

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF BIOLOGICAL CHEMISTRY

Patrick O'Brien, 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.	2000	Stanford University
B.S.	1994	Santa Clara University

Professional Record:

2004-present	Assistant Professor of Biological Chemistry, University of Michigan
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Summary of Evaluation:

Teaching: Dr. O'Brien has excelled in teaching as well as research. Since 2004, Dr. O'Brien has taught in the Biochemistry Critical Analysis 597 course for first and second year biological chemistry Ph.D. students. From 2007-2008, he taught the Biochemistry 673 course, Kinetics and Mechanism. Dr. O'Brien has also paired with another colleague in the Department of Biological Chemistry to create the BioChem 552 course, Biochemistry for Medical Scientists. This course focuses on the critical analysis of seminal publications in the field of biochemistry. During his time at this University, Dr. O'Brien has also taught ChemBio 501, Introduction to Chemical Biology, Biochem 650, Eukaryotic Gene Expression, Chem 548, Current Topics, Interface of Chemistry & Biology and ChemBio 601, Critical Analysis in Chemical Biology. Dr. O'Brien has received well above average teaching evaluations in all of his teaching roles. For example, one student wrote: "overall the instructor was an excellent teacher." This seems to be the consensus among students instructed by Dr. O'Brien. In addition to classroom teaching, Dr. O'Brien does a superb job of mentoring. He has mentored one postdoctoral fellow and one research associate, as well as seven graduate students. There have also been 16 graduate students who have done rotations in his laboratory. There is always at least one undergraduate student working in his lab, but he has mentored 13 undergraduate students to date. Dr. O'Brien has served on 32 thesis dissertation committees, six of which he chaired. He also served on 20 preliminary examination committees.

Research: Dr. O'Brien's research seeks to understand the mechanisms by which DNA damage is repaired. He has extensive expertise in studying the enzymology of nucleic acid-modifying proteins using a variety of biophysical and biochemical techniques to study interactions between repair proteins and DNA and to dissect pathways and catalytic mechanisms for DNA replication and repair enzymes. A key focus of his laboratory over the past several years has been the study

of the human base excision repair pathway. This pathway is responsible for repairing an estimated 10,000 damaged nucleotides every day in each human cell. His lab takes two general approaches to addressing important questions in the area of DNA repair. In the first approach he performs in-depth mechanistic analysis to dissect individual steps in the reaction of a given enzyme to understand how substrate specificity is determined and how catalysis is achieved. The second approach is to study these enzymes as entire pathways in cell extracts and in fully reconstituted systems using recombinant proteins. This in-depth look at the human base excision repair pathway has also advanced our fundamental understanding of the dynamic properties of DNA binding proteins and therefore impacts a wide variety of nuclear processes, such as DNA replication, repair, and transcriptional regulation. Some notable accomplishments include the development of sophisticated biochemical assays to monitor diffusion of proteins along DNA (*Biochemistry*, 2008 and *ACS Chemical Biology*, 2010) and the application of pre-steady state kinetics and fluorescence spectroscopy to dissect the kinetic mechanism of human alkyladenine DNA glycosylase (*Biochemistry*, 2009). These findings led to the prediction and recent demonstration that glycosylases can efficiently recognize unpaired (bulged) nucleotides and delete them, resulting in increased frequency of frameshift mutations (*J. American Chemical Soc.*, 2009 and *J. Biological Chemistry*, 2010). Dr. O'Brien is currently expanding the focus of the lab to study other DNA repair pathways and especially the catalytic mechanism of DNA ligases that catalyze the ultimate step in most types of repair. The biochemical expertise in assaying DNA repair pathways is currently being used to develop improved assays for determining the repair phenotype of cancer cells and to identify novel inhibitors of these enzymes. As DNA damaging agents are widely used in the treatment of cancer, improved knowledge of repair phenotype and the availability of inhibitors have promise in improving cancer chemotherapies. Over the past 12 years, Dr. O'Brien has published 27 peer-reviewed articles in well-refereed journals, including *ACS Chemical Biology*, *Biochemistry*, the *Journal of the American Chemical Society*, the *Journal of Biological Chemistry* and *Nature*. He served as guest editor for a thematic issue of *Current Opinion in Chemical Biology* in 2010. Dr. O'Brien's contributions have been recognized by an increasing number of speaking invitations. In 2009 he was asked to speak at various meetings, including the Gordon Research Conference on Enzymes, Coenzymes, and Metabolic Pathways and the Massachusetts Institute of Technology. In 2010 he was invited to speak at Vanderbilt University School of Medicine and the FASEB Conference on Nucleic Acid Enzymes. In early 2011, Dr. O'Brien presented talks at both Washington University School of Medicine in St. Louis and at Thomas Jefferson University in Philadelphia. Most recently, he was invited to speak at the Gordon Research Conference on DNA repair. Dr. O'Brien was the recipient of a Ruth L. Kirchstein fellowship from the NIH (2002-2004) and his research is currently supported by a R01 from the National Cancer Institute of the NIH (2007-2012) and an American Cancer Society Research Scholar Fellowship (2011-2015).

