BIOGRAPHICAL SKETCH

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NAME: Vladimir P Badovinac

eRA COMMONS USER NAME (credential, e.g., agency login): badovinac

POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Belgrade, Belgrade, Yugoslavia	BS	1988-1994	Molecular Biology
University of Belgrade, Belgrade, Yugoslavia	MSc	1994-1997	Immunology
University of Belgrade, Belgrade, Yugoslavia	Ph.D.	1997-1999	Immunology
University of Iowa, Iowa City, IA	Postdoc	1999-2002	Microbiology/Immunol.

A. Personal Statement:

My long-term interest lies in elucidating the mechanisms that govern T cell responses after infection and/or immunization. We are interested in exploring the pathways that are involved in Ag-specific T cell homeostasis *in vivo* and exploring how the manipulation of these pathways can be used to facilitate the generation and maintenance of productive memory T cell responses in health and disease. I have pursued this interest using mouse models of bacterial and viral infections for over 15 years and these studies have resulted in over 80 published papers so far.

B. Positions and Honors:

Training and Academic Positions

1994-1999 **Assistant Research Scientist,** Department of Immunology, Institute for Biological Research, University of Belgrade, Belgrade, Yugoslavia.
1995-1999 **Assistant**, Faculty of Biology, University of Belgrade, Belgrade, Yugoslavia
1999-2002 **Postdoctoral Associate,** Department of Microbiology, University of Iowa, Iowa City, IA; laboratory of John T Harty, Ph.D.
2002-2003 **Assistant Research Scientist**, Department of Microbiology, University of Iowa, Iowa City, IA;
2003-2006 **Associate Research Scientist**, Department of Microbiology, University of Iowa, Iowa City, IA;
2006-12/07 **Research Scientist**, Department of Microbiology, University of Iowa, Iowa City, IA;
12/07-06/14 **Assistant Professor**, Department of Pathology, University of Iowa, Iowa City, IA;
05/09-07/14 **Assistant Professor**, Interdisciplinary Graduate Program in Immunology, University of Iowa, Iowa City, IA;
03/11- **Member**: Holden Comprehensive Cancer Center, Iowa City, IA;
07/14- **Associate Professor (with tenure)**, Department of Pathology, University of Iowa, Iowa City, IA;
12/16- **Associate Professor (with tenure)**, Department of Microbiology, University of Iowa, Iowa City, IA;

Professional Experience

2002- **Ad hoc reviewer:** Journal of Immunology, Viral Immunology, Neuroscience Letters, BMC Immunology, Clinical Nutrition, The Journal of Experimental Medicine, PloS Pathogens, Journal of Virology, Cellular and Molecular Life Sciences, Cancer Immunology Immunotherapy, Trends in Immunology, PloS One, European Journal of Immunology, Aging Cell, Cell Reports, Vaccine, Nature Reviews Immunology, Frontiers in Immunological Memory, Immunity, Molecular Therapy, CE-JI, Nature Communications, Nature Medicine, Journal of Clinical Investigations, Journal of Leukocyte Biology, Scientific Reports, Cell Systems, Science Translational Medicine

2009- **Ad hoc reviewer:** PRMRP Peer Review (Listeria vaccine for infectious disease and cancer); Cancer Research UK; National Project Proposals, Ministry of Science and Technological Development, Republic of Serbia; Merieux Research Grants, NIH (2012/05 ZAI1 PA-I (M1) 1 NIAID Investigator initiated Program Projects Applications (PO1)), COM Carver Medical Research Initiative and Collaborative grants, Deutsche Forschungsgemeinschaft (German Research Foundation), ANR, NIH Special Emphasis Panels

2013-15 Elected general Council Member, Autumn Immunology Conference

2015- Academic Editor, PLoS ONE

2015- Associate Editor, AAI, Journal of Immunology

2015- AAI Career Advisory Board

Awards and Honors:

2001-4 **Leukemia & Lymphoma Society Fellow Award**, The Leukemia & Lymphoma Society

