OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

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NAME: Michele M. Kosiewicz

eRA COMMONS USER NAME (credential, e.g., agency login): mmkosi01

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
Mansfield University	BA	1981	Biology
Binghamton University	MA	1987	Biology
Binghamton University	Ph.D.	1992	Biology
University of Miami School of Medicine	Post-doc	1993	Immunology
Schepens Eye Res Inst, Harvard Medical School	Post-doc	1996	Immunology

A. Personal Statement

I have significant expertise working in the areas of immunoregulation and tolerance in the context of autoimmunity, and have been involved in these areas of research for >18 years. I have worked with a variety of inflammatory/autoimmune diseases including type 1 diabetes, systemic lupus erythematosus (SLE), inflammatory bowel disease, autoimmune gastritis and autoimmune ovarian dysgenesis, and have experience in the mucosal immunology field. For the last 10 years, my laboratory has focused on spontaneous models of SLE and type 1 diabetes, and have extensive experience working with long-term mouse models of these two autoimmune diseases. I have also had a long-time interest in the development of therapeutic strategies for the treatment of SLE. Based on my experience and expertise in animal models of autoimmunity, immunoregulation and the development of therapeutic strategies, I believe that my team is uniquely positioned to carry out the proposed study.

B. Positions.

Positions and Employment

1992-93 Post-doctoral Fellow, Dept. of Microbiology & Immunology, University of Miami School of Medicine (Mentor: J. Wayne Streilein)

1993-96 Post-doctoral Fellow, Schepens Eye Research Institute, Dept. of Ophthalmology, Harvard Medical School (Mentor: J. Wayne Streilein)

1996-99 Assistant Professor of Research, Division of Gastroenterology & Hepatology, Dept. of Internal Medicine, University of Virginia Health Sciences Center, Charlottesville, VA

1996-00 Faculty, Beirne B. Carter Center for Immunology Research, University of Virginia Health Sciences Center, Charlottesville, VA

1999-00 Assistant Professor (tenure-eligible), Division of Gastroenterology & Hepatology, Dept. of Internal Medicine, University of Virginia Health Sciences Center, Charlottesville, VA

2000-2004 Assistant Professor (tenure-track), Dept. of Microbiology and Immunology, University of Louisville Health Sciences Center, Louisville, KY
2000-pres Member, James Graham Brown Cancer Center, University of Louisville, Louisville, KY
2001-pres Associate Faculty, Institute for Cellular Therapeutics, University of Louisville, Louisville, KY
2004-pres Associate Professor (with tenure), Dept. of Microbiology and Immunology, University of Louisville Health Sciences Center, Louisville, KY

Other Experience and Professional Memberships

1996-pres American Association of Immunologists - Regular member
2001, 2002 NIH, Immunological Sciences Study Section, ad hoc reviewer
2002-2006 Associate Editor, Journal of Immunology
2003-present The Welcome Trust, ad hoc reviewer
2004 NIH, Transplantation, Tolerance and Tumor Immunology Study Section, ad hoc reviewer
2005-present Swiss National Science Foundation, ad hoc reviewer
2005-2007 NIH, Hypersensitivity, Autoimmune, Immune mediated diseases Study Section, ad hoc reviewer
2007-2011 NIH, Hypersensitivity, Autoimmune, Immune mediated diseases Study Section, perm member
2004-present Editorial Board, Current Immunology Reviews
2007 NIH, Centers of Excellence on Complementary and Alternative Medicine, ad hoc reviewer
2008 NIH, NIDDK, Special Emphasis DP2 “Type I Diabetes Award”, ad hoc reviewer
2008-13 Member, Committee on the Status of Women, American Association of Immunologists
2009-present Review panel, Lupus Research Institute/Alliance for Lupus Research
2011-present Editorial Board, Autoimmunity
2012 Special Emphasis Panel, NIH/NIAID, U01 grants for the Cooperative Study Group for Autoimmune Disease Prevention
2012 Special Emphasis Panel, ZRG1 IMM-D (02), NIH
2013 Special Emphasis Panel, NIAID Investigator-Initiated Program Project Applications (P01), NIH
2013 Special Emphasis Panel, Hypersensitivity, Autoimmunity and Immune-mediated Diseases (HAI) Overflow, NIH
2014 NIH, Hypersensitivity, Autoimmune, Immune mediated diseases Study Section, ad hoc reviewer
2015 Special Emphasis Panel, NIH Transformative Research Award (R01)
2015 NIH, Hypersensitivity, Autoimmune, Immune mediated diseases Study Section, ad hoc reviewer
2016 Special Emphasis Grant Review Panel, ZRG1 IMM-D, NIH
2016 NIH, Hypersensitivity, Autoimmune, Immune mediated diseases Study Section, ad hoc reviewer
2016-17 Frontiers in Microbiology, Special Topics Editor: The Gut Microbiome in Health and Disease
2017 NIH, Hypersensitivity, Autoimmune, Immune mediated diseases Study Section, ad hoc reviewer
2018-present Editorial Board, Review Editor, Frontiers in Immunology – Autoimmune & Autoinflammatory Disorders
2019 NIH, R15 Immunology Panel

