Approved by the Regents
May 17, 2012

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF PEDIATRICS AND COMMUNICABLE DISEASES

Linda M. McAllister-Lucas, M.D., associate professor of pediatrics and communicable diseases, without tenure, Department of Pediatrics and Communicable Diseases, is recommended for the granting of tenure to be held with her title of associate professor of pediatrics and communicable diseases, Department of Pediatrics and Communicable Diseases, Medical School.

Academic Degrees:

M.D.	1996	Vanderbilt University
Ph.D.	1994	Vanderbilt University
B.A.	1987	Carleton College, Northfield, MN

Professional Record:

2010-present	Associate Professor of Pediatrics and Communicable Diseases, without tenure, University of Michigan
2004-2010	Assistant Professor of Pediatrics and Communicable Diseases, University of Michigan
2002-2004	Lecturer, Department of Pediatrics and Communicable Disease, University of Michigan

Summary of Evaluation:

Teaching: Dr. McAllister-Lucas contributes to the educational mission at the University of Michigan through all levels. She has served as a faculty mentor for premedical undergraduates, medical students, pediatric residents, pediatric hematology and oncology (PHO) fellows, UROP students, graduate students, MSTP students, post-doctoral fellows and several of our junior faculty. Dr. McAllister-Lucas teaches in the Medical School's M2 hematology sequence, and she contributes lectures to the pediatric resident and pediatric PHO fellow crash courses. She supervises medical students, interns and residents on the PHO inpatient and outpatient services. She mentors fellows throughout their training as a primary attending physician in the outpatient clinic and contributes lectures to formal education sessions. From 2002-2010, she played a critical role as the director of the Pediatric Tumor Board, an important aspect of academic learning for PHO fellows. She has also played a critical role in national education efforts by contributing lectures to the UM Medical School Annual Pediatric Board Review Course and to the American Academy of Pediatrics (AAP) Pediatrics Review and Education Program (PREP) Review course. Her mentees have received numerous research awards including Department of

Pediatrics Post-Doctoral Research Awards, a UM Comprehensive Cancer Center Research Award, and the Nancy Newton Loeb and Helen L. Kay Pediatric Cancer Research Awards.

Research: Dr. McAllister-Lucas' research interests lie in the elucidation of key intracellular events that regulate the NF-kappaB signaling pathway and their influence on the pathogenesis of inflammatory and malignant disease. Her studies have focused on investigating the role of Bcl10 and MALT1, two proteins whose genes were originally identified as targets of recurrent chromosomal translocation in lymphoma, as regulators of NF-kappaB transcriptional activation, cellular proliferation and inflammation. Her laboratory discovered that a protein complex composed of CARMA, Bcl10 and MALT1 (CBM), mediates activation of the NF-kappaB transcription factor in response to stimulation of the Angiotensin type 1 receptor, thereby providing the first evidence that the CBM complex performs a critical function outside of lymphocytes. Her laboratory's first manuscript describing this role for the CBM complex, along with two other independent studies that were published "back-to-back," provided compelling evidence that the CBM complex constitutes the long-sought-after "missing link" between G-Protein Coupled Receptor (GPCR) stimulation and NF-kappaB activation. In subsequent publications, Dr. McAllister-Lucas and her colleagues went on to demonstrate that GPCR-induced, CBM-mediated stimulation of NF-kappaB plays a critical role in the pathogenesis of vascular inflammation and atherosclerosis. In addition to these investigations of the CBM complex, Dr. McAllister-Lucas' laboratory has also elucidated the mechanisms by which API2-MALT1, a fusion oncoprotein created by recurrent chromosomal translocation in a subset of Mucosa Associated Lymphoid Tissue (MALT) lymphomas, contributes to disease pathogenesis. First, Dr. McAllister-Lucas and colleagues demonstrated that the API2 portion of the fusion forms several protein-protein interactions that are critical to oncogenic function. Then, later, Dr. McAllister-Lucas and colleagues demonstrated that the MALT1 portion of this fusion possess proteolytic activity that is critical to its ability to promote lymphomagenesis. These exciting findings revealed a new paradigm for the mechanism by which fusion oncoproteins promote cancer and identified the MALT1 proteolytic domain as a potential new therapeutic target. As such, this work was published in *Science*, one of the top high-impact scientific journals. Dr. McAllister-Lucas' discoveries have been the subject of numerous high profile review articles. As evidence of her expertise and the quality of her scientific contributions, Dr. McAllister-Lucas' publications have been cited more than 1,300 times and her expertise in NF-kappaB signaling has led to several additional research collaborations. Dr. McAllister-Lucas has been funded thus far through four R01 grants where she is either the principal investigator or the co-investigator. She has also received funding from two UMCCC grants and from a private foundation. Her research insights have been presented at national and international meetings, and she has been invited to give research presentations at several peer biomedical research institutions, including the Cleveland Clinic, University of Iowa, and Vanderbilt University. Within clinical oncology, she is the institutional PI on a Children's Oncology Group (COG) pilot study for B-cell leukemia/lymphoma, is co-director of a Hematopathology Tissue Bank Initiative and participates in numerous other clinical research activities.

