BIOGRAPHICAL SKETCH

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NAME: DENZIN, LISA K.

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

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)	END DATE MM/YYYY	FIELD OF STUDY
University of Wisconsin, Madison, WI	BS	05/1987	Medical Microbiology
University of Illinois, Urbana, IL	MS	05/1989	Microbiology
University of Illinois, Urbana, IL	PHD	05/1992	Microbiology
Yale University School of Medicine, New Haven, CT	Postdoctoral Fellow	09/1997	Immunology

A. Personal Statement

My research over the last twenty-five years has provided me with strong biochemical, cell biological and immunological training. As a graduate student I studied the molecular mechanisms by which antibodies bind to antigens. Then as a postdoctoral fellow in the laboratory of Dr. Peter Creswell I explored the biochemical and cell biological pathways by which MHC class II molecules acquire antigenic peptides in the endosomes of cells. Over the past twenty years my own lab has applied biochemical, cell biological and immunological techniques to the question of how peptide loading of MHC class II molecules is modulated in vivo during immune responses. Our studies have uncovered the essential role of HLA-DM and HLA-DO (H2-O in mice) in modulating peptide loading of MHC class II and have shown how these molecules work together to regulate immunity and perhaps autoimmunity. Over the last seven years I have worked closely with Dr. Golovkina to understand the mechanism by which H2-O controls the immune response to mouse retroviruses. Our synergistic efforts showed that H2-O expression blocks the development of the neutralizing antibody response to retroviruses and that retroviral resistant I/LnJ mice have a null allele of H2-Oβ (beta chain of H2-O). We also defined naturally occurring alleles of human DOA and DOB with altered function and genetically linked them to the outcomes of human chronic viral responses. These findings were reported in *Immunity* and *The Journal of Immunology*. In this R01 application, we will apply what we have learned and the unique tools we have generated and will generate to define, at the molecular level, the novel and undefined pathways and mechanism by which H2-O functions to control the immune response to viruses. Dr. Golovkina's expertise as a virologist, immunologist and geneticist together with my expertise in the immunology, biochemistry, cell biology of the MHCII class II pathway ensure that we have the knowledge, leadership, training, expertise, and motivation necessary to successfully carry out the proposed research project. Our success in working collaboratively is evident from five recent joint publications that were supported by R01-AI117535 and R56-AI117535 (New Retroviral Restriction Factor; NIH/NIAID; PI-Golovkina, T; CoI-Denzin, LK).

1. Cullum E, Graves AM, Tarakanova VL, Denzin LK, Golovkina T. MHC Class II Presentation Is Affected by Polymorphism in the *H2-Ob* Gene and Additional Loci. J Immunol. 2021 Jul 1;207(1):5-14. PubMed Central PMCID: PMC8674376.
2. Cullum E, Dikiy S, Beilinson HA, Kane M, Veinbachs A, Beilinson VM, Denzin LK, Chervonsky A, Golovkina T. Genetic Control of Neonatal Immune Tolerance to an Exogenous Retrovirus. J Virol. 2020 Nov 23;94(24) PubMed Central PMCID: PMC7925187.
3. Graves AM, Virdis F, Morrison E, Álvaro-Benito M, Khan AA, Freund C, Golovkina TV, Denzin LK. Human Hepatitis B Viral Infection Outcomes Are Linked to Naturally Occurring Variants of *HLA-DOA* That Have Altered Function. J Immunol. 2020 Aug 15;205(4):923-935. PubMed Central PMCID: PMC7415708.
4. Denzin LK, Khan AA, Virdis F, Wilks J, Kane M, Beilinson HA, Dikiy S, Case LK, Roopenian D, Witkowski M, Chervonsky AV, Golovkina TV. Neutralizing Antibody Responses to Viral Infections Are

Linked to the Non-classical MHC Class II Gene H2-Ob. Immunity. 2017 Aug 15;47(2):310-322.e7. PubMed Central PMCID: PMC5568092.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2020 - 2022	Reviewer (Ad hoc), NIH/NCI, Institutional Training and Education Study Section (Subcommittee F)
2020 - 2020	Reviewer, NIH/NIAID, Special Emphasis Panel, Emergency Awards: Rapid Investigation of SARS-CoV-2 and COVID-19
2017 -	Member, Editorial Board, Journal of Biological Chemistry
2016 -	T32 External Advisory Board Member, Fox Chase Cancer Center, Philadelphia, PA
2014 - 2018	Member, NIH/NCI, Institutional Training and Education Study Section (Subcommittee F)
2013 - 2015	Reviewer, L'Oréal USA Fellowships For Women in Science
2011 -	Associate Professor, Child Health Institute of NJ, Rutgers Robert Wood Johnson Medical School, Department of Pediatrics, Rutgers, The State University of NJ, New Brunswick, NJ
2008 - 2013	Associate and Section Editor, The Journal of Immunology
2007 - 2011	Member, NIH/NIAID, Cellular and Molecular Immunology-B Study Section
2005 - 2011	Associate Professor, Weill Cornell Graduate School of Medical Sciences, New York, NY
2005 - 2011	Associate Member, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, Immunology Program, New York, NY
2003 - 2007	Reviewer (Ad hoc), NIH/NIAID, CIM-A, CIM-B, Special Emphasis Panels, and Autoimmunity Centers of Excellence
2002 - 2008	Member, Advisory Board, The Journal of Experimental Medicine
2001 - 2011	Scientific Director, Monoclonal Antibody Core Facility, Sloan-Kettering Institute, New York, NY
1998 - 2005	Assistant Professor, Weill Cornell Graduate School of Medical Sciences, New York, NY
1998 - 2005	Assistant Member, Memorial Sloan-Kettering Cancer Center, Sloan-Kettering Institute, Immunology Program, New York, NY
1997 - 1998	Assistant Professor, Duke University Medical Center, Department of Immunology, Druham, NC
1992 - 1997	Research Associate, HHMI, Yale Univ. Medical School, Mentor: Peter Cresswell, Ph.D., New Haven, IL
1987 - 1990	Teaching Assistant, University of Illinois, Urbana, IL

