

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

Marilia Cascalho M.D.,Ph.D., associate professor of surgery, with tenure, Department of Surgery, and associate professor of microbiology and immunology, without tenure, Department of Microbiology and Immunology, Medical School, is recommended for promotion to professor of surgery, with tenure, Department of Surgery, and professor of microbiology and immunology, without tenure, Department of Microbiology and Immunology, Medical School.

Academic Degrees:

Ph.D.	1998	University of California, San Francisco and University of Lisbon
M.D.	1986	Faculdade de Medicina de Lisboa, Lisbon, Portugal

Professional Record:

2008 - Present	Associate Professor of Surgery, University of Michigan
2008 - Present	Associate Professor of Microbiology and Immunology, University of Michigan
2000 - 2008	Assistant Professor, Mayo Clinic

Teaching: Dr. Cascalho has had a long-term commitment to mentoring and teaching. She has mentored medical, graduate, and undergraduate students, post-doctoral fellows, and junior faculty. Her impact is evident as several of her graduate students and post-doctoral fellows have gone on to pursue careers in academic medicine and are co-authors in numerous publications. Dr. Cascalho has been particularly successful in mentoring junior faculty. When those activities have intersected with her own work, they have resulted in long-life collaborations with engineers, clinicians, and other scientists. These collaborations have led to subsequent funding of NIH R01 grants, a novel business venture and numerous publications. Dr. Cascalho is currently an active instructor, teaching Microbiology 812 and Cellular and Molecular Biology 850. From 2015-2018, she established the curriculum and was the course director for Immunology 851. Immunology 851 was developed with the goal of challenging the students to debate different points of view using ancillary references. This course was very successful, and while it started with only immunology graduate students, the course has subsequently attracted biomedical engineering, cell and molecular biology, pharmacology and even psychology graduate students. Dr. Cascalho serves on numerous dissertation and examination committees. In April 2021, she taught a course, B Cell, Aging and Impact on Transplantation, at the International Society for Heart and Lung Transplantation annual meeting.

Research: Dr. Cascalho's research focuses on the study of B cell responses to transplantation, genetic determinants of immunity, host defense, immunotherapies, and vaccines. In her investigations centered on immune responses after kidney transplantation, she discovered that every transplant recipient produces B cell responses to the graft, even when donor-specific antibodies cannot be detected in the blood. This discovery shifted the evaluation of allo-immunity from antibodies to donor-specific B cells and established new criteria to discern protective from damaging immune reactions against the graft. Dr. Cascalho has been awarded an NIH R01 grant to fund this research. In a second line of inquiry, she discovered that the highly polymorphic *TNFRSF13B* gene, controls innate immune B cells that in turn regulate complement activation and govern resistance to certain enteric pathogens. Studying human subjects and mice models expressing frequent *TNFRSF13B* polymorphisms, she

demonstrated that the immune pathways controlled by *TNFRSF13B* determine outcomes in transplantation, the progression of multiple myeloma, susceptibility to enteric pathogens and susceptibility to Systemic Lupus Erythematosus. Dr. Cascalho was awarded an NIH R21 grant to fund this research.

Dr. Cascalho also discovered that C3d, a non-catalytic product of complement, enhances generation of anti-tumor immunity without producing notable toxicity. This research yielded a patent, two invention disclosures, and a manuscript, and is funded by grants from the Cancer Center and the State of Michigan. Another line of novel investigation has focused on approaches to optimize vaccines to prevent diseases caused by mutable viruses. Dr. Cascalho has developed a preliminary prototype of a mutable vaccine to HIV-1. The research has originated multiple publications, Department of Defense funding, invention disclosures and one patent. Recognizing the need for therapies against SARS-CoV-2, Dr. Cascalho isolated anti-SARS-CoV-2 specific B cells and cloned their antibodies to generate recombinant human monoclonal antibodies. The research originated several manuscripts and an invention disclosure.

