

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL
DEPARTMENT OF BIOLOGICAL CHEMISTRY

Approved by the Regents
May 15, 2008

E. Neil G. Marsh, Ph.D., Associate Professor of Biological Chemistry, without tenure, Department of Biological Chemistry, Medical School, is recommended for promotion to Professor of Biological Chemistry, without tenure, Department of Biological Chemistry, Medical School [also Professor of Chemistry, with tenure, Department of Chemistry, College of Literature, Science, and the Arts].

Academic Degrees:

Ph.D.	1988	University of Cambridge, England
B.A.	1985	Christ's College, University of Cambridge, England,

Professional Record:

2007–Present	Professor of Chemistry, University of Michigan
2005–Present	Associate Professor of Biological Chemistry, University of Michigan
2001–2007	Associate Professor of Chemistry, University of Michigan
1995–2000	Assistant Professor of Chemistry, University of Michigan

Summary of Evaluation:

Teaching: Dr. Marsh is an effective and dedicated teacher and is also an honors advisor for Biochemistry Concentration. In particular, he provides advice to students in choosing research mentors in the Departments of Biological Chemistry and Chemistry. Dr. Marsh has taught the first term of the two-term Biochemistry core course sequence that is jointly taught by the Biological Chemistry and Chemistry departments. At the graduate level, he has also taught several courses in the Chemical Biology Graduate curriculum that typically have a significant enrollment from Biological Chemistry graduate students. These include Biological Chemistry 673, and the Chemical Biology and Protein Chemistry special topics courses (Chemistry 525 and Chemistry 528). Other teaching-related activities include his acting as an advisor for chemistry students with a Biochemistry concentration and serving on the Chemistry Department curriculum committee. Dr. Marsh has received above average evaluations in all of his teaching roles.

Dr. Marsh has spearheaded a major reorganization of the undergraduate biochemistry curriculum to tailor it to the needs of graduating majors emphasizing the importance of chemical principles to modern biochemistry while recognizing that biochemistry is a broadly based discipline that extends from the physical sciences into all areas of the biological and medical sciences. Changes that have been instituted include two new courses in biophysical chemistry (Chemistry 453 and Chemistry 454). Chemistry 453 provides grounding in the basic principles of thermodynamics, statistical mechanics and kinetics, but is specifically oriented towards the needs of biochemists. Chemistry 454 emphasizes physical techniques and their application to biochemical problems. With these new courses, there is now a complete series of upper level courses, Chem 451, 452, 453 and 454 specifically tailored to the education of biochemistry concentrators.

Research: Dr. Marsh is recognized as a world expert in the field of enzymology, which includes the structure and mechanism of free radical enzymes, modulating protein structure and function using non-canonical amino acids and the strategies for assembling proteins into nano-scale architectures. He is well known for his important contributions to our understanding of (a) enzyme catalyzed reactions that involve free radical intermediates and (b) the function of coenzyme B₁₂.

Dr. Marsh's group has performed a number of technically sophisticated experiments that have answered some long-standing mechanistic questions about catalysis by B₁₂-dependent enzymes. These experiments reported in some 40 publications in high profile biochemical journals (*J. Biol. Chem.*, *Biochemistry*), have also provided insights into the mechanisms used by radical enzymes in general. For example, his group has conducted a wide range of kinetic experiments on glutamate mutase, including measuring the effects of having different hydrogen isotopes at C-4 of glutamate and the trapping of short-lived radical intermediates. The results have led to an identification of what intermediates exist (e.g. glycyl radical, acrylate) during the glutamate to methylaspartate conversion and a determination of the free energy profile for different substeps in the overall reaction. Dr. Marsh has also conducted detailed investigations on the effects of various mutations of the protein and investigated the reaction of the enzyme and with substrate analogs such as methylene aspartate, which have proved mechanistically informative.

He has expanded his work recently to include the *de-novo* design of extensively fluorinated 'Teflon' proteins, also a topical area of modern biochemistry. Perfluorocarbons exhibit unique and useful physical properties that are not found in nature. For example, Teflon derives its highly inert and non-stick properties from the perfluorinated polymer polytetrafluoroethylene. We are examining the effects of replacing 'greasy' hydrophobic amino acids that are found in the interior of proteins with extensively fluorinated analogs to create a 'Teflon' interior. We expect that such proteins may exhibit useful new properties such as increased thermal stability, resistance to unfolding in organic solvents, and resistance to degradation by proteases. Teflon proteins may also exhibit novel protein:protein interactions and provide model systems to test theories of protein folding.

Recent and Significant Publications:

Cheng MC and Marsh ENG: Evidence for coupled motion and hydrogen tunneling the reaction catalyzed by glutamate mutase. *Biochemistry* 46:883-888, 2007.

Yoon M, Patwardhan A, Qiao C, Mansoorabadi S, Menefee AL, Reed GR and Marsh ENG: The reaction of adenosylcobalamin-dependent glutamate mutase with 2-thioglutarate. *Biochemistry* 45:11650-11657, 2006.