Recent and Significant Publications:

Taylor MR, Conrad JA, Wahl DR, O'Brien PJ: Kinetic mechanism of human DNA ligase I reveals magnesium-dependent changes in the rate-limiting step that compromise ligation efficiency. *J Biol Chem* 286:23054-23062, 2011.

Hedglin M, O'Brien PJ: Hopping enables a DNA repair glycosylase to efficiently search both strands and bypass a bound protein. *ACS Chem Biol* 5:427-436, 2010.

Lyons DM, O'Brien PJ: Human base excision repair creates a bias toward -1 frameshift mutations. *J Biol Chem* 285:25203-25212, 2010.

Baldwin MR, O'Brien PJ: Coordination of the initial steps of human base excision repair via nonspecific DNA binding interactions. *Biochemistry* 49:7879-7891, 2010.

Wolfe AE, O'Brien PJ: Kinetic mechanism for alkyladenine DNA glycosylase-catalyzed flipping and excision of 1, N⁶ – ethenoadenine. *Biochemistry* 48:11357-11369, 2009.

Service: With respect to departmental service, Dr. O'Brien was elected by biological chemistry faculty to serve on the Departmental Advisory Committee (2008-2010). He also served on the Graduate Students Admissions Committee (2006-2008), the Computer and Technology Committee (2005-2008) and the Department Equipment Committee (2004-2008). He served on the Curriculum Committee (2010), and is currently chairing the Graduate Recruitment Committee and serving on the Medical School Teaching Committee. In terms of external service, Dr. O'Brien has been a reviewer for prestigious journals such as *Biochemistry*, the *Proceedings of the National Academy of Sciences* and *Chemistry and Biology*. Dr. O'Brien was an *ad hoc* grant reviewer for the National Science Foundation and the University of Michigan Faculty Grants and Awards Committee. He is a member of the American Chemical Society (1994-present) and the American Society for Biochemistry and Molecular Biology (2010-present).

External Reviewers:

Reviewer A: "On balance Professor O'Brien has a solid productive program that has begun to show some creative sparks and broadened directions that augur well for the significance of his program to provide discoveries for a much broader community."

Reviewer B: "Dr. O'Brien has put together an outstanding research program and distinguished himself as one of the bright investigators [of his cohort] in the field. Over the years, he had become a world-class expert in mechanistic analysis of base-excision repair. His work is distinguished by thorough analyses and clarity of presentation, which results from his thinking about biochemical problems with a great deal of biological insight. Dr. O'Brien has contributed significantly to the evolving picture of mechanistic basis for recognition of damaged DNA by glycosylases."

Reviewer C: "My own impression is that Dr. O'Brien has had a very positive impact in the field of glycosylase biochemistry. The papers are solid and each reports useful new information."

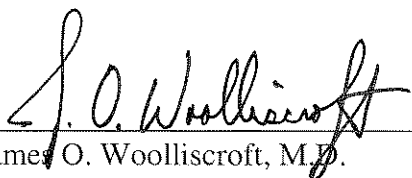
Reviewer D: "Dr. O'Brien began his independent career in a dark time of science funding. Nevertheless, he has pulled down significant grants from the NIH and ACS. This is not a small accomplishment during these tough times. I feel that his research is expanding in a number of exciting directions, and he has a very strong chance of remaining funded in the long run given the respect his work is garnering in the wider DNA repair community. In this regard, I was

present at a talk he gave at the FASEB meeting in 2010, which his talk received high praise from prominent scientists from both the United States and Europe.”

Reviewer E: “In reviewing Dr O’Brien’s publications during his appointment at the University of Michigan, I am impressed by the quality and consistency of the work in mechanistic enzymology. The research has been innovative, exhibits exceptional depth in the support of conclusions, and is at the forefront of a sophisticated and highly competitive field. Based on this productivity, I consider Dr. O’Brien to be one of *the* most promising investigators of his generation. It is obvious that the University of Michigan Medical School has done an outstanding job in fostering his development, and congratulations are in order regarding this success.”

Summary of Recommendation:

Dr. O’Brien has made excellent progress as an independent investigator and is a superb academic citizen. He has performed well in research, teaching, and service. Accordingly, I am pleased to recommend Patrick O’Brien, Ph.D. for promotion to associate professor of biological chemistry, with tenure, Department of Biological Chemistry, Medical School.



James O. Woolliscroft, M.D.

Dean

Lyle C. Roll Professor of Medicine

May 2012