

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

Irina Grigorova, Ph.D., assistant professor of microbiology and immunology, Department 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.	2005	University of California
M.S.	1999	Moscow State University
B.S.	1996	Russian Federation Moscow State University

Professional Record:

2010 – present	Assistant Professor of Microbiology and Immunology, University of Michigan
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Summary of Evaluation:

Teaching: Dr. Grigorova has engaged in extensive teaching of immunology as she is the only B cell immunologist. She fulfills a critical teaching role for the department by instructing students in an essential component of the immunology curriculum, that relating to B cell immunology. In the graduate school, Dr. Grigorova has taught the humoral immunity module of 640 Cellular and Molecular Immunology course since 2011. Since 2012, she also lectures on the topic of B cell signal transduction in the 619/641 Advanced Immunology course. Dr. Grigorova has also acted as a research mentor for a number of different trainees in her laboratory including two full time Ph.D. students, five rotating graduate students, two masters students, a post-doctoral fellow, seven undergraduates and two high school students. She has been closely involved in all aspects of research mentorship in her laboratory including instructing trainees in literature research, critical thinking, hypothesis testing, ethical conduct of research, presentation of research findings and networking. The quality of Dr. Grigorova's mentorship is underscored by the fact that both full time Ph.D. students were awarded prestigious Immunology Program Herman and Dorothy Miller Fund Awards for their final years of training in her laboratory. Furthermore, both students graduated and are currently engaged in post-doctoral training at other institutions. Dr. Grigorova has also served on twelve dissertation committees of graduate students at the University of Michigan and has thus also contributed substantially to the research training of students outside of her own laboratory.

Research: Dr. Grigorova has continued to explore the mechanisms of lymphocyte participation in *in vivo* immune responses with a strong emphasis on understanding how T cells collaborate with B cells to induce their differentiation into antibody secreting plasma cells and memory B cells. Understanding how T cells and B cells cooperate in immune responses is critical from several different biological and clinical perspectives, not least of which is improved vaccine design. She has made important fundamental discoveries in this area. Building upon an earlier observation that B cells acquire antigen only transiently at the outset of the immune response, she sought to

determine whether such transient antigen acquisition was sufficient for participation in the antibody response. Her group also examined if delayed interaction of these antigen-primed B cells with helper T cells resulted in their long-term inactivation or even elimination from the immune repertoire as other, earlier, studies had suggested they might. Using complex transgenic lymphocyte adoptive transfer models combined with intra-vital microscopy, Dr. Grigorova resolved these outstanding issues. Dr. Grigorova has investigated which factors are most critical for the entry of B cells into germinal centers in lymph nodes during an ongoing immune response and which chemoattractant molecules are required for their communication with T follicular regulatory cells at these sites. These studies have revealed temporal constraints for B cell entry into germinal centers dependent on the length of time since their most recent exposure to antigen and have also revealed a critical role for the CCL3 chemokine for B cell interaction with T follicular regulatory cells in germinal centers. Using a novel experimental approach, Dr. Grigorova has recently shown that under conditions of limiting T cell help, BCR signal strength is an important factor that governs the recruitment of B cells into the germinal center response. This finding challenges the prevailing view that the magnitude of T cell help alone dictates B cell entry into the germinal center reaction. She has been well funded through the NIH, industry and private foundations. Dr. Grigorova has published 20 peer-reviewed articles and has been invited to present her research on seven occasions nationally and internationally.

Recent and significant publications:

Turner J, Fang K, Grigorova L: B cell receptor crosslinking can augment T cell help mediated germinal center B cell selection. *Cell Reports* (in press) 2018.

Turner J, Benet Z, Grigorova I: Antigen Acquisition Enables Newly Arriving B Cells To Enter Ongoing Immunization-Induced Germinal Centers. *J Immunol* 199(4):1301-1307, 2017.

Turner J, Marthi M, Benet Z, Grigorova I: Transiently antigen-primed B cells return to naive-like state in absence of T-cell help. *Nat Commun.* 8:15072, 2017.

Turner J, Benet Z, Grigorova I: Transiently antigen primed B cells can generate multiple subsets of memory cells. *PLoS One* 12(8): e0183877, 2017.