Recent and Significant Publications:

Platt JL, Garcia de Mattos Barbosa M, Huynh D, Lefferts AR, Katta J, Kharas C, Bassis CM, Wobus CE, Geha RS, Bram RJ, Nunez G, Kamada N, Cascalho M: *TNFRSF13B* polymorphisms counteract microbial adaptation to natural IgA. *JCI Insight*. 2021 Jun 10:148208. doi: 10.1172/jci.insight.148208. Online ahead of print. PM34111031

Garcia de Mattos Barbosa M, Liu H, Huynh D, Shelley G, Keller ET, Emmer BT, Sherman E, Ginsburg D, Kennedy AA, Tai AW, Wobus C, Mirabeli C, Lanigan TM, Samaniego M, Meng W, Rosenfeld AM, Luning Prak ET, Platt JL, Cascalho M: IgV somatic mutation of human anti-SARS-CoV-2 monoclonal antibodies governs extent of neutralization and breadth of reactivity. *JCI Insight* 6: e147386, 2021. PM33769311

Platt JL, Silva I, Balin SJ, Lefferts AR, Ross TM, Carroll MC, Cascalho M. C3d Regulates immune checkpoint blockade and enhances antitumor immunity: *JCI Insight* 2: e90201, 2017. PM28469081/PMC5414554.

Tsuji S, Stein L, Kamada N, Nuñez G, Bram R, Sousa A, Platt JL, Cascalho M: TACI-deficiency enhances antibody avidity and clearance of an intestinal pathogen. *J Clin Invest* 124: 4857-4866, 2014. PM25271628

Cascalho M, Balin SJ, Platt JL. The mutable vaccine for mutable viruses: *Immunotherapy* 9: 659-667, 2017. PM28653569

Service: Dr. Cascalho is the co-director of the Transplant Biology Program at the Medical School. At the institutional level, she serves on the Graduate School Admissions Committee for the Immunology Program and for the Department of Microbiology and Immunology. She has served as a member of the Development Advisory Committee of the University Senate, from 2019-2021, and is currently a member of the Research Advisory Committee of the University Senate. She has served on numerous review panels for the NIH, including panels evaluating R01, PO1, R21, U19 and RAID applications. Dr. Cascalho reviews manuscripts for numerous journals and at the international level, and currently is a member of the Basic Science Committee for the International Society for Heart and Lung Transplantation. She has been a reviewer for the AST-TIRN program and for European grant agencies such as the Wellcome Trust and the Austrian Government.

External Reviewers:

Reviewer A: “Dr[.] Cascalho’s work is creative, thoughtful and rigorous. Importantly, Dr. Cascalho’s research is achieving an upward trajectory that leverages her long-term strength in molecular investigations of the immunoglobulin gene and B cells not only in transplantation, but also in infectious diseases and tumor immunity where experimental models are considerably more tractable...Thus Dr. Cascalho’s research program is demonstrating a significant growth, and she is very well-funded with grants from NIH (R01, R21), DOD and private foundations.”

Reviewer B: “In conclusion, Dr. Cascalho has demonstrated consistent high level productivity in immunology research and has advanced the field significantly. She is an international thought leader in B cell biology and her work meets the requirements for someone being consider for promotion at University of Michigan and my institution.”

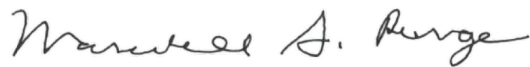
Reviewer C: “...Marilia is recognized as a leader in the B cell field, both at the basic and translational levels...Marilia has shown no sign of slowing down; quite the contrary; she is contributing to many areas of B cell biology, more and more moving to translation immunology. In my opinion, Marilia is clearly deserving of this promotion, and she will remain a positive force at UM for years to come.”

Reviewer D: “The publications summarized in Dr. Cascalho’s Bibliographic Notes are first rate, published in leading journals such as the *Journal of Clinical Investigation*...Her grant funding is outstanding – it exceeds that of individuals in her field. Her national and international recognition is excellent based on my knowledge of her work and invitations to national and international meetings, including the prestigious FOCIS meeting in 2019.”

Reviewer E: “Dr. Cascalho has developed a trusted and impressive reputation in the area of B cell biology and has been a continual contributor to the field with highly significant publications...I feel one of the most important metrics is the mentoring by faculty of undergraduates, graduate students and post-doctoral fellows. In this category, Dr. Cascalho’s record is superlative.”

Summary of Recommendation:

Dr. Cascalho is an international thought leader in B cell biology. She is highly respected by her colleagues and is known to be an outstanding and creative scientist, educator, and academic leader in the field of immunology. I am pleased to recommend Marilia Cascalho, M.D., Ph.D. for promotion to professor of surgery, with tenure, Department of Surgery, and professor of microbiology and immunology, without tenure, Department of Microbiology and Immunology, Medical School.



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

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