculty career, he has had uninterrupted NIH support; he was awarded a K08 and then a K02 from the NIH, both on the first attempt. In addition to the K02, his current federal support includes a VA Merit Award, an R01, and an R21. Finally, Dr. Wang's scholarship has been recognized at the national level through invitations to serve as a regular member of study sections of the American Heart Association and the NIH.

Recent Significant Publications:

Meng H, Zhang X, Hankenson KD, Wang MM: Thrombospondin2 potentiates Notch3/Jagged1 signaling. *Journal of Biological Chemistry* 284(12):7866-74, 2009.

Meng H, Peng Y, Hasan R, Yu G, Wang MM: Nuclear contrast angiography: A simple method for morphological characterization of cerebral arteries. *Brain Research* Epub, 2009. [Featured on cover.]

Lee S, Chae C, Wang MM: p150/glued modifies nuclear estrogen receptor function, *Molecular Endocrinology* 23(5):620-9, 2009.

Meng H, Liu T, Borjigin J, Wang MM: Ischemic stroke destabilizes circadian rhythms. *Journal of Circadian Rhythms* 6:9, 2008.

Xu Y, Traystman RJ, Hurn PD, Wang MM: Neurite localized estrogen receptor-alpha mediates rapid signaling by estrogen. *J Neurosci Res* 74:1-11, 2003.

Service: Dr. Wang is the chief of neurology at the Ann Arbor VA Hospital. In this role, he is responsible for 9.5 FTE, the operation of a key clinical service, and the administrative interface between the University and the VA system. He also serves on the Clinical Executive Board and the Advisory Board to the Chief of Staff at the VA. Finally, he is a regular member of the VA Research and Development Committee. Dr. Wang is a respected and well-trained clinical stroke neurologist. His clinical activities, accounting for approximately 20% of his effort, include outpatient clinics and inpatient service at University Hospital and at the Ann Arbor VA Hospital. As a stroke neurologist, he also participates in the Brain Injury Group, which responds 24/7 to acute stroke calls for the hospital system. This voluntary clinical activity, which includes nighttime on call, is provided as a service to the hospital and also provides Dr. Wang the opportunity to be involved in clinical trials run at Michigan. Because of his interest in CADASIL, Dr. Wang has become a nationally recognized expert in clinical diagnosis and treatment of this disorder. He sees CADASIL patients nationwide and is frequently contacted by patient groups and individuals for advice.

External Review:

Reviewer A: "His work has brought him acclaim as an outstanding investigator in clinical and translational neuroscience research, and a well-deserved reputation at both the national and

international levels...based on Dr. Wang's innovative approach to research, his quality of research and his contributions to the field, I would rate him in the top 3% nationally among outstanding individuals in the field. He has clearly put the Department of Neurology at the University of Michigan Medical School on the map for his translational neuroscience research. It is fair to predict that Dr. Wang will excel in his research endeavors for years to come."

Reviewer B: "Dr. Wang has a record of scholarly achievement that is at the highest level....He has clear evidence of a national recognition in the stroke field and has also had invitations to speak internationally."

Reviewer C: "He is an excellent clinician scientist and a productive member of the outstanding stroke program at your institution...Dr. Wang has developed a national reputation as a clinician scientist with a new and important set of discoveries. His focus is crucial for progress with a vexing disease. I believe his reputation, productivity, recognition at a national level and accomplishments warrant awarding of tenure and promotion to Associate Professor."

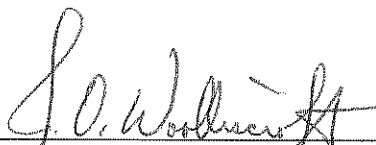
Reviewer D: "He is unique—teaching, seeing patients, and performing cutting-edge science. It would be a coup for your department to find a way to keep him...His track record is superb. He has held numerous grants from the NIH, the Veterans Administration, and the American Heart Association. This is top-notch work and clearly, his peers and reviewers think so too."

Reviewer E: "He has gathered an exceptional number of scientific and professional accolades that among many others include NIH and American Heart Association awards and a VA merit award. He has published numerous high profile, refereed publications in prestigious scientific journals...He is also an outstanding speaker. I have heard Dr. Wang present many times and his presentations are provocative and stimulating."

Reviewer F: "Dr. Wang has a significant track record of service locally at the University of Michigan...and nationally on review panels...and as a journal referee for several journals."

Summary and Recommendation:

Dr. Michael Wang is an outstanding neurologist, who provides important clinical service as a stroke/vascular specialist. He is a nationally recognized clinician-scientist and has already made outstanding contributions to scholarship, service and education. His past success and promise for the future amply justify promotion to associate professor, with tenure, in the Department of Neurology and associate professor, without tenure, in the Department of Molecular and Integrative Physiology.


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

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