Approved by the Regents
May 19, 2011

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN
MEDICAL SCHOOL
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

Maria B. Sandkvist, Ph.D., assistant professor of microbiology and immunology, Medical School, is recommended for promotion to associate professor of microbiology and immunology, with tenure, Department of Microbiology and Immunology, Medical School.

Academic Degrees:

Ph.D.	1992	Umeå University, Sweden
B.S.	1984	Umeå University, Sweden

Professional Record:

2005-present	Assistant Professor of Microbiology and Immunology, University of Michigan
2005	Assistant Professor of Internal Medicine, University of Maryland

Summary of Evaluation:

Teaching: Dr. Sandkvist is a dedicated teacher of undergraduate and graduate students. She directs a major graduate course in the department, Microbiology 607, a literature-based course with a focus on bacterial pathogenesis. She also teaches in Microbiology 512, a grant writing course designed to prepare graduate students for writing fellowships. She is a member of a team (her responsibility is 25% of the course) that teaches Microbiology 405, an infectious diseases course taken by undergraduates majoring in microbiology. In the 405 and 607 courses, Dr. Sandkvist commits roughly 25 hours of contact and presentation time for each, whereas 512 requires closer to 40 hours per semester. She consistently receives strong evaluations from her students who rate her highly for her knowledge of the material and her level of preparation in the classroom. Her teaching has included a considerable amount of new material preparation for an assistant professor and she has done extremely well with it. Her talent and commitment to teaching follows through in her training of students both in the department and around campus as well. She has attracted three graduate students, two undergraduate students and three postdoctoral fellows to train with her since she joined the faculty at Michigan. These students and fellows have been successful publishing their work in good journals and obtaining honors and awards as well as opportunities for presenting their work at international meetings in the field. Dr. Sandkvist is sought after by students in other labs to serve on their thesis committees, having served on 11 of these since 2005.

Research: Dr. Sandkvist studies mechanisms by which bacterial pathogens deliver toxins during infection. Her work is at the interface of basic and translational science, as she is identifying new targets for drug development to combat important and deadly pathogens, including those

causing cholera, Legionnaire's Disease and food poisoning. As a graduate student, Dr. Sandkvist set out to identify the mechanism by which toxin is assembled and secreted from *V. cholerae*. This work led her to discover of a set of genes required for toxin secretion; she named these "extracellular protein secretion" genes, or *eps*. The discovery of the *eps* Type II secretion system was understood by other cholera researchers as a major finding, and firmly established her as a major investigator in the field of cholera research, notwithstanding that she was still a graduate student. Over the years she has made several key observations regarding the structure and function of the Eps proteins, leading to the general hypothesis they appear to form a large protein complex that spans the entire cell envelope. Further, she demonstrated that the complex is an integral feature of outer membrane integrity in *V. cholerae*. In addition, she published an important paper showing that membrane phospholipids are also a component of the secretion process by regulating the activity of a key ATPase in the Eps system. She has applied many investigative approaches to understanding the nature of this complex and recently has established a very fruitful collaboration with a group at University of Washington led by Dr. Wim Hol, to analyze the molecular structure of these proteins using X-ray crystallography. This work has led to a series of publications describing the structures and interactions required for Eps regulated secretion. Her work, both that carried out in her own laboratory as well as that done in collaboration with the Hol laboratory, is becoming the paradigm for our understanding of how similar multi-protein complexes regulate secretion in other bacteria, including several pathogenic species. Her recent work as an independent investigator has applied cutting edge proteomic approaches to identify all of the proteins that are secreted by the Eps system. This work has let to identification of several proteases – proteins that degrade other proteins – which may also be contributing in yet undiscovered ways to the biology and pathogenicity of *V. cholerae*. In addition, because the Eps proteins are found in so many other disease-causing bacteria, they make attractive targets for developing new classes of anti-microbial compounds. To this end, Dr. Sandkvist has taken advantage of the expertise available at the UM Center for Chemical Genomics to screen large libraries of compounds that block secretion from the *V. cholerae* Eps. Molecules she identifies will serve as potential lead compounds for further drug discovery and will also have great value as research reagents to probe the molecular interactions required in protein secretion. Her work is routinely published in outstanding journals and she has been invited to present seminars and lectures around the world. Additionally, her widely appreciated expertise has led to invitations to chair sessions at several important meetings in the field of microbiology, as well as to write review articles covering recent literature in the field of protein secretion.

