

PROMOTION RECOMMENDATION
UNIVERSITY OF MICHIGAN MEDICAL SCHOOL
DEPARTMENT OF INTERNAL MEDICINE

Approved by the Regents
May 15, 2008

Joseph Holoshitz, M.D., Associate Professor of Internal Medicine, with tenure, Department of Internal Medicine, Medical School, is recommended for promotion to Professor of Internal Medicine, with tenure, Department of Internal Medicine, Medical School.

Academic Degrees:

M.D.	1978	Hebrew University, Jerusalem, Israel
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Professional Record:

1993-Present	Associate Professor of Internal Medicine, University of Michigan
1989-1993	Assistant Professor of Internal Medicine, University of Michigan
1985-1992	Senior Lecturer in Medicine, Tel Aviv University (concurrent with U of M appointment)
1981-1985	Instructor in Medicine, Tel Aviv University

Summary of Evaluation:

Teaching: Dr. Holoshitz's commitment to teaching has been substantial and has involved instructing trainees at multiple levels in both clinical and laboratory settings. In the clinical setting, he has supervised medical residents and students for two months each year on the General Medicine Inpatient Service and the Rheumatology Consult Service. Dr. Holoshitz is one of only a handful of specialists in the Department of Internal Medicine who continues to volunteer each year for teaching and clinical duty on the General Internal Medicine Inpatient Service. Dr. Holoshitz has also supervised many Rheumatology fellows, residents and medical students in the Rheumatology Clinic. He has been a member of the Rheumatology Fellowship Selection Committee for the past 16 years, interviewing, ranking and recruiting all of the Rheumatology fellows in our program during that interval. In the laboratory, he has supervised a wide range of trainees, ranging from undergraduate students to advanced post-doctoral scientists. Several have gone on to independent research careers or distinguished faculty positions. All trainees with whom Dr. Holoshitz has worked in a clinical setting have filled out quantitative evaluations. Consistently, medical students and internal medicine residents who have worked closely with him for intervals of two to four weeks have ranked his teaching in the excellent to outstanding range and added specific comments attesting to his dedication and effectiveness as a clinical teacher. Dr. Holoshitz has displayed outstanding teaching skills in formal lecture settings as well as informal seminars. A 2006 Department of Internal Medicine Grand Rounds delivered by Dr. Holoshitz was especially noteworthy for the ground-breaking nature of the data presented as well as its meticulous preparation and compelling delivery.

Research: Dr. Holoshitz's research has focused on the role of lymphocytes in autoimmunity, particularly in relationship to rheumatoid arthritis. He gained an international reputation early in his career as a pioneer in the field of T-cell autoimmunity, and was one of the leaders in establishing a role for T-lymphocytes in rheumatoid arthritis. He then went on to provide

important insights into the function and specificity of gamma delta T-cell subsets. More recently, his research has moved in new directions, although still grounded in understanding the role of lymphocytes in autoimmune disease. His most recent papers have documented several unique, surprising and entirely novel phenomena related to rheumatoid arthritis. Dr. Holoshitz has shown that overproduction of sphingosine-1-phosphate by rheumatoid arthritis B-lymphocytes causes impaired susceptibility to programmed cell death of these cells. These findings are entirely novel both with respect to mechanisms of B-cell survival in RA and regarding the signaling pathway that he identified. In a second recent paper, Dr. Holoshitz used B-lymphoblastoid lines derived from patients with RA and their unaffected monozygotic twins to uncover epigenetic changes associated with RA, involving expression of several different molecules that may be targets of the immune response and also participants in inflammatory pathways. Remarkably, several molecules identified as over-expressed in the B-lymphoblastoid lines through microarray analysis were also found to be over-expressed in RA synovial tissue. This work was highlighted by the National Institutes of Health on its website and reported widely in both scientific and lay media. Finally, in his most recent work, Dr. Holoshitz has discovered a completely new mechanism for association of specific MHC alleles with immune mediated disease. It is important to understand that up to this point, despite the clear association of various MHC alleles with various autoimmune diseases, the mechanism of such associations has not been established for a single disease. Dr. Holoshitz has found that peptides derived from an RA-associated MHC allele actually bind to another receptor on the cell surface, calreticulin, and trigger nitric oxide signaling in cells as a result of this receptor binding. Such allele-specific metabolic activity of the MHC was hitherto completely unexpected and will create a new paradigm for understanding autoimmunity. This ground breaking work is currently supported by a highly competitive award from the Research and Education Foundation of the American College of Rheumatology. His recent work has also spawned several grant applications to the NIH, and funding of one or more of these proposals is highly likely in the near future.

Recent and Significant Publications:

Ling S, Pi X and Holoshitz J. The rheumatoid arthritis shared epitope triggers innate immune signaling via cell surface calreticulin. *J Immunol*. In Press, 2007.

