

PROMOTION RECOMMENDATION  
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL  
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

Roland P. Kwok, Ph.D., Assistant Professor of Obstetrics and Gynecology, Department of Obstetrics and Gynecology, Medical School, is recommended for promotion to Associate Professor of Obstetrics and Gynecology, with tenure, Department of Obstetrics and Gynecology, Medical School. [He also holds appointment as Research Assistant Professor, Reproductive Sciences Program, Department of Obstetrics and Gynecology and Assistant Professor of Biological Chemistry, Department of Biological Chemistry, Medical School.]

Academic Degrees:

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| Ph.D. | 1991 | University of Pittsburgh   |
| M.Sc. | 1985 | University of Saskatchewan |
| B.Sc. | 1982 | Chu Hai College, Hong Kong |

Professional Record:

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| 1998-Present | Assistant Professor of Obstetrics and Gynecology, University of Michigan   |
| 1998-Present | Assistant Professor of Biological Chemistry, University of Michigan  |
| 1998-Present | Research Assistant Professor, Reproductive Sciences Program, Department of Obstetrics and Gynecology, University of Michigan |

Summary of Evaluation:

Teaching: Since 2000, Dr. Kwok has been the course co-director for Critical Analysis (BC597), a two-credit class that meets twice a week. This class teaches first-year Biochemistry graduate students to read and analyze scientific papers. It is a team-taught class, which is normally composed of 9 to 10 biochemistry faculty. Each faculty lead two 1.5 hour classes which focus on discussing scientific papers. In addition to the two 1.5 hour class discussions and coordinating class activity, Dr. Kwok attended all lectures given by all other faculty. Dr. Kwok has also taught Eukaryotic Gene Expression (BC652) from 2001 to 2003. In 2005, Dr. Kwok gave one 1.5 hour lecture to students in Mechanism of Eukaryotic Gene Expression (BC650). Dr. Kwok has mentored three postdoctoral fellows, one of whom is now an Assistant Professor at Brown University. In addition, he has mentored several graduate and undergraduate students and has served on six preliminary examination committees and seven dissertation committees.

Research: One project in Dr. Kwok's laboratory is to investigate the mechanism by which acetylation of transcription factors affects transcription. Two papers were published in this area. The first paper showed for the first time that adenoviral protein E1A is acetylated by CBP and P/CAF at nuclear localization signal of E1A, and that acetylation of E1A retains E1A in the cytoplasm. This was the first paper to show that acetylation of lysine residues within the nuclear

localization signal blocks nuclear trafficking of a protein. Dr. Lundblad and Dr. Kwok shared the senior authorship of this paper because they contributed equally to this work. The second paper in this area demonstrated that acetylation of the transcription factor CREB affects its transactivation activity. This was the first paper to demonstrate that a component of the cAMP-signaling pathway is affected by acetylation. These recent findings as preliminary results, together with his body of work characterizing the CBP protein, provided the scientific justification and hypotheses for Dr. Kwok's pending RO1 application, which has been favorably reviewed, receiving a priority score of 156 (11.2 percentile) and is pending congressional approval of the NIH budget.

A separate project in Dr. Kwok's laboratory is studying how protein acetylation leads to the anti-cancer effects of a new series of anti-cancer agents, histone deacetylase inhibitors. Histone deacetylase inhibitors are experimental therapeutics that are on the verge of clinical use for several cancers, even though there has been no precise understanding about how they target and kill cancer cells. In collaboration with Dr. Valerie Castle, Chair of the Department of Pediatrics, and Dr. Anthony Opipari in the Department of Obstetrics and Gynecology, Dr. Kwok has demonstrated that treatment with HDAC inhibitors induces apoptosis in neuroblastoma (NB) cancer cells through a non-chromatin-dependent mechanism. The novel mechanism he discovered involves the acetylation-sensitive action of Ku70. Their work showed that, depending on its acetylation state, Ku70 can act as either an inhibitor or inducer of apoptosis in NB cells and that histone deacetylase inhibitors act by toggling its acetylation status. They recently published these results in *PNAS*. The publication of this paper prompted considerable interest in this novel mechanism by the scientific and pharmaceutical communities. Dr. Kwok was invited to describe their model and the implications of this mechanism by writing a perspective on this work (including published and unpublished data) by the Editor-in-Chief of *Cell Cycle*, Dr. Blagosklonny. This was published in *Cell Cycle* in 2005. These and additional results are being incorporated in two manuscripts which define other essential components of the acetylase-deacetylase machinery that are necessary for this class of therapeutics to selectively and effectively engage this mechanism. An RO1 application, on which Dr. Kwok will be the principal investigator, is also being developed based on these discoveries.

In addition to the two major projects described above, Dr. Kwok has collaborated with colleagues inside and outside of the University of Michigan, and resulted in six collaborative papers. Dr. Kwok has 30 peer-reviewed publications, 12 of which were published since his appointment at the University of Michigan. He received a pre-doctoral fellowship from NIH in 1990, a NRSA from NIH in 1993, and served as a Leukemia Society Research Special Fellow from 1997 to 2000.

