## BIOGRAPHICAL SKETCH

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NAME: Melissa Michelle Mavers

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

POSITION TITLE: Instructor of Pediatrics, Division of Stem Cell Transplantation and Regenerative Medicine

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 Miami (Florida) | BS | 05/2003 | Microbiology and Immunology |
| Saint Louis University School of Medicine | PhD | 10/2009 | Microbiology and Immunology |
| Saint Louis University School of Medicine | MD | 05/2011 | Medicine |
| University of California Los Angeles | Residency | 06/2014 | Pediatrics |
| Stanford University, Palo Alto, CA | Fellowship | 06/2017 | Pediatric Hematology-Oncology |

### A. Personal Statement

I am an Instructor of Pediatrics in the Division of Stem Cell Transplantation and Regenerative Medicine (SCTRM) at Stanford University/Lucile Packard Children's Hospital, with a research focus on immune regulation of graft-versus-host disease (GVHD). I completed the MD/PhD program at Saint Louis University School of Medicine, in the laboratory of Dr. Harris Perlman, where I demonstrated a novel role for the cyclin dependent kinase inhibitor p21 in suppression of inflammatory cytokine production and reduction in inflammatory disease. This project led to the publication of two first-author original research manuscripts, a first author review, and a middle-author research paper. During this time, I trained in immunology and gained research experience in molecular biology, which helped to shape my current goal of using cutting edge technology to investigate methods of immune modification to suppress GVHD. Additional training included Pediatrics Residency at the University of California Los Angeles and Pediatric Hematology/Oncology Fellowship at Stanford University.

I am now conducting research on innovative approaches to prevent GVHD under the mentorship of Dr. Robert Negrin. I have shown that activation of death receptor 3 with a novel fusion protein leads to *in vivo* expansion and activation of murine regulatory T cells and GVHD suppression. This project, presented at the annual meeting of the American Society for Transplantation and Cellular Therapy (ASTCT) and published as a first author original research paper, allowed me to develop skills in proteomic and transcriptomic analyses. These skills, together with the collaborations I have established with experts in CyTOF and multiomic analyses, will ensure successful completion of the proposed project. I have now developed a method for robust *in vitro* expansion of human invariant natural killer T (iNKT) cells, an innate lymphocyte which suppresses GVHD in mice, and showed equivalent cytokine production regardless of expansion method. These data were presented at the annual meetings of the American Society of Hematology and ASTCT. I have also used flow cytometry to show heterogeneity of human iNKT cells, which cluster into 3 populations upon tSNE analysis. These data provide the foundation and feasibility for the proposed project in which I will further define human iNKT cell heterogeneity and develop strategies for targeted isolation of immunosuppressive iNKT cells, yielding critical preclinical data to inform the design of a future clinical trial. This work supports my career objective to develop a robust research program as a physician scientist with expertise in pediatric SCTRM and immune regulation of GVHD.

## B. Positions and Honors

**Positions and Employment**

| | | |
|---|---|---|
| 2000-2001 | Washington University School of Medicine, St. Louis, MO<br>(John P. Atkinson, *Binding properties of human factor B and C3b*) | Lab Technician |
| 2001-2002 | University of Miami School of Medicine, Miami, FL<br>(Vincent Moy, *AFM studies of cell adhesion, PEG construct biocompatibility*) | Lab Technician |
| 2002-2003 | University of Miami School of Medicine, Miami, FL<br>(Glen Barber, *Characterization of functional interaction of VP19 and PKR*) | Undergraduate Honors Thesis |
| 2003-2003 | Saint Louis University School of Medicine, St. Louis, MO<br>(Ali Shilatifard, *Analysis of histone acetylation proteins*) | Graduate Rotation |
| 2004-2004 | Saint Louis University School of Medicine, St. Louis, MO<br>(Maulik Shah, *Evaluation of adenoviral construct effect on macrophage activation)* | Graduate Rotation |
| 2005-2007 | Saint Louis University School of Medicine, St. Louis, MO<br>(Maulik Shah, *Analysis of immune response to basal cell carcinoma and evaluation of imiquimod treatment*) | Graduate Research |
| 2007-2008 | Saint Louis University School of Medicine, St. Louis, MO | Graduate Research *-and-* |
| 2008-2009 | Northwestern University, Chicago, IL<br>(Harris Perlman, *Elucidation of the role of the cyclin dependent kinase inhibitor p21 in suppression of inflammatory cytokine production and treating inflammatory diseases)* | Visiting Scholar |
| 2015-present | Stanford University School of Medicine, Stanford, CA<br>(Robert Negrin, *Expansion of regulatory and invariant natural killer T cells to suppress graft-versus-host disease)* | Fellowship/Post-doc Research |
| 2017-present | Stanford University School of Medicine, Stanford, CA<br>Department of Pediatrics, Division of Stem Cell Transplantation and Regenerative Medicine<br>Lucile Packard Children's Hospital | Instructor (**start: 7/1/17**) |