Li L and Marsh ENG: Mechanism of Benzylsuccinate synthase probed by substrate exchange. *J Am Chem Soc* 128: 16056 -16058, 2006.

Lee H-Y, Lee K-H, Al Hashimi HM and Marsh ENG: Modulating protein structure with fluorinated amino acids: increased stability and native-like structure conferred on a 4-helix bundle protein by hexafluoroisoleucine. *J Am Chem Soc*, 128:337-343, 2006.

Cheng MC and Marsh ENG: Pre-steady state measurement of intrinsic secondary tritium isotope effects associated with the homolysis of adenosylcobalamin and the formation of 5'-deoxyadenosine in glutamate mutase. *Biochemistry* 43:2155-2158, 2004.

Service: Dr. Marsh was invited by the Medical School Executive Committee to serve on the Task Force on Team Science. This committee is a ten-person team selected to study the impact of large team science and interdisciplinary work upon academic promotional expectations and research endeavors in the Medical School. He is a member of the Department's Biological Chemistry Curriculum Committee and assists in coordinating and developing new courses, revision of existing courses and has oversight of the graduate curriculum. Interdepartmentally, Dr. Marsh, as a member of the Chemistry-Biology Interface NIH Training Grant Committee, oversees the administration, appointment and requirements for students who participate in this training program. Dr. Marsh is also Chair of the Chemical Biology Admissions Committee. Other committees include the Department of Chemistry's Executive Committee, and the Long Range Planning Committee, which helps develop a five-year plan covering all aspects of departmental activities. His service contributions have been excellent.

Extramural service activities have included Dr. Marsh serving as an ad hoc member of an NIH Biochemistry Study Section, a member of the *Faculty of 1000* web-based reviewing service, and a manuscript reviewer for many high profile chemistry and biochemistry journals, including the *Journal of Biological Chemistry* and *Biochemistry*. He was the vice-chair of the Bioorganic Chemistry Gordon Conference in June 2004 and chaired the meeting in 2005. This is a major honor in this competitive field. He organized a symposium entitled "Protein Design" for the National American Chemistry Society meeting in New York in September of 2003.

External Review:

Reviewer A: "I was recently asked to nominate individuals who worked in the field of chemical biology as potential Chair for a growing department of chemistry in the United States. Neil Marsh was number one on my list..."

Reviewer B: "Without a doubt, Dr. Marsh has made significant (and seminal) contributions to our understanding of the mechanism of glutamate mutase...His publications are clearly written and serve as models of experimental design and rigor...Dr. Marsh ranks among the top enzymologists of her age group, both in creativity and productivity."

Reviewer C: "If Dr. Marsh were a member of our faculty, he would be promoted to professor without question. He is innovative in research, cares about education and is dedicated to science....The University of Michigan is fortunate to have such a talented scientist to consider for promotion."

Reviewer D: "Through Dr. Marsh's systematic and fundamental studies of these enzyme systems, his research group has become one of the world leaders in investigating radicals in enzymatic catalysis...In short, Dr. Marsh is the complete package. He is a respected, leading researcher in the fields of radical enzymology and *de novo* protein design, and he has been an exemplary faculty member in your department."

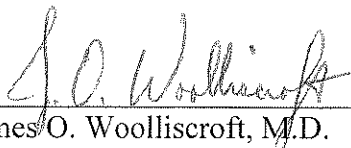
Reviewer E: "...Neil continues to distinguish himself as a highly respected member of the enzymological community...I am sure that he would be promoted to the rank of Professor of Biochemistry at (my institution)."

Reviewer F: "He has not restricted himself to a single method, or spectroscopic method, as so many others in the field have, but has been relentless in using the right method to answer the question at hand...I think Neil's promotion is a 'slam dunk,' and I support it with considerable enthusiasm and without hesitation."

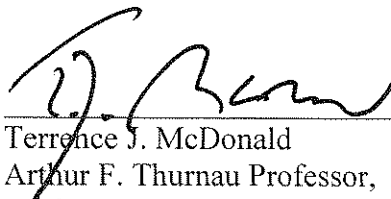
Reviewer G: "Neil has made significant and substantial contributions to the enzymology of free radicals as well as to [sic] use the fluorinated amino acids in protein design...Reading the papers it is clear that the studies have been performed carefully and rigorously, which is a hallmark of Neil's scientific contributions."

Summary of Recommendation:

Dr. E. Neil G. Marsh has performed very well in research, teaching and service. In recognition of his accomplishments, we enthusiastically support his promotion to Professor, without tenure, in the Department of Biological Chemistry to be held in conjunction with his title of Professor, with tenure, in the Department of Chemistry, College of Literature, Science, and the Arts.



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



Terrence J. McDonald
Arthur F. Thurnau Professor,
Professor of History, and Dean
College of Literature, Science, and the Arts

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