2005-6 **American Cancer Society (ACS) Seed Grant,** American Cancer Society

2008- **Honorary Member,** Immunological Society of Serbia

2010 **AAI Junior Faculty Travel Grant,** AAI Baltimore 2010

2011 **AAI Junior Faculty Travel Grant,** AAI San Francisco 2011

2015- **Honorary Member,** Serbian society of Molecular Biology

C. Contributions to Science

1) Regulating primary CD8 T cell responses to infections. Following initial encounter with the pathogen, CD8 T cells embark on a program of differentiation that is marked by distinct phases of activation, intense proliferation, developing effector functions that is followed by a significant reduction in total numbers, and eventually stable maintenance for the life of the host. Several studies, including ours, collectively indicate that the expansion, contraction, and memory phases of the CD8 T cell response are largely if not completely independent of continued Ag display, suggesting that relatively brief encounter with Ag is sufficient to instigate the full program of CD8 T cell differentiation. However, it has become clear that, in addition to Ag, a variety of signals must be integrated by the responding T cells to generate optimal responses and ensure proper regulation of T cell homeostasis. For instance, we were able to show that inflammatory cytokines, stimulated by infection or vaccination with strong adjuvants, provide important signals that directly shape the Ag-specific CD8 T cell responses. Few examples of our publications on this general topic are listed below:

a. **Badovinac VP**, AR Tvinnereim, and JT Harty. Regulation of antigen-specific $CD8^+$ T cell homeostasis by perforin and IFN-γ. **Science** 290, 1354-1357 (2000)

b. **Badovinac VP**, BB Porter, and JT Harty. Programmed contraction of CD8+ T cells after infection. **Nat. Immunol.** 3, 619-626 (2002)

c. **Badovinac VP**, BP Porter, and JT Harty. $CD8^+$ T cell contraction is controlled by early inflammation. **Nat. Immunol.** 5, 809-817 (2004)

d. He B, S Xing, C Chen, P Gao, L Teng, Q Shan, JA Gullicksrud, MD Martin, S Yu, JT Harty, **VP Badovinac**, K Tan, and HH Xue. CD8 T cells utilize highly dynamic enhancer repertoires and regulatory circuitry in response to infections. **Immunity** 45, 1341-1354 (2016)

2) Generation and differentiation of memory CD8 T cells. The ability to develop and sustain populations of memory CD8 T cells after infection and/or immunization is a hallmark of the adaptive immune response and a basis for protective vaccination against infectious disease. Understanding the input signals that shape the characteristics of the memory CD8 T cell response and how manipulations of those signals has the potential to re-shape CD8 T cell memory and improve the efficacy of vaccination have been and continue to be a research emphasis in my laboratory. Some of the relevant publications in this area are listed below:

a. **Badovinac VP***, KAN Messingham*, A Jabbari, JS Haring, and JT Harty. Accelerated $CD8^+$ T cell-memory and prime-boost response after dendritic-cell vaccination. **Nat. Med.** 11, 748-756 (2005)

b. Harty JT, and **VP Badovinac**. Shaping and reshaping CD8 T cell memory. **Nat. Rev. Immunol.** 8, 107-119 (2008)

c. Nolz JC, D Rai, **VP Badovinac***, and JT Harty*. Division-linked generation of 'death-intermediates' regulates the numerical stability of memory CD8 T cells. **PNAS** 109, 6199-6244 (2012) PMCID: PMC3341021

d. Martin MD, MT Kim, Q Shan, R Sompallaie, HH Xue, JT Harty, and **VP Badovinac**. Phenotypic and functional alterations in circulating memory CD8 T cells with time after primary infection. **PLoS Pathog.** 11, e1005219 (2015) PMCID: PMC4618693