Honors and Awards

1989 Cambridge University Travel Award to England
1992-94 NIH Individual National Research Service Award (NRSA)
1994-96 NIH Individual National Research Service Award (NRSA)
1996 Cora Verhagen Travel Fellowship to Japan
1997-99 Career Development Award - Crohn's and Colitis Foundation of America
2012,13,14 AAI Laboratory Travel Grant
2015 Profiled in Lupus Research Update, Alliance for Lupus Research
2015 Selected for Alliance for Lupus Research/SLE Lupus Foundation multi-media interview (1 of 3 out of 70 researchers), New York, NY
2015 Selected for Alliance for Lupus Research/Lupus Research Institute/SLE Lupus Foundation presentation to lupus patients/donors (1 of 4 out of 70 researchers)
2016 Interviewed (by Stephanie Pappas) and highlighted on the online Rheumatology Network (formerly Journal of Musculoskeletal Medicine).

C. Contributions to Science

1. **Immunoregulation in an immune privilege site**. My early work was in the area of immunoregulation or tolerance in an immune privilege site, the eye. One of the tolerogenic mechanisms that is thought to contribute to immune privilege is the induction of active suppression, i.e., "suppressor" T cells, that can prevent the induction of the immune response. In a seminal study, we found that this form of tolerance could also inhibit an established effector T cell response, i.e., the suppressor T cells induced via administration of antigen into the eye not only prevent the activation of naive T cells, but can also suppress activated effector T cells. In another study, we also found that CD8 suppressor cells that are induced by administration of antigen into the eye, may be induced via an unique antigen processing pathway. And in a third study, we found that administration of antigen into the eye results in the systemic suppression of IFNγ-producing T cells through the induction of TGFβ-producing T cells. Taken together these studies contributed significantly to our understanding of the mechanisms that mediate tolerance in immune privilege organs.
    a. **Kosiewicz, M.M**., S. Okamoto, S. Miki, B. Ksander, T. Shimizu, and J.W. Streilein. 1994. Imposing deviant immunity on the presensitized state. *J. Immunol.* 153:2962-2973.
    b. **Kosiewicz, M.M**. and J.W. Streilein. 1996. Intraocular injection of a class II-restricted peptide induces an unexpected population of CD8 regulatory T cells. *J. Immunol.* 157:1905-1912.
    c. **Kosiewicz, M.M.**, P. Alard, and J.W. Streilein. 1998. Alterations in cytokine production following intraocular injection of soluble protein antigen: impairment in IFNγ and induction of TGFβ and IL-4 production. *J. Immunol.* 161:5382-5390.
    d. Streilein, J.W., S. Okamoto, Y. Hara, **M. Kosiewicz**, and B. Ksander. 1997. Blood-borne signals that induce anterior chamber-associated immune deviation after intracameral injection of antigen. *Invest. Ophthalmol. & Visual Sci.* 38:2245-2254.