**Professional Memberships**

| | |
|---|---|
| 2014-2018 | American Society of Hematology, Associate Member |
| 2016-present | Alpha Omega Alpha Honor Medical Society, Member |
| 2018-present | American Society for Transplantation and Cellular Therapy, Member |

**Honors and Other Experience**

| | |
|---|---|
| 1999 | Barry M. Goldwater merit-based scholarship, University of Miami (1999-2003) |
| 2001 | Universidad Iberoamericana Exchange Program Scholarship, Mexico City, Mexico |
| 2003 | Graduated *Magna cum laude*, University of Miami |
| 2003 | Saint Louis University, MD/PhD Scholarship (2003-2011) |
| 2005 | Saint Louis University, AOA Medical Student Research Forum Finalist |
| 2006 | St. Baldrick's Fundraiser shavee, 3rd highest fundraiser in St. Louis, MO |
| 2007 | Keystone Symposia Travel Scholarship and Poster Presentation |
| 2008 | 1st place, Saint Louis University Graduate Student Research Symposium |
| 2008 | American College of Rheumatology Annual Scientific Meeting Oral Platform Presentation |
| 2009 | American College of Rheumatology Graduate Student Achievement Award |
| 2015 | Board Certification in General Pediatrics, American Board of Pediatrics |
| 2016 | Induction into Alpha Omega Alpha Honor Medical Society |
| 2017 | American Society of Hematology Annual Meeting Poster Presentation |
| 2017 | Eureka Institute for Translational Medicine, 9th Annual International Certificate Program |
| 2017 | ASBMT Clinical Research Training Course |
| 2017 | St. Baldrick's Foundation Grant Reviewer |
| 2018 | Manuscript reviewer for Human Gene Therapy, St. Baldrick's Foundation Grant Reviewer |
| 2018 | Planning Committee and Session Moderator, Inaugural Stanford MCHRI Symposium |
| 2018 | American Society for Blood and Marrow Transplantation Poster Presentations |
| 2019 | 10th Annual Stanford Pediatrics Research Retreat Outstanding Oral Presentation Award |
| 2019 | Board Certification in Pediatric Hematology/Oncology, American Board of Pediatrics |

## C. Contributions to Science

**1. Clinical Contributions:** My contributions as pertaining to my clinical career have focused on applying my knowledge of the previously undescribed immunopathology contributing to the signs and symptoms of patients diagnosed with rare medical diseases to write case reports advancing knowledge of these diseases and making important recommendations to physicians. In addition, I contributed substantially to the first ever analysis of mental health in patients with a rare genodermatosis.

a. **Mavers M**, Blaufuss T, Friedman H, Becker BA, and Jain AK. Eosinophilic Esophagitis in a Pediatric Patient with Herpes Simplex Virus Esophagitis. A Cause or a Consequence? *Open J of Clin & Med Case Reports* 2015;6(1):1036.
b. Shah M, **Mavers M**, Bree A, Fosko S, and Lents N. Quality of life and depression assessment in nevoid basal cell carcinoma syndrome. *Int J Dermatol* 2011 Mar;50(3):268-76. PMID21342158.
c. Shah M, Bogucki B, **Mavers M**, deMello DE, Knutsen A. Cardiac conduction abnormalities and congenital immunodeficiency in a child with Kabuki syndrome: case report. *BMC Med Genet* 2005 Jul;6:28. PMC1190177.

**2. Modulation of inflammatory disease:** My graduate research contributions focused on elucidating novel pathophysiologic mechanisms of inflammation and autoimmunity. My work concentrated on the role of cyclin dependent kinase inhibitor p21 in the inhibition of macrophage activation and inflammatory disease and led to several key publications. My results were critical in describing novel peptidomimetic therapies effective in reducing murine inflammatory arthritis. In addition, I wrote an important review article which was the first to provide an assessment of the field of therapeutics targeting signaling pathways in rheumatoid arthritis.

a. **Mavers M**, Cuda CM, Misharin AV, Gierut AK, Agrawal H, Weber E, Veis Novack D, Haines III GK, Balomenos D, and Perlman H. Cyclin-dependent kinase inhibitor p21, via its C-terminal domain, is essential for resolution of murine inflammatory arthritis. *Arthritis Rheum* 2012 Jan;64(1):141-52. PMC3253189.
b. Scatizzi JC, Hutcheson J, Pope RM, Firestein GS, Koch AE, **Mavers M**, Smason A, Agrawal H, Haines III GK, Chandel NS, Hotchkiss RS, and Perlman H. Bim-Bcl-2 homology 3 mimetic therapy is effective at suppressing inflammatory arthritis through the activation of myeloid cell apoptosis. *Arthritis Rheum* 2010 Feb;62(2):441-51. PMC2848986.
c. **Mavers M**, Ruderman EM, and Perlman H. Intracellular signal pathways: potential for therapies. *Curr Rheumatol Rep* 2009 Oct;11(5):378-85. PMC3033497.
d. Scatizzi JC*, **Mavers M***, Hutcheson J, Young B, Shi B, Pope RM, Ruderman EM, Samways DSK, Corbett JA, Egan TM, and Perlman H. The CDK domain of p21 is a suppressor of IL-1β-mediated inflammation in activated macrophages. *Eur J Immunol* 2009 Mar;39(3):820-5. PMC2734089.
***co-first authors***