3) CD8 T cell responses to repeated Ag stimulations. Repetitive Ag stimulation by prime-boost vaccination or pathogen re-encounter increases memory CD8 T cell numbers, but the impact on the memory CD8 T cell differentiation is not well understood. We were able to show that the magnitude of the proliferative expansion, duration and extension of contraction, and tissue distribution of ensuing memory CD8 T cell populations are clearly dependent on the Ag-exposure history. Importantly, every additional Ag stimulation (i.e. primary to quaternary) leads to an increase in the number of differentially regulated genes and, thus, to further differentiation of memory CD8 T cells. As a consequence of this stepwise process, each additional Ag encounter results in memory CD8 T cell populations that possess a unique repertoire of regulated genes and biological pathways. Selected publications in this area are below:

a. Wirth TC, H-H Xue, D Rai, JT Sabel, T Bair, JT Harty*, and **VP Badovinac***. Repetitive antigen stimulation induces stepwise transcriptome diversification but preserves a core signature of memory CD8 T cell differentiation. **Immunity** 33, 128-140 (2010) PMCID: PMC2912220

b. Martin MD, SA Condotta, JT Harty, and **VP Badovinac**. Population dynamics of naïve and memory CD8 T cell responses after antigen stimulations in vivo. **J. Immunol.**188, 1255-1265 (2012) PMCID: PMC3262935

c. Rai D, MD Martin, and **VP Badovinac**. The longevity of memory CD8 T cell responses after repetitive antigen-stimulations. **J. Immunol.**192, 5652-5659 (2014) PMCID: PMC4127884

d. Khan SH, MD Martin, GR Starbeck-Miller, HH Xue, JT Harty, and **VP Badovinac**. The timing of stimulation and IL-2 signaling regulate secondary CD8 T cell responses. **PLoS Pathog.** 11, e1005199 (2015)

4) Detection and analysis of pathogen-specific CD8 T cell responses. Our ability to track pathogen-specific CD8 T cell responses in vivo is critically dependent on the experimental models available. Thus, our long-standing interest lies in developing and/or improving state of the art models to study T cell responses after infection and/or vaccination. Examples are listed below:

a. **Badovinac VP**, KAN Messingham, SE Hamilton, and JT Harty. Regulation of $CD8^+$ T cells undergoing primary and secondary responses to infection in the same host. **J. Immunol.** 170, 4933-4942 (2003)

b. **Badovinac VP**, Haring JS, and JT Harty. Initial TCR-transgenic precursor frequency dictates critical aspects of the CD8 T cell response to infection. **Immunity** 26, 827-841 (2007) PMCID: PMC1989155

c. Rai D, N-LL Pham, JT Harty, and **VP Badovinac**. Tracking the total CD8 T cell response to infection reveals substantial discordance in magnitude and kinetics between inbred and outbred hosts. **J. Immunol.**183, 7672-7681 (2009) PMCID: PMC2808048

d. Schmidt NW, NS Butler, **VP Badovinac**, and JT Harty. Extreme CD8 T cell requirements for anti-malarial immunity following immunization with radiation attenuated sporozoites. **PLoS Path.** 6, e1000998 (2010) PMCID: PMC2904779

5) Impairment and recovery of T cell responses after sepsis. Polymicrobial sepsis represents a leading cause of death in most intensive care units, and patients who survive severe sepsis often display severely compromised immune function with deficits in innate and adaptive immune responses. One hallmark of the general immune suppression observed during polymicrobial sepsis is diminished T cell immunity. There are clear knowledge gaps in our understanding of how, when and the extent to which sepsis-associated impairment of CD4 and CD8 T cell-mediated immunity recovers and understanding the mechanisms behind sepsis-induced changes in the homeostasis of naïve and pre-existing memory CD4 and CD8 T cell responses will lead to new approaches aimed at restoring adaptive immunity in individuals surviving sepsis. For instance, our recent papers revealed that sepsis significantly compromises the host's ability to mount optimal CD4 and CD8 T cell responses to newly introduced Ag presented in the context of acute or chronic systemic or localized model infections. We also revealed a previously unappreciated role for sepsis in shaping the quantity and functionality of infection- or vaccine-induced pre-existing memory CD8 T cells.

