Approved by the Regents
May 14, 2009

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF BIOLOGICAL CHEMISTRY

Raymond C. Trievel, 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:

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| Ph.D. | 2000 | University of Pennsylvania |
| B.S. | 1995 | University of Delaware |

Professional Record:

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| 2003-present | Assistant Professor of Biological Chemistry, University of Michigan |

Summary of Evaluation:

Teaching: In the realm of teaching, Dr. Trievel is co-director of the Department of Biological Chemistry's *Mechanisms of Eukaryotic Gene Expression* (BC650), which he helped initiate and has been taught as a three credit course since 2004. From 2004-2008, Dr. Trievel taught multiple sessions of Biological Chemistry's 597 *Critical Analysis* course. In 2007, Dr. Trievel taught in the interdepartmental Chemical Biology Doctoral Program, Chemical Biology 601, *Critical Analysis in Chemical Biology*. The student evaluations available for all of these classes consistently rank Dr. Trievel's teaching as well above average. Dr. Trievel has done a superb job of mentoring two postdoctoral fellows, one Ph.D. student, and six undergraduate students. A former postdoctoral fellow, Jean-Francois (Jeff) Couture, was awarded a Canadian Institutes of Health Research (CIHR) Postdoctoral Fellowship. Dr. Couture is now an assistant professor in the Department of Biochemistry, Microbiology and Immunology at the University of Ottawa. Two former undergraduate students, Glenn Hauk and Patricia Ortiz-Tello, while working in Dr. Trievel's laboratory, published articles and went on to Johns Hopkins University and were awarded an Intramural Research Training Award (IRTA) and Post-Baccalaureate Fellowship, respectively. Dr. Trievel has served on nine dissertation committees and ten preliminary examination committees for both the Department of Biological Chemistry and the Chemical Biology Doctoral Program. He also has mentored a total of eleven rotation students.

Research: Dr. Trievel studies the chromatin modifying enzymes and their associated factors and the mechanisms by which genes are transcribed. He has been at Michigan for just over five years but has already established himself as an excellent independent investigator. Soon after his arrival, his laboratory determined the crystal structures of two human histone methyltransferases, SET7/9 and SET8, in complex with their cognate protein substrates. Papers on these topics were published in *Nature Structural & Molecular Biology* and *Genes & Development*, respectively.

His laboratory also solved the structure of the WD40 protein WDR5, a subunit of the mixed lineage leukemia (MLL) histone methyltransferase complex and determined the mechanism by which WDR5 anchors this complex to chromatin through its binding to histone H3. In addition to his structural projects, Dr. Trievel has developed what is expected will be a widely applicable, coupled fluorescent assay for monitoring methylation reactions. He licensed this assay through the University's Office of Technology Transfer and filed for a U.S. Patent ("A Coupled Fluorescent Assay for S-adenosylmethionine-dependent methyltransferases") on the technology; the assay is now available commercially through Assay Design, Inc. Collectively, his results enabled Dr. Trievel to obtain NIH R01 grant support that began in January of 2006. With this funding, he is continuing to investigate the substrate specificity and catalytic mechanism of histone methyltransferases and has also initiated studies of the enzymes that reverse this modification.

Dr. Trievel's laboratory is involved in several interdisciplinary research projects through collaborations with intramural and extramural investigators. They are in the initial phases of establishing an intramural collaboration with Drs. Jay Hess and Yali Dou in the Department of Pathology to develop high-throughput assays to identify small molecule inhibitors of histone methyltransferases that contribute to the onset and progression of various forms of leukemia. These molecules could serve as lead compounds for novel therapeutics designed to treat cancer. He has also initiated a collaboration with Dr. Kristen Verhey, Department of Cell and Developmental Biology, and Dr. Roland Kwok, Department of Obstetrics and Gynecology, to study the structure and function of tubulin modifying enzymes, including tubulin tyrosine ligases, acetyltransferases, polyglutamylases, and polyglycylases. Dr. Trievel has been involved in several collaborations with extramural investigators, including Dr. Judd Rice, USC. They published an article in *FEBS Letters*. He is collaborating with Dr. Ali Shilatifard, Stowers Institute to characterize the enzymatic mechanism and specificity of COMPASS, a yeast histone H3 Lysine-4 methyltransferase complex. Another long-standing collaboration is with Dr. Robert Houtz, University of Kentucky, who studies the methylation of the plant enzyme Rubisco by Rubisco large subunit methyltransferase (LSMT). They have published an article in *Biochemistry*. Their laboratories have recently collaborated with Dr. Tom Walz, Harvard University, to determine the cryo-electron microscopy structure of Rubisco in complex with LSMT. Dr. Trievel is also collaborating with Dr. Lorraine Pillus, UCSD, to characterize the structure and function of yeast homocitrate synthase (HCS), an enzyme in the fungal lysine biosynthetic pathway. They have determined the crystal structure of the enzyme to elucidate its biological functions with the goal of developing inhibitors to treat fungal infections. These interdisciplinary projects have expanded Dr. Trievel's understanding of the molecular mechanisms underlying protein modifications and their regulatory roles in gene expression and signal transduction.