2. **TGFβ and tolerogenic macrophages**. My laboratory has also contributed significantly to our understanding of the mechanisms underlying the tolerogenic properties of tolerogenic/immunoregulatory macrophages (TGFβ-treated Mϕ). We have found that TGFβ-treated Mϕ can directly delete naïve T cells, and have explored how both CD4 and CD8 regulatory cells are induced by TGFβ-treated Mϕ as well as the mechanisms utilized by both of these regulatory T cell populations to inhibit naïve T cell induction and suppress activated T cell function. The ultimate goal is to develop therapeutic strategies for the prevention/treatment of autoimmune disease using the information generated from these studies .
    a. P. Alard, S. Clark, and **Kosiewicz, M.M**. 2003. Deletion, but not anergy, is involved in TGFβ-treated antigen-presenting cell-induced tolerance. *Int. Immunol*. 15:1-9.
    b. P. Alard, S. Clark, and **Kosiewicz, M.M**. 2004. Mechanisms of tolerance induced by TGFβ-treated APC. CD4 regulatory T cells prevent the induction of the immune response in naive mice possibly through a mechanism involving TGFβ. *Eur. J. Immunol*. 34:1021-1030.
    c. **Kosiewicz, M.M**., P. Alard, Shuang Liang and S. Clark. 2004. Mechanisms of tolerance induced by TGFβ-treated APC. CD8 regulatory T cells inhibit the effector phase of the immune response in primed mice through a mechanism involving FasL. *Int. Immunol*. 16:697-706.
    d. Z. Gu, A.Y. Chhabra, P. Alard, D.R. Warner, and **M.M. Kosiewicz**. FcγRI is required for TGFβ-treated macrophage-induced tolerance. 2013. *Immunobiology*. April;218:1200-1206.

3. **Regulatory T cell biology and mechanisms of autoimmunity.** As described above I have had a long-term interest in immunoregulation and regulatory (formerly suppressor) T cells. We were among the first laboratories to show that $CD4^+CD25^+Foxp3^+$ regulatory T cell (Treg) could be induced or converted in the periphery (i.e., extrathymically) from $CD4^+CD25^-$ (non-regulatory) T cells. This was a critical finding as it provided early evidence that Treg conversion, previously shown only *in vitro*, may occur *in vivo*. In other studies, we have found that antigen presenting cells (APC) from autoimmune-prone (NOD) mice were less effective at activating syngenic Tregs suggesting that this could be a mechanism underlying the failure of Tregs to effectively suppress activation of potential

disease-mediating effector T cells. We also found that these same APC may be unable to support peripheral conversion of Tregs in NOD mice (manuscript in preparation). In another study, although we found no differences in inherent Treg function (*in vitro*) between non-autoimmune and autoimmune-prone strains of mice, we did find that frequencies of Tregs and particularly, the $CD103^+$ Tregs (a highly potent subset), are in some cases dramatically decreased in strains of mice predisposed to develop autoimmune disease, including NOD and NZBxNZW)F1 (BWF1) mice. Taken together, our findings contribute to the growing body of knowledge concerning Tregs and autoimmunity.

a. Shuang Liang, Pascale Alard, Yuan Zhao, Sarah Parnell, Sherry L. Clark, and **Michele M. Kosiewicz**. 2005. Conversion of $CD4^+CD25^-$ cells into $CD4^+CD25^+$ regulatory cells *in vivo* requires B7 co-stimulation, but not the thymus. *J. Exp. Med*. 201:127-137.

b. Colleen F. Tucker, Doreen L. Nebane-Ambe, Anita Chhabra, Sarah A. Parnell, Yuna Zhao, Pascale Alard, and **Michele M. Kosiewicz**. 2011. Decreased frequencies of $CD4^+CD25^+Foxp3^+$ cells and the potent $CD103^+$ subset in peripheral lymph nodes correlate with autoimmune disease predisposition in some strains of mice*. Autoimmunity*. Sep;44(6):453-64.

c. Pascale Alard, Jean N. Manirarora, Sarah A. Parnell, Jason L. Hudkins, Sherry L. Clark and **Michele M. Kosiewicz**. 2006. Deficiency in NOD APC function may be responsible for sub-optimal $CD4^+CD25^+$ T cell-mediated regulation and Type 1 diabetes development in NOD mice. *Diabetes*. 55:2098-2105.

d. Jean N. Manirarora, **Michele M. Kosiewicz**, Sarah A. Parnell and Pascale Alard. 2008. APC Activation Restores Functional CD4CD25 Regulatory T Cells in NOD Mice that Can Prevent Diabetes Development. *Plos One*. 3(11):e3739.