Honors

2001 - 2005	Adler Chair for Junior Faculty, SKI, Memorial Sloan-Kettering Cancer Center, 2001-2005
2001 - 2004	Bressler Scholar, SKI, Memorial Sloan-Kettering Cancer Center, 2001-2004
1995 - 1997	Fellowship, Patrick and Catherine Weldon Donaghue Research Foundation, 1995-1997
1992 - 1995	Fellowship, Howard Hughes Medical Institute, 1992-1995
1988 - 1989	DeBoer Fellowship in Microbiology, University of Illinois, 1988-1989

C. Contribution to Science

1. As a postdoctoral fellow with Peter Cresswell in the Immunobiology Section at the Yale University School of Medicine, I initiated my studies on the MHC class II (MHCII) antigen processing and presentation pathway. My studies in the Cresswell laboratory were focused on the mechanisms by which MHCII molecules acquire peptide cargo in the endosomes of cells. My initial biochemical and cell biological studies showed that MHC class II peptide loading is catalyzed in vivo by the MHCII-like molecule HLA-DM. DM was not only essential for removing remnants of the invariant chain from the MHCII peptide binding grove but was also necessary to stabilize empty MHCII. Subsequent studies went on to show that DM activity is directly opposed by HLA-DO. My studies showed that DO binds to DM thereby inhibiting the ability of DM to load MHCII with peptides. Thus, DM allows for peptide loading of MHCII while DO activity modulates the ability of DM to load MHCII with peptides. These studies formed the foundation for my independent research program.

a. Denzin LK, Sant'Angelo DB, Hammond C, Surman MJ, Cresswell P. Negative regulation by HLA-DO of MHC class II-restricted antigen processing. Science. 1997 Oct 3;278(5335):106-9. PubMed PMID: 9311912.
b. Denzin LK, Hammond C, Cresswell P. HLA-DM interactions with intermediates in HLA-DR maturation and a role for HLA-DM in stabilizing empty HLA-DR molecules. J Exp Med. 1996 Dec 1;184(6):2153-65. PubMed Central PMCID: PMC2196380.
c. Denzin LK, Cresswell P. HLA-DM induces CLIP dissociation from MHC class II alpha beta dimers and facilitates peptide loading. Cell. 1995 Jul 14;82(1):155-65. PubMed PMID: 7606781.
d. Denzin LK, Robbins NF, Carboy-Newcomb C, Cresswell P. Assembly and intracellular transport of HLA-DM and correction of the class II antigen-processing defect in T2 cells. Immunity. 1994 Oct;1(7):595-606. PubMed PMID: 7600288.

2. As an independent investigator, I developed a research program with the goal of understanding the immunological consequences of DO regulation of DM-mediated MHCII peptide loading in vivo. Our initial studies started in humans and showed that DO expression tightly regulated during B cell activation. Our studies showed that DO levels are high in naive and resting B cells but very low in activated, germinal central B cells, presumably because GC B cells require efficient interaction with CD4 T cells to survive the GC reaction. Transcriptional studies showed that the DOB gene is differentially regulated compared to the other MHCII genes, providing a potential mechanism for down regulation in GC BB cells. Our initial studies also established mouse models that allowed us to prove that DO inhibits DM-mediated MHCII peptide loading in vivo. Finally, these early studies also established that DO is expressed in DCs and is not restricted to B cells as initially reported. Collectively, these initial studies established that DO inhibits DM in vivo and that the impact of DO on the immune response is likely broader than initially appreciated since DO is expressed in B cells and DCs.

   a. Fallas JL, Yi W, Draghi NA, O'Rourke HM, Denzin LK. Expression patterns of H2-O in mouse B cells and dendritic cells correlate with cell function. J Immunol. 2007 Feb 1;178(3):1488-97. PubMed PMID: 17237397.
   b. Fallas JL, Tobin HM, Lou O, Guo D, Sant'Angelo DB, Denzin LK. Ectopic expression of HLA-DO in mouse dendritic cells diminishes MHC class II antigen presentation. J Immunol. 2004 Aug 1;173(3):1549-60. PubMed PMID: 15265882.
   c. Hake SB, Tobin HM, Steimle V, Denzin LK. Comparison of the transcriptional regulation of classical and non-classical MHC class II genes. Eur J Immunol. 2003 Sep;33(9):2361-71. PubMed PMID: 12938212.
   d. Glazier KS, Hake SB, Tobin HM, Chadburn A, Schattner EJ, Denzin LK. Germinal center B cells regulate their capability to present antigen by modulation of HLA-DO. J Exp Med. 2002 Apr 15;195(8):1063-9. PubMed Central PMCID: PMC2193692.

