

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF BIOLOGICAL CHEMISTRY

Approved by the Regents
May 14, 2009

Bruce A. Palfey, Ph.D., assistant professor of biological chemistry, Department of Biological Chemistry, Medical School, is recommended for promotion to associate professor of biological chemistry, with tenure, Department of Biological Chemistry, Medical School.

Academic Degrees:

Ph.D.	1994	University of Michigan
M.S.	1989	Drexel University
B.S.	1985	Pennsylvania State University

Professional Record:

2003–present	Assistant Professor of Biological Chemistry, University of Michigan
1996–2003	Lecturer, Department of Biological Chemistry, University of Michigan

Summary of Evaluation:

Teaching: Dr. Palfey teaches quite extensively and has been extraordinarily active in teaching enzymology and biophysical chemistry in courses covering kinetics and calorimetry. Dr. Palfey is co-director of Biological Chemistry 597, Critical Analysis, and gives three hours of lecture, and is course director of Biological Chemistry 673, Kinetics and Mechanism, and gives 19 hours of lecture. Thirty-six students took Biological Chemistry 673 for credit along with several students who audited the course. He also teaches nine hours of lectures in the Biophysics/Chemistry 520 course and individual lectures in several other courses. Dr. Palfey's student evaluations have been outstanding (i.e. 4.9/5.0). In addition to classroom teaching, he has trained two postdoctoral fellows and one postdoctoral trainee, four UM Ph.D. graduate students, and one graduate Ph.D. student visiting from Thailand currently in his laboratory. Dr. Palfey has served on 19 dissertation committees.

Research: Dr. Palfey's research is in the area of enzyme mechanisms, and he is an expert in kinetics. His laboratory studies the mechanisms of flavin-containing enzymes involved in pyrimidine metabolism. Because pyrimidines are components of nucleic acids, are modified in the maturation of RNA, and are involved in the synthesis of lipids and glycoproteins, pyrimidine metabolism is critical to life. A number of oxidation and reduction reactions utilizing flavins occur in the myriad of pyrimidine interconversions. Dr. Palfey is studying several of these in order to elucidate their reaction mechanisms. By knowing the mechanisms in great detail, he will learn how enzymes accelerate reactions and should be able to design specific inhibitors that may be of therapeutic value. His studies are guided by the philosophy that enzymes should be studied as reactants, at substrate-level concentrations, rather than as catalysts. This approach

enables Dr. Palfey to directly observe events at the active site using a number of spectroscopic and kinetic methods. The flavin prosthetic group (a derivative of vitamin B₂) assists him greatly in his studies by acting as a spectral reporter group in the active site as it participates in the events of catalysis. Dr. Palfey's work and collaborations have been published in highly regarded scientific journals. Even in these difficult funding times, Dr. Palfey has consistently had NIH R01 funding and is currently funded through November of 2011.

Dr. Palfey is taking an interdisciplinary approach to understanding enzyme mechanisms. It is difficult to overstate the importance of structures in enzymology, so he is collaborating with crystallographers and he has even started to solve a few structures himself. However, structures offer only a static picture of enzymes; it is becoming increasingly apparent that dynamic processes are critical in catalysis. Therefore, he has been collaborating with biophysicists in order to probe the dynamics of dihydroorotate dehydrogenases. Single-molecule microscopy, performed in collaboration with Professors Duncan Steel and Ari Gafni, have detected dynamic heterogeneity in enzymes, and have shown that the active sites of a dimeric enzyme are cooperatively linked. They are now turning their attention to a more complex dihydroorotate dehydrogenase; single-molecule spectroscopy will allow his group to track dynamic interactions in a tetrameric enzyme. In collaboration with Professor Erik Zuiderweg, Dr. Palfey is detecting by NMR spectroscopy large changes in the dynamics of a dihydroorotate dehydrogenase caused by ligand binding. Many of the affected residues are quite distant from the binding site; this work will allow Dr. Palfey to map the propagation of catalytically important dynamic changes in the enzyme.

Recent and Significant Publications:

Fagan RL, Jensen KF, Björnberg O, and Palfey BA: Mechanism of flavin reduction in the class 1A dihydroorotate dehydrogenase from *Lactococcus lactis*. *Biochemistry* 46:4028-4036, 2007.

Wolfe AE, Thymark M, Gattis SG, Fagan RL, Hu YC, Johansson E, Arent S, Larsen S, and Palfey BA: The interaction of benzoate pyrimidine analogs with the class 1A dihydroorotate dehydrogenase from *Lactococcus lactis*. *Biochemistry* 46:5741-5753, 2007.