#### Recent and Significant Publications:

Subramanian C, Opipari AW, Bian X, Castle VP, Kwok RPS: Ku70 acetylation mediates neuroblastoma cell death induced by histone deacetylase inhibitors. *Proc Natl Acad Sci* 102:4842-4847, 2005.

Subramanian C, Opipari AW, Castle VP, Kwok RPS: Histone deacetylase inhibition induces apoptosis in neuroblastoma. *Cell Cycle* 4(12):1741-1743, 2005.

Kuo HY, Chang CC, Jeng JC, Hu HM, Lin DY, Maul G, Kwok RPS, Shih HM: SUMO modification negatively modulates the transcriptional activity of CREB-binding protein via the recruitment of Daxx. *Proc Natl Acad Sci* 102:16973-16978, 2005.

Lu Q, Hutchins AE, Doyle CM, Lundblad JR, Kwok RPS: Acetylation of CREB by CBP enhances CREB-dependent transactivation. *J Biol Chem* 278:15727-15723, 2003.

Madison DL, Yaciuk P, Kwok RPS, Lundblad JR: Acetylation of the adenovirus-transforming protein E1A determines nuclear localization by disrupting association with Importin- $\alpha$ . *J Biol Chem* 277:38755-38763, 2002.

Service: Dr. Kwok is a member of the Endocrine Society, the American Association for the Advancement of Science, and the American Society for Biochemistry and Microbiology. Dr. Kwok serves as an ad hoc reviewer for the *Journal of Biological Chemistry*, *Journal of Virology*, *Molecular and Cellular Biology*, and the *Proceedings of the National Academy of Sciences*. In addition, he serves as a grant reviewer for the Breast Cancer Research Program, MBC-5, Department of Defense, and for the National Science Foundation. Dr. Kwok has also served as a member of the Department of Biological Chemistry Advisory Committee (1999-2000), Chair of the Department of Biological Chemistry Seminar Committee (1999-2000), a member of the Program Committee, Reproductive Sciences Program (2000-2001), and as a member of the Training Committee, Reproductive Sciences Program (2003-2004).

#### External Review:

Reviewer A: "...his bibliography, although is not extensive, includes publications in very impressive journals...He is well respected based upon the invitations he has received to present in several prestigious settings. His work is excellent as judged by the publications I received, the quality of the journals in which he is published, and his recent impressive NIH score."

Reviewer B: "These are all solid, significant, scholarly works. The studies make significant contributions to understanding transcriptional regulation and certainly have an impact in the field."

Reviewer C: "Dr. Kwok's initial observation was that CREB binding protein (CBP) functions as a coactivator for CREB-mediated transcription. The impact of this single finding can be best understood by the number of papers that cite Dr. Kwok's original Nature papers (over 2000). Since these early papers, which have given Dr. Kwok national and international recognition, he has continued his studies into the function of CBP...This work has continued to provide key insight into the role of CBP and other histone acetyltransferases in the regulation of transcription. For example, Dr. Kwok's more recent work has been seminal in providing clear and convincing data that acetylation of transcription factors and viral proteins alter their ability to regulate transcription."

Reviewer D: "Since joining the faculty of the University of Michigan Dr. Kwok has continued his studies on transcriptional regulation and has authored or co-authored 9 publications, many of which are in high impact scientific journals (JBC, Molecular

Endocrinology, PNAS). It is important to note that these publications address complex problems in nuclear transcription factors and that they present very detailed, technically complex and carefully crafted experiments which lie well beyond the realm of 'me too' science."

Reviewer E: "In addition to his scientific accomplishments, Roland has also shown real evidence of citizenship in teaching and thesis committee membership. These skills, along with his ability to collaborate effectively with other investigators in his department, no doubt enhance Roland's value to the University."

Reviewer F: "Dr. Kwok has picked interesting and highly relevant topics to investigate as an independent scientist, and it appears he will continue to address these questions in the foreseeable future. He should be encouraged to do so. His research papers are cleanly performed and elegantly developed."

Reviewer G: "Dr. Kwok's research has made important and crucial impact on this field of study. Dr. Kwok is recognized nationally and likely internationally as an emerging and important leader in this scientific area."

Summary of Recommendation:

Dr. Kwok has proven himself to be a very capable researcher and teacher. His research focus is important and it is anticipated that his laboratory will continue its scholarly, scientific, and educational pursuits and will be an asset to the Department of Obstetrics and Gynecology as well as the University of Michigan Health System as a whole. I am pleased, therefore, to recommend Dr. Kwok for promotion to Associate Professor of Obstetrics and Gynecology, with tenure.



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Allen S. Lichter, M.D., Dean  
*Newman Family Professor  
of Radiation Oncology*

May 2006