Recent and Significant Publications:

Couture J-F, Collazo E, Ortiz-Tello PA, Brunzelle JS, and Trievel RC: Specificity and mechanism of JMJD2A, a trimethyllysine-specific histone demethylase. *Nat Struct Mol Biol* 14:689-695, 2007. (Cover article; mini-review of this article: pgs. 682-684).

Couture J-F, Collazo E, and Trievel RC: Molecular recognition of histone H3 by the WD40 protein WDR5. *Nat Struct Mol Biol* 13:140-146, 2006.

Couture J-F, Hauk G, Thompson MJ, Blackburn GM, and Trievel RC: Catalytic roles for carbon-oxygen hydrogen bonding in SET domain lysine methyltransferases. *J Biol Chem* 281:19280-19287, 2006.

Couture J-F, Collazo E, and Trievel RC: Molecular recognition of histone H3 by the WD40 protein WDR5. *Nat Struct Mol Biol* 13:140-146, 2006.

Couture J-F, Collazo E, Brunzelle J, and Trievel RC: Structural and functional analysis of SET8, a histone H4 Lys-20 methyltransferase. *Genes Dev* 19:1455-1465, 2005.

Service: Dr. Trievel has served on two Graduate Student Admissions Committees, sometimes concurrently. He was on the Admissions Committee for the Department of Biological Chemistry from 2004-2006 and for the Chemical Biology Ph.D. Program from 2004-2008, and served as the liaison between these two committees. He also has served on the Department of Biological Chemistry's Equipment Committee (2003-2004). He was elected by the faculty to the Departmental Advisory Committee and served from 2004-2006. Since 2006, Dr. Trievel has served on the Protein Structure, Dynamics, and Design Initiative Committee, for the University of Michigan. Dr. Trievel has been invited to speak at the 2009 annual meeting of the American Society of Biochemistry and Molecular Biology in New Orleans, and to chair a session entitled "Chromatin Recognition and Assembly."

External Review:

Reviewer A: "Ray's papers are first rate–exciting, well written, and conclusive–and are all in high-profile journals....I also heard him give an outstanding lecture at the 2006 FASEB Summer Conference on Biological Methylation...Ray is a central player in this still emerging field and his achievements and leadership are well appreciated."

Reviewer B: "Simply put, I have deep respect for Ray's ability as a scientist and view him as one of the top structural biologists in the area of histone modifying enzymes....In summary, Ray has a winning research program and has emerged as one of the top structural biologist in his age group."

Reviewer C: "In short, Dr. Trievel has exploited his time as a new Assistant Professor at Michigan to become, I believe, one of the finest structural biologists [of his cohort] around. The quantity and high impact of his work at Michigan attest to this assessment."

Reviewer D: "...his papers all show a high quality of structure determination and make significant contributions to understanding the action of methyltransferases. This is an important area of research and Trievel has become a highly visible contributor. Judging by his publications he must be one of the leaders in the field."

Reviewer E: "All of these studies are quite valuable contributions, marked by attention to significant biological problems, an understanding of the important questions, and the ability to select and focus quickly on these questions from within the flood of new information in this field. Dr. Trievel is a major asset to the community of scientists interested in regulation of gene expression."

Reviewer F: "Dr. Trievel's main interest is lysine modification in histones, an interest he carries forward from his postdoctoral training. This is a hot field because of the role of histone modification in the control of gene expression....Dr. Trievel has made significant contributions to defining the peptide specificities of histone methyltransferases. The quality of his structural papers is very good to excellent."

Reviewer G: "The impact of Trievel's work will be huge as it becomes increasingly clear that epigenetics is governed by the histone code....Looking through Dr. Trievel's materials that you provided he seems a strong candidate for promotion and tenure. He has started a steady stream of high impact papers, he managed to get funded by NIH in this climate, he is sought as a speaker for seminars and meetings and he seems fully engaged in teaching and service at your University. .....Dr. Trievel's case would have easily passed the [promotion and tenure committee at my institution]..."

Summary of Recommendation:

Dr. Trievel is a very productive and highly respected investigator. He is a valued colleague both inside and outside the University of Michigan. I enthusiastically support Dr. Trievel's promotion to associate professor, with tenure, in the Department of Biological Chemistry.

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

May 2009