Benet Z, Marthi M, Fang K, Wu R, Turner J, Gabayre J, Ivanitskiy M, Sethi S, Grigorova I: CCL3 promotes germinal center B cells sampling by follicular regulatory T cells in murine lymph nodes. *Frontiers Immunology* Sept.13,9:2044, 2018.

Service: Dr. Grigorova has been a willing and enthusiastic participant in administrative and service duties. At the departmental level, she has served on numerous committees, including the Graduate Studies Committee and the Appointments, Promotions and Awards Committee. At the national level, she has been a reviewer for high impact factor journals including *Immunity*, the *Proceedings of the National Academy of Sciences* and *PLOS Pathogens*. Dr. Grigorova has served on National Institutes of Health study sections, has been invited to join the Executive Council Board of Advisors for the Autumn Immunology Conference as a council board member.

External Reviewers:

Reviewer A: “She has demonstrated not only the ability to perform at the highest standard in an established laboratory but, importantly, has also maintained a high quality output whilst building her own laboratory and growing as an independent researcher.”

Reviewer B: “I consider two of Dr. Grigorova’s independent publications to be outstanding; her Nature Communications paper that defines the duration of B cell competence to present antigen and participate in an immune response following initial contact with cognate antigen, the role of T cells in sustaining activation and the consequence of pulsatile versus chronic exposure to antigen. In showing that an antigen stimulated B cell has only an approximately 36 hour window in which to interact with a cognate T cell, and chronic stimulation leads to rapid cell death this work suggests the existence of a clock in B cells that controls fate. I also consider her 2017 paper in the Journal of Immunology to be outstanding.”

Reviewer C: “Dr. Grigorova is a very promising scientist who has already made multiple contributions to the field. She has developed an independent research focus analyzing the mechanisms that influence B cell responses and successfully obtained research funding. Based upon the high quality of her papers, I believe that she will continue to be successful in obtaining research funding. Furthermore, her national reputation is evolving.”

Reviewer D: “On balance, then, I believe Dr. Grigorova is well worthy of this promotion. She is a well-trained scientist, tackling important immunological concepts with well-designed and novel approaches, with exciting results that have changed, and no doubt will continue to challenge, existing paradigms of B cell activation and tolerance.”

Reviewer E: “Dr. Grigorova has made valuable contributions to our understanding of B cell activation and differentiation *in vivo* in response to antigen. Her work on B cell antigen acquisition, early activation, and germinal center responses have been solid contributions to the literature.”

Reviewer F: “Overall, I judge Dr. Grigorova as a scientist with a history of success during her Ph.D. and postdoctoral work who has not yet shown in her independent laboratory efforts the full potential suggested by this prior history.”

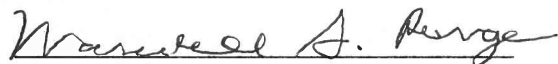
Reviewer G: “All in all, I am in favor of Dr. Grigorova’s promotion. She is a talented investigator working in an important area of immunology and her group is producing quality papers under her leadership. I am confident that some of those pending grants will be funded. I recommend that you promote Dr. Grigorova for these reasons.”

Reviewer H: “Irina Grigorova is a superb biophysical immunologist who is developing a growing reputation for scientific excellence. My own work has benefited from her recent independent research papers and keen analyses on the germinal center (GC) response. I can, therefore, recommend her promotion and grant of tenure with enthusiasm.”

Reviewer I: “Her senior author papers each provide important insights into how memory B cells form, and these discoveries provide critical knowledge for vaccine development...She has already made valuable contributions to the Department of Microbiology and Immunology at the University of Michigan and her many positive attributes suggest that she will continue to do so in the future.”

Summary of Recommendation:

Dr. Grigorova is a talented researcher who is asking some of the most central questions relating to T cell-B cell collaboration in humoral immunity. Her discoveries thus far are provocative and have challenged existing dogma in her field. She is an excellent mentor and educator and has outstanding service contributions. I am pleased, therefore, to recommend Irina Grigorova, Ph.D. for promotion to associate professor of microbiology and immunology, with tenure, Department of Microbiology and Immunology, Medical School.



Marschall S. Runge, M.D., Ph.D.
Executive Vice President for Medical Affairs
Dean, Medical School

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