Relevant Publications:

a. Condotta SA, D Rai, BR James, TS Griffith, and **VP Badovinac**. Sustained and incomplete recovery of naïve CD8 T cell precursors after sepsis contributed to impaired CD8 T cell responses. **J. Immunol.** 190, 1991-2000 (2013) PMCID: PMC3578009

b. Duong S, SA Condotta, D Rai, MD Martin, TS Griffith, and **VP Badovinac**. Poly-microbial sepsis alters Ag-dependent and –independent memory CD8 T cell functions. **J. Immunol.** 192, 3618-3625 (2014) PMCID: PMC4001259

c. Condotta SA, SH Khan, D Rai, TS Griffith, and **VP Badovinac**. Poly-microbial sepsis increases susceptibility to chronic viral infection and exacerbates CD8 T cell exhaustion. **J. Immunol.** 195, 116-125 (2015) PMCID: PMC4475506

d. Strother RK, DB Danahy, DI Kotov, TA Kucaba, ZR Zacharias, TS Griffith, KL Legge, and **VP Badovinac**. Polymicrobial sepsis diminishes dendritic cell numbers and function directly contributing to impaired primary CD8 T cell responses in vivo. **J. Immunol.** 197, 4301-4311 (2016)

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/vladimir.badovinac.1/bibliography/40699415/public/?sort=date&direction=descending

D. RESEARCH SUPPORT

ONGOING

R01GM113961 (PI: Badovinac) 9/2015 - 8/2019
NIH/NIGMS 2.88 Calendar
Impairment and recovery of CD8 T cell responses after sepsis
Define the extent to which polymicrobial sepsis impairs CD8 T cell immunity

R01AI114543 (MPI: Badovinac and Harty) 10/2014 - 9/2019
NIH/NIAID 1.2 Calendar
Memory CD8 T cell localization and protection from influenza
We will identify properties of memory CD8 T cells with the capacity to induce subtype transcending protection against influenza virus infection.

R21AI119160 (MPI: Badovinac and Xue) no cost extension 6/2015 - 5/2018
NIH/NIAID 1.2 Calendar
Molecular mechanisms controlling differentiation of memory CD8 T cells
To define the molecular mediators that are responsible for functional changes in memory CD8 T cells generated after repeated Ag-encounters.

R01GM115462 (PI: Griffith) 10/2016 - 9/2020
NIH/NIGMS 1.2 Calendar
Alterations in CD4 T cells during sepsis
Define the extent to which polymicrobial sepsis impairs CD4 T cell immunity. Role: Co-Investigator

COMPLETED

R01AI083286 (PI: Badovinac) 07/2009 - 06/2013
NIH/NIAID
Memory CD8 T cell responses after multiple antigen encounters
The long-term goal is to define the extent to which multiple antigen stimulations change the resulting memory CD8 T cell populations

R21AI096850 (MPI: Badovinac and Harty) 02/2012 - 01/2014
NIH/NIAID
Cellular intermediates in stable memory CD8 T cell maintenance
The long-term goal is to understand the molecular mediators resulting in balanced life and death during stable memory CD8 T cell maintenance.

Holden Comprehensive Cancer Center, University of Iowa 9/2014 - 8/2016
Oberley Seed Grant (PI: Badovinac)
Enhancing anti-tumor CD8 T cell responses for immunotherapy
To test the novel approaches (dendritic cell immunization in combination with cytokine therapy and blockade inhibitory receptors) for treatment of existing tumors in preclinical models of melanoma and fibrosarcoma.

I01 BX001324 (PI: Griffith) 10/2012 - 9/2016
Veterans Health Administration Merit Review Program
Suppression of T cell immunity during sepsis
The long-term goal is to analyze primary CD8 T cell responses to secondary infection after sepsis and determine the role of TRAIL in sepsis-induced immunosuppression. Role: Co-Investigator (20% salary support only)

R21AI115149 (PI: Xue) 6/2015 - 5/2017
NIH/NIAID
Epigenetic regulation of pathogen-specific CD8 T cells
To define the extent to which epigenetic modification coordinate dynamic gene regulation, generate heritable imprint of ‘antigen encounter’ in the genome and shape the enhancer landscape during differentiation of naïve to effector and memory pathogen-specific CD8 T cells. Role: Co-Investigator