Recent and Significant Publications:

Rosebeck S, Madden L, Jin X, Gu S, Apel IJ, Appert A, Hamoudi RA, Noels H, Sagaert X, Van Loo P, Baens M, Du MQ, Lucas PC, McAllister-Lucas LM: Cleavage of NIK by the API2

MALT1 fusion oncoprotein leads to noncanonical NF-kappaB activation. *Science* 331:468-472, 2011.

McAllister-Lucas LM, Jin X, Gu S, Siu K, McDonnell S, Ruland J, Delekta PC, Van Beek M, Lucas PC: The CARMA3-Bcl10-MALT1 signalosome promotes angiotensin II-dependent vascular inflammation and atherogenesis. *Journal of Biological Chemistry* 285:25880-25884, 2010.

McAllister-Lucas LM, Lucas PC: Finally, MALT1 is a protease. *Nature Immunology* 9:231-233, 2008.

McAllister-Lucas LM, Ruland J, Siu K, Jin X, Gu S, Kim DS, Kuffa P, Kohrt D, Mak TW, Nunez G, Lucas PC: CARMA3/Bcl10/MALT1-dependent NF-□B activation mediates angiotensin II-responsive inflammatory signaling in non-immune cells. *Proceedings of the National Academy of Sciences* 104:139-144, 2007.

Lucas PC, Kuffa P, Gu S, Kohrt D, Kim DS, Siu K, Jin X, Swenson J, and McAllister-Lucas LM: A dual role for the API2 moiety in API2-MALT1-dependent NF-□B activation: heterotypic oligomerization and TRAF2 recruitment. *Oncogene* 26:5643-5654, 2007.

Service: Divisionally Dr. McAllister-Lucas has served as the director of the Pediatric Hematology Oncology Tumor Board, and serves on our Recruitment and Retention, Clinical Database, PHO fellow research steering and GME Committees. Departmentally she has served as a moderator for the Annual Pediatric Research Symposium and as member of the Research Advisory Committee, and is a member of the resident selection committee. Dr. McAllister-Lucas participates as a Ph.D. thesis committee member for graduate students in the Cellular and Molecular Biology Program. She is a member of the Medical School MSTP Advisory Committee, and in July 2011, she was appointed as the Associate Director of the UM MSTP program. Dr. McAllister-Lucas serves as attending physician on the inpatient PHO service for four to six weeks per year and one day per week in the outpatient PHO clinic. Her excellent and compassionate care has been recognized by Best Doctors in America and America's Top Doctors.

External Reviewers:

Reviewer A: "Her recent publication this year in *Science* was a major advancement in the field of understanding the critical signal transduction pathways regulating NF-KB activation particularly in MALT lymphomas, but it has worldwide implications in other malignancies that involved the NF-KB pathway."

Reviewer B: "...I would rate Dr. McAllister-Lucas in the top 5% of faculty in pediatric hematology/oncology. She is well-known nationally and I think her work will have a profound impact on both the clinical and laboratory biology of hematological malignancies."

Reviewer C: "...Dr. McAllister-Lucas has displayed her superb scientific abilities in a number of areas. Her research and leadership roles have already made an impact and influenced the field

of inflammation, immunology, and cancer. Indeed, she is highly respected and well regarded in our research community…"

Reviewer D: "Her scholarly contributions in the area of basic research into signaling transduction pathways is very strong and she has provided important insights into the role of chronic inflammation in the development of MALT lymphomas. This research is original and is establishing Dr. McAllister-Lucas as a leader this field. In addition she has strong contributions in the areas of clinical activities, teaching and administration."

Reviewer E: "She has clearly been successful in establishing an independent academic laboratory during her time as Assistant Professor of Pediatric Hematology and Oncology at the University of Michigan; and has remained productive in her research endeavors despite the challenges of simultaneously practicing as a well-trained, nationally-recognized pediatric oncologist."

Summary of Recommendation:

Dr. McAllister-Lucas provides outstanding contributions to all core areas of the university's academic mission. Her diligence in the laboratory has been rewarded with significant extramural funding from multiple agencies. Dr. McAllister-Lucas is a pillar of her divisional program and is advancing its infrastructure toward translational and institutional phase I studies in lymphoid malignancies. Her most recent work has resulted in multiple publications in high-impact journals including *Science*. I strongly recommend Linda M. McAllister-Lucas, M.D. for the granting of tenure to be held with her title of associate professor of pediatrics and communicable diseases, Department of Pediatrics and Communicable Diseases, Medical School.

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

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