3. Whereas the in vivo role of DM was apparent, the more subtle function of DO in vivo has been more enigmatic. Recent data from our lab, however, has shown that modulation of the MHCII antigen-processing pathway by DO can have profound immunological effects. In particular, we showed that DO expression shapes the overall MHCII-self-peptide repertoire and, in doing so, promotes T cell tolerance. This idea is supported by our published studies, showing that dampening DM activity by expression of DO in the DCs of Non-Obese Diabetic (NOD) mice is protective against T1D. Other studies provided a potential role for DO during immune responses. H2-O (mouse DO) expression in B cells increase the activation threshold for B cells to enter the germinal center and our most recent studies showed that H2-O controls the neutralizing antibody response to mouse retroviruses and potentially HCV and HBC in humans. Finally, our studies have shown that H2-O levels are modulated by activation of the innate immune system in DCs, providing a mechanism to optimally activate the MHCII peptide loading pathway in DCs after pathogen encounter. Collectively these studies have established an essential role for H2-O in modulating immunity and potentially autoimmunity and that small changes in the MHCII-peptide repertoire presented to the immune system are sufficient to alter the outcome of an immune response.

   a. Denzin LK, Khan AA, Virdis F, Wilks J, Kane M, Beilinson HA, Dikiy S, Case LK, Roopenian D, Witkowski M, Chervonsky AV, Golovkina TV. Neutralizing Antibody Responses to Viral Infections Are

Linked to the Non-classical MHC Class II Gene H2-Ob. Immunity. 2017 Aug 15;47(2):310-322.e7. PubMed Central PMCID: PMC5568092.

b. Porter GW, Yi W, Denzin LK. TLR agonists downregulate H2-O in CD8alpha- dendritic cells. J Immunol. 2011 Oct 15;187(8):4151-60. PubMed Central PMCID: PMC3186832.

c. Draghi NA, Denzin LK. H2-O, a MHC class II-like protein, sets a threshold for B-cell entry into germinal centers. Proc Natl Acad Sci U S A. 2010 Sep 21;107(38):16607-12. PubMed Central PMCID: PMC2944729.

d. Yi W, Seth NP, Martillotti T, Wucherpfennig KW, Sant'Angelo DB, Denzin LK. Targeted regulation of self-peptide presentation prevents type I diabetes in mice without disrupting general immunocompetence. J Clin Invest. 2010 Apr;120(4):1324-36. PubMed Central PMCID: PMC2846047.

4. Finally, my scientific career has been continually influenced by my thesis studies that I performed in the Department of Microbiology at the University of Illinois-Urbana. The goal of my studies was to understand the molecular interactions that mediate antibody binding to specific antigen. To perform these studies, I generated and characterized some of the first single-chain antibodies. Using the model hapten antigen fluorescein my studies verified the importance of light chain fluorescein contact residues in the binding pocket of a high affinity anti-fluorescein monoclonal antibody. My later studies went on to perform structure-function studies with other monoclonal antibodies specific for fluorescein and showed that each specific antibody binding site used different contact residues and molecular interactions to mediate fluorescein binding. The results of my biophysical structure-function studies have been confirmed by the many crystal structures of antibodies bound to antigen that have been solved over the last 25 years.

a. Denzin LK, Gulliver GA, Voss EW Jr. Mutational analysis of active site contact residues in anti-fluorescein monoclonal antibody 4-4-20. Mol Immunol. 1993 Oct;30(15):1331-45. PubMed PMID: 8232321.

b. Hoo WF, Lacy MJ, Denzin LK, Voss EW Jr, Hardman KD, Kranz DM. Characterization of a single-chain T-cell receptor expressed in Escherichia coli. Proc Natl Acad Sci U S A. 1992 May 15;89(10):4759-63. PubMed Central PMCID: PMC49163.

c. Denzin LK, Voss EW Jr. Construction, characterization, and mutagenesis of an anti-fluorescein single chain antibody idiotype family. J Biol Chem. 1992 May 5;267(13):8925-31. PubMed PMID: 1577730.

d. Denzin LK, Whitlow M, Voss EW Jr. Single-chain site-specific mutations of fluorescein-amino acid contact residues in high affinity monoclonal antibody 4-4-20. J Biol Chem. 1991 Jul 25;266(21):14095-103. PubMed PMID: 1856233.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/lisa.denzin.1/bibliography/public/