**3. Immune regulation in hematopoietic stem cell transplantation:** My postdoctoral research investigates mechanisms to enhance immune regulation of graft-versus-host disease (GVHD), with specific focus on expansion and activation of immunosuppressive cells. I have pursued two approaches for *in vivo* regulatory T cell (Treg) expansion and activation. In the first, I have shown that *in vivo* activation of the death receptor 3 (DR3) pathway with a novel fusion protein incorporating the endogenous DR3 ligand leads to murine Treg expansion. I extensively characterized the activation status of the expanded cells using proteomic and transcriptomic techniques and demonstrated their suppression of GVHD. The second approach focuses on invariant natural killer T (iNKT) cells which have been shown to cause *in vivo* Treg expansion and GVHD suppression in mice. For this work-in-progress, I have demonstrated the heterogeneity of human iNKT cells through flow cytometric analyses and defined optimal conditions for their robust *ex vivo* expansion (with similar cytokine production profiles regardless of expansion method used). I have also written a significant review article extensively summarizing the literature on iNKT cell-mediated suppression of GVHD, as well as a review of natural killer cells in the treatment of leukemia with and without stem cell transplantation.

a. **Mavers M**, Simonetta F, Nishikii H, Ribado JV, Maas-Bauer K, Alvarez M, Hirai T, Turkoz M, Baker J, Negrin RS. Activation of the DR3-TL1A axis in Donor Mice Leads to Regulatory T cell Expansion and Activation with Reduction in Graft-Versus-Host Disease. *Front Immunol* 10:1624, 2019. PMC6652149.
b. **Mavers M** and A Bertaina. High risk leukemia: past, present and future role of NK cells. *J Immunol Res* Apr 15 2018:1586905. PMC5925205.

**C. Contributions to Science (continued)**

**3. Immune regulation in stem cell transplantation (continued):**

c. **Mavers M***, Maas-Bauer K*, Negrin RS. Invariant natural killer T cells as suppressors of graft-versus-host disease in allogeneic hematopoietic stem cell transplantation. *Front Immunol* Jul 31 2017;8:900. PMC5534641. **co-first authors*

d. Nishikii H, Kim BS, Yokoyama Y, Chen Y, Baker J, Pierini A, Alvarez M, **Mavers M**, Mass-Bauer K, Pan Y, Chiba S, Negrin RS. DR3 signaling modulates the function of Foxp3+ regulatory T cells and the severity of acute graft versus host disease. *Blood* Dec 15 2016;128(24):2846-2858. PMC5159706.

**D. Additional Information: Research Support and/or Scholastic Performance**

**<u>Completed Research Support</u>**

St. Baldrick's Foundation Fellowship (Mavers) 07/01/16-09/30/19
Title: Expansion of Treg and iNKT cells to suppress graft-versus-host disease
Role: Principal Investigator (Fellow)
The primary goal of this project is to develop optimized strategies for expansion of regulatory immune cells for suppression of GVHD and to further understand the properties of the expanded populations.

Tashia and John Morgridge Endowed Postdoctoral Fellowship (Mavers) 07/01/15-06/30/17
Children's Health Research Institute, Stanford University
Title: Expansion of regulatory and invariant natural killer T cells to suppress graft versus host disease
Role: Principal Investigator (Fellow)
The aims of this proposal are to develop strategies to expand regulatory T cells ($T_{reg}$) and invariant natural killer T (iNKT) cells *in vivo* with enhanced function in suppression of graft versus host disease (GVHD) and to explore the critical interaction between iNKT cells and $T_{reg}$ cells in suppression of GVHD.

American Medical Association Seed Grant (Mavers) 04/01/06-03/31/07
Title: Identification of tumor-associated antigens in basal cell carcinoma
Role: Principal Investigator (Trainee)
The goals of this proposal are to identify basal cell carcinoma (BCC) tumor-associated antigens via serological analysis of cDNA expression libraries (SEREX) using serum from BCC nevoid syndrome patients and to validate expression and immunological reactivity of these antigens.

American College of Rheumatology Research and Education Preceptorship (Mavers) 06/08
Title: Evaluation of the efficacy of peptidomimetics to $p21^{(WAF1/CIP1)}$ in the treatment of K/BxN serum transfer induced arthritis
Role: Principal Investigator (Trainee)
The aim of this proposal is to determine the effectiveness of treating the IL-1β-dependent serum-transfer murine model of arthritis with a peptide mimetic to $p21^{(WAF1/CIP1)}$ *in vivo*.