e. Korte EA, Caster DJ, Barati MT, Tan M, Zheng S, Berthier CC, Brosius FC 3rd, Vieyra MB, Sheehan RM, **Kosiewicz M**, Wysoczynski M, Gaffney PM, Salant DJ, McLeish KR, Powell DW. 2017. ABIN1 Determines Severity of Glomerulonephritis via Activation of Intrinsic Glomerular Inflammation. *Am J Pathol*. 2017 Dec;187(12):2799-2810.

f. Zhao, Y, P. Alard, **M. Kosiewicz**. 2019. High thymic ouput of effector CD4+ cells may lead to a Treg:T effrctor imbalance in the periphery in NOD mice. *J. Immunol. Res*. June 11;2019:8785263. doi: 10.1155/2019/8785263

5. **Mucosal immunology, microbiota, therapeutic strategies in inflammatory/autoimmune diseases.** As an Assistant Professor in the division of Gastroenterology at the University of Virginia, I developed an interest and expertise in the area of mucosal immunology and gut inflammation. I further developed and characterized the only naturally occurring spontaneous murine model of Inflammatory Bowel Disease (SAMP1/YIT) exhibiting pathology that is remarkably similar to Crohn's Disease in humans with T cell-mediated generated skip lesions in the terminal ileum. Our most recent project involves the study of the relationship between the gut mucosa, microbiota, immunoregulation, sex and lupus. We have found that the gut microbiota of male (NZBxNZW)F1 (BWF1) mice differs in composition from the lupus-prone BWF1 female, and appears to protect males from disease via a mechanism involving tolerogenic dendritic cells (DC) in the mesenteric lymph nodes and Treg conversion (manuscript submitted). We anticipate that this work will contribute significantly to our understanding of the role that sex, microbiota and immunoregulation play in the development of and/or protection from lupus, and could lead to the development of novel therapeutic strategies for the prevention and/or treatment of lupus.

a. **Kosiewicz, M.M**., C. Nast, A. Krishnan, J. Rivera-Nieves, C.A. Moskaluk, S. Matsumoto, K. Kozaiwa, and F. Cominelli. 2001. Th-1-type responses mediate spontaneous ileitis in the SAMP1/Yit model of Crohn's disease. *J. Clin. Invest*. 107:695-702.

b. **MM Kosiewicz**, Arin L Zirnheld, and Pascale Alard. 2011. Gut microbiota, immunity and disease: a complex relationship. *Front Cell Infect Microbiol*. 2011;2:180. Epub 2011 Sept 5.

c. **M.M. Kosiewicz**, GW Dryden, A.Y. Chhabra, P. Alard. 2014. Relationship between gut microbiota and development of T cell associated disease. *FEBS Letters*. Nov 17;588(22):4195-206.

Complete List of Published Work in MyBibliography
http://www.ncbi.nlm.nih.gov/sites/myncbi/1veLrh8qqSxAj/bibliograpahy/49071726/public/?sort=date&direction=ascending

Ongoing Research Support

Target Identification in Lupus Grant Kosiewicz (PI) 02/01/2015-1/31/2019-NCE
Alliance for Lupus Research
Sex and microbiota influence on immunoregulation and disease in BWF1 mice
The goal of this project is to identify and test microbial metabolites that protect against disease in the BWF1 model of lupus.
Role: PI

R01 AR067188-01 Kosiewicz (PI) 9/01/2015-8/31/2020
Interplay of androgens, microbiota and immunoregulation in lupus
The goals of this project are to determine the role that androgens play in altering male microbiota and the mechanisms underlying male microbiota-mediated prevention of lupus in female mice.
Role: PI

NSF DMS1516011 Collaborative (multi-investigator) Research Grant Kosiewicz (co-PI) 9/01/2015-8/31/2019-NCE
Modeling Immune Dynamics of RNA Viruses In Reservoir and Nonreservoir Species
The goal of this project is to develop new mathematical models and methods, stochastic and deterministic, based on *in vitro* experiments that distinguish between persistence, viral clearance, or severe pathology in reservoir and non-reservoir hosts.

Role: Multi-PI