Recent and Significant Publications:

Korotkov KV, Gray MD, Kreger A, Turley S, Sandkvist M, and Hol WGJ: Calcium is essential for the major pseudopilin in the Type 2 Secretion System. *J Biol Chem* 284:25466-25470, 2009.

Lybarger SR, Johnson TL, Gray M, Sikora AE, and Sandkvist M: Docking and assembly of the Type II secretion complex of Vibrio cholerae. *J Bacteriol* 191:3149-3161, 2009.

Camberg J, Johnson TL, Patrick M, Abendroth J, Hol WGJ, and Sandkvist M: Synergistic stimulation of EpsE ATP hydrolysis by EpsL and acidic phospholipids. *EMBO J* 26:19-27, 2007.

Sikora A, Lybarger SR, and Sandkvist M: Compromised outer membrane integrity in *Vibrio cholerae* type II secretion mutants. *J Bacteriol* 189:8484-8495, 2007.

Johnson TL, Abendroth J, Hol WGJ, and Sandkvist M: Type II Secretion: from structure to function. Review; *FEMS Microbiology Letters* 205:175-186, 2006.

Service: Dr. Sandkvist is sought out for service on faculty committees, bringing the same focus and discernment to these activities as she does to her research and teaching. She has a reputation among her colleagues for equanimity and reason, and she carries out administrative and service responsibilities extremely effectively. In the Department of Microbiology, she has served on the Graduate Studies Committee, the Departmental Appointments, Promotions and Awards Committee, the Operating Committee for the Molecular Mechanisms in Microbial Pathogenesis (MMMP) Training Program, as a member of a Joint Faculty Appointment Task Force, as well as on the search committee for the Multi-scale Cell Mechanics Cluster hire. In addition, she has organized a monthly faculty research meeting designed to assist all faculty within the department in sharing their research ideas and getting feedback to enhance grant proposal and paper writing. This is an enormous amount of service for an assistant professor, speaking to Dr. Sandkvist's reputation for hard-work, fairness, and open mindedness in all she does.

External Review:

Reviewer A: "...Dr. Sandkvist has become a world leader in the study of the Type II secretion system. She has published many exceptional papers on the mechanistic details of the secretion process, including the crystal structure and biochemical function of many of the individual protein components. The importance of her results to the field of microbiology are great [sic], and have positively influenced many areas ranging from industrial microbiology to infectious disease to the search for new antibiotics and enhanced vaccines."

Reviewer B: "She is certainly regarded as the most knowledgeable scientist in the US of type II secretion machines; her international reputation is also on a trajectory to place her at the top of her field world-wide."

Reviewer C: "...Dr. Sandkvist's research, as evidenced by her papers, grant support, invited talks, and broad external service, has had a significant impact on our field. To my mind, she has clearly established herself as a productive and influential independent investigator."

Reviewer D: "Her research is of the highest scholarly standards, has been cited over 2000 times, and has appeared in very high quality journals. She has been invited as a speaker and has chaired sessions to numerous international meetings."

Reviewer E: "All through her work Maria Sandkvist showed her ability to establish her very own research line with very attractive ideas she has herself developed. By doing so she successfully put her own print in the field."

Reviewer F: "Her vigorous record of achievement has really taken off during [the] last five years at Michigan, and earns my unhesitating support."

Summary of Recommendation:

Dr. Sandkvist has distinguished herself as an outstanding researcher who has earned the respect of her peers in the field, as well as the admiration of her Michigan colleagues. She is a leader in a competitive and important field of research whose work is both basic and translational. Her insights and contributions have been important and novel and is clearly on a trajectory to make continued important observations in her research. Her teaching is extensive and well-done, covering a range of topics of interest to students at many levels of education at Michigan. Her service is exemplary, demonstrating effective leadership and helpful collegiality. She has met the challenges of establishing herself as a scholar and educator at Michigan, and is exceedingly qualified for promotion to associate professor, with tenure.

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

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