Shi J, Dertouzos J, Gafni A, Steel D, and Palfey BA: Single-molecule kinetics reveals new signatures of half-sites reactivity in dihydroorotate dehydrogenase A in catalysis. *Proc Natl Acad Sci USA* 103:5775-5780, 2006.

Palfey BA and Fagan RL: An analysis of the kinetic isotope effects on initial rates in transient kinetics. *Biochemistry* 45:13631-13640, 2006.

Gattis SG and Palfey BA: Direct observation of the participation of flavin in product formation by *thyX*-encoded thymidylate synthase. *J Am Chem Soc* 127:832-833, 2005.

Service: On the departmental front, besides serving on the department's Biological Chemistry Curriculum Committee since 2004, Dr. Palfey joined the Computer and Technology Committee in 2003 and served as the chair from 2004–2006. He also was elected by the faculty to the Departmental Advisory Committee and served from 2004–2006. Dr. Palfey was a member of the Medical School's Bioinformatics Molecular Modeling Faculty Search Committee in 2003–2004. From 2004 to the present, Dr. Palfey has served on the Chemical Biology Curriculum Committee and the Chemical Biology Program Committee. Service to the University of Michigan includes

serving on the Biophysics Faculty Search Committee (2004-2005), Chemical Biology Graduate Admissions Committee (2005–present) and the Chemical Biology Executive Committee (2005–present).

External Review:

Reviewer A: “I believe Bruce must be considered an up and coming star in the field of mechanistic enzymology in general, and among those at the top of the field in the area of flavoenzyme mechanisms. Bruce has NIH funding until 2011, no trivial accomplishment in these difficult fiscal times.”

Reviewer B: “There is evidence of leading scholarship in a research area, contributions to the teaching mission of the institution at both the undergraduate and graduate levels, participation in international professional societies, and involvement in service on national review panels. Based on this evaluation, I conclude it would be appropriate and timely to continue with the promotion process.”

Reviewer C: “Prof. Palfey is the latest, hopefully not the last, in the long and distinguished line of flavin biochemists at the University of Michigan begat by Vince Massey....There are few enzymologists of his caliber operating today. He easily clears the bar in terms of science- he chooses important problems, is productive, publishes in quality journals and has achieved prominence on a national and international level.”

Reviewer D: “...I consider Dr. Palfey to be in the top 10% of enzymologists in his peer group world-wide; he is no longer simply promising but delivering in spades on the promise the Department of Biological Chemistry presumably identified in appointing him an Assistant Professor.”

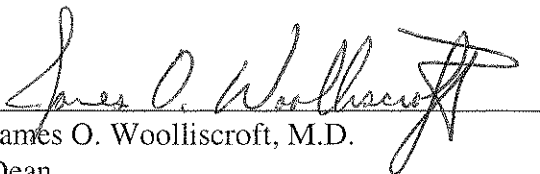
Reviewer E: “He has made important contributions to the application of time-resolved spectroscopy to define enzyme mechanisms and his work is always of the highest quality....I think very highly of Dr. Palfey because he has the ability to understand complex reactions and the fortitude to carry out detailed studies rigorously to answer biologically important questions.”

Reviewer F: “...Dr. Palfey has excelled in each area that is traditionally used at research institutions for promotion and tenure. He is publishing regularly in excellent journals and has won (and renewed) NIH funding. He has built a lab that includes students at all levels who are publishing as first authors. Collaborations have been established nationally and internationally. He has successfully organized meetings and delivered numerous talks at all levels. Importantly, he has established a research area where he is considered a leader, and this has led to invitations to write reviews and organize symposia.”

Reviewer G: “If [Dr. Palfey] were a faculty member [at my institution] (what a wonderful prospect!), my colleagues would support him vigorously for promotion and tenure...and I am confident their recommendations would carry.”

Summary of Recommendation:

Dr. Bruce A. Palfey has performed very well in teaching, service and research. He has made great progress as an independent investigator and is an excellent academic citizen. I enthusiastically support his promotion to associate professor, with tenure, in the Department of Biological Chemistry.

A handwritten signature in cursive script, reading "James O. Woolliscroft". The signature is written in black ink and is positioned above a horizontal line.

James O. Woolliscroft, M.D.

Dean

Lyle C. Roll Professor of Medicine

May 2009