Ling S, Li Z, Borschukova O, Xiao L, Pumpens P, and Holoshitz J: The rheumatoid arthritis shared epitope increases cellular susceptibility to oxidative stress by antagonizing an adenosine-mediated anti-oxidative pathway. *Arthritis Res Therapy* 9, R5, 2007.

Pi X, Tan S-Y, Hayes M, Xiao L, Shayman JA, Ling S and Holoshitz J: Sphingosine kinase 1 – mediated inhibition of Fas death signaling in rheumatoid arthritis B lymphoblastoid cells. *Arthritis Rheum* 54:754-64, 2006.

Haas C, Creighton CJ, Pi X, Maine I, Koch EA, Haines GK III, Ling S, Chinnaiyan AM and Holoshitz J: Identification of genes modulated in rheumatoid arthritis using cDNA microarray analysis of disease-discordant monozygotic twin cells. *Arthritis Rheum* 54:2047-2060, 2006.

Ling S, Lai A, Borschukova O, Pumpens P and Holoshitz J: Activation of nitric oxide signaling by the rheumatoid arthritis shared epitope. *Arthritis Rheum* 54:3423-3432, 2006.

Service: Dr. Holoshitz's service to the Division of Rheumatology and to the University of Michigan has been exemplary. In the Division of Rheumatology he has been a long term member of the Fellowship Selection Committee, the Faculty Search Committee, the Executive Committees of the Multipurpose Arthritis Center, and more recently, the Rheumatic Disease Core Center, and in addition has been Associate Chief for Research of the Division of Rheumatology. He has also served on numerous committees of the SACUA and on the Department of Internal Medicine Associate Chair Research Advisory Committee. He is currently serving on mentorship committees for two junior faculty members in Rheumatology and it is worth noting that when those individuals were asked to nominate members of their mentoring committee, Dr. Holoshitz was their first choice. He will undoubtedly be serving on additional mentoring committees as this system of support for our faculty and trainees becomes more widely implemented. In all of these administrative activities, Dr. Holoshitz is sought out for his exceptional analytic capabilities and his gift for identifying and articulating critical issues clearly and constructively.

Professional Work: Dr. Holoshitz's clinical service in the Division of Rheumatology and the Department of Internal Medicine is far greater than the amount expected of a physician scientist. He maintains a busy Rheumatology clinic on a weekly basis and rounds for two months each year, one month on the Rheumatology Consult Service and one on the General Medicine Inpatient Service, both very intensive clinical assignments. He has proven himself to be a very knowledgeable, careful and effective clinician in all of these settings.

External Review:

Reviewer A: "...Dr. Holoshitz has developed new and important concepts that advance our understanding of rheumatoid arthritis. He undoubtedly has established himself as a scholar in the field. His contributions are creative and innovative, and he has impacted the field by exploring novel models and pathways rather than by following established paths."

Reviewer B: "...I can testify that these papers of Dr. Holoshitz reflect outstanding science in terms of their originality, rationale, breadth of techniques, experimental execution, conclusions, and insights provided...Dr. Holoshitz is an innovator. His recent work is of the highest caliber of any that is being done on the pathogenesis of rheumatoid arthritis."

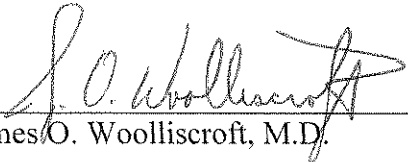
Reviewer C: "His contributions to understanding autoimmune diseases, especially rheumatoid arthritis, are significant and with his recent observations he is poised to make more major breakthroughs in this area."

Reviewer D: "...he has a long history of innovation and creativity in his investigations and his current work shows how he continues to stimulate and move the field forward with new ideas and directions having relevance to rheumatoid arthritis."

Reviewer E: "His more recent work has undergone significant advances over the last year. These studies are highly creative and provocative...This work is quite groundbreaking, and if confirmed and extended, may be a possible explanation for a genetic association that has eluded clear explanation for several decades."

Summary of Recommendation:

Dr. Joseph Holoshitz is an unusually creative physician scientist whose research has been truly groundbreaking in the fields of rheumatoid arthritis and autoimmunity. He has also distinguished himself as an excellent clinician and teacher as well as an effective contributor to University administrative activities and to the scientific community nationally. Based on his many accomplishments and his stature as a physician scientist, I am delighted to support his promotion to Professor, with tenure, in the Department of Internal Medicine.

A handwritten signature in cursive script, appearing to read "J. O. Woolliscroft", written over a horizontal line.

James O. Woolliscroft, M.D.

Dean

Lyle C. Roll Professor of Medicine

May 2008