Name of Applicant (Last, First, Middle): Shapiro, Melanie Rose

FELLOWSHIP APPLICANT BIOGRAPHICAL SKETCH

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NAME OF FELLOWSHIP APPLICANT	POSITION TITLE
Melanie Rose Shapiro	Postdoctoral Associate
eRA COMMONS USER NAME (credential, e.g., agency login) mrshapir	

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Maryland, College Park, MD	BS	2011 - 2015	Cell Biology & Molecular Genetics
University of Florida, Gainesville, FL	PhD	2015 - 2020	Immunology & Microbiology
University of Florida, Gainesville, FL	Postdoctoral	Present	Immunology

A. Personal Statement

My fascination with autoimmunity began as a natural consequence of a childhood diagnosis of type 1 diabetes (T1D). While my parents do not have a scientific background, they tried their best to instill hope in me, by excitedly sharing news articles describing the “cure for diabetes” that was “only five years away” from becoming a reality. Years of these stories failing to come to fruition compelled me to seek out the T1D literature myself. My scientific literacy improved as I became introduced to names of some of my personal heroes, individuals who have dedicated their careers toward understanding how T1D develops with the ultimate goal of cure or prevention.

With this shared goal, I pursued my graduate education at the University of Florida Diabetes Institute (UFDI) with co-mentorship by Drs. Mark Atkinson and Todd Brusko. My mentors have pushed the field forward tremendously through leadership of the Network for Pancreatic Organ donors with Diabetes (nPOD) program to provide novel insights into pathology of the pancreas and draining lymph nodes in human T1D. Additionally, their development of a UFDI biobank harboring thousands of blood samples from subjects with varying degrees of risk for T1D, has provided a means to distinguish peripheral markers of progression toward onset in living patients. These biobanks as well as their expertise were critical for my dissertation studies involving the identification of insulin-like growth factors (IGFs) as pre-T1D biomarkers, demonstration of IGF1-mediated promotion of the homeostatic proliferation of regulatory T cells, and characterization of immune dysregulation in a family with a novel *IGF1R* mutation.

The UFDI is certainly a unique institution in terms of its resources for studying the heterogeneity of human T1D, and for this reason, I chose to stay on as a postdoctoral associate. While I plan to remain involved in IGF-related research, with this new appointment, I will be shifting my focus toward attaining additional bioinformatics skills, with an emphasis on whole genome single nucleotide polymorphism (SNP) analysis. My goal is to use these tools to enhance diabetes prediction and/or precision medicine efforts. As a patient-researcher, I know that insulin is simply not a cure and therefore, I commit my career to further improving our knowledge of T1D pathogenesis. Along the way, I hope to inspire other individuals with T1D to read often, think creatively, and push the envelope of what we know about T1D so that we can decrease the physical, financial, and emotional burden of this lifelong disease on future generations.

B. Positions and Honors

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
Howard Hughes Medical Institute/Montgomery County Public Schools Internship	06/10	08/11	Immunology	National Institutes of Health, Bethesda, MD	Dr. Tomoshige Kino
Gemstone Honors Research Program	09/12	05/15	Behavioral Neuroscience	University of Maryland, College Park, MD	Dr. Erica Glasper

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
HHMI Undergraduate Research Fellow	02/12	05/15	Immunology	University of Maryland, College Park, MD	Dr. Wenxia Song
Graduate Research Assistant	07/15	05/20	Immunology	University of Florida, Gainesville, FL	Drs. Mark Atkinson & Todd Brusko
Postdoctoral Associate	05/20	Present	Immunology	University of Florida, Gainesville, FL	Dr. Todd Brusko

Academic and Professional Honors

2019 Best Oral Presentation, Pediatric Science Research Day, University of Florida
2018 Exemplary Graduate Student Award, Experimental Pathology, University of Florida
2018 Advancement to Candidacy Award, University of Florida
2015-2018 Grinter Scholarship, University of Florida
2015 Summa Cum Laude, University of Maryland
2011-2015 Banneker/Key Scholar, University of Maryland
2011 Diabetes Scholars Foundation Scholarship Recipient

Funding

2018-2020 F31 DK-117548-01, **Shapiro** (PI). Predoctoral Individual National Research Service Award. Roles of the Insulin-like Growth Factor Axis in Pre-Type 1 Diabetes Immune Regulation.
2018 T32 DK108736-01A1, Trainee, Atkinson (PI). Interdisciplinary Graduate Program in Type 1 Diabetes and Biomedical Engineering.
2017 Children's Miracle Network Research Award, University of Florida, $20,000
2013-2014 HHMI Gemstone Research Fellowship, University of Maryland, $4000
2012-2015 HHMI Undergraduate Research Fellowship, University of Maryland, $7,500/year

Teaching Experience & Student Mentorship

2017-2019 John Gallagher, Undergraduate Student.
John contributed to insulitis scoring, pancreas dissections, murine blood glucose measurement, and genotyping under my supervision.
2016-2019 Joshua Longfield, Undergraduate Student.
Joshua managed SNP genotyping and a diabetes incidence study for our mouse colony, while assessing how CD226 modulates TCR signaling via phosflow for his honors thesis.
2013 Principles of Biology I Laboratory, Teaching Assistant
2013 Topics in Science, Technology, and Society, Section Leader
2012 Freshman Honors Colloquium: Introduction to Gemstone, Section Leader

Outreach

2017, 2019 Friends for Life, UF Diabetes Institute Representative
2017-2018 Touched by Type One, UF Diabetes Institute Representative
2012-2014 Innoworks Science Summer Camp, Co-Director, Deputy Director, Curriculum Chair

C. Contributions to Science

I. *Characterizing insulin-like growth factors as biomarkers with immunological impacts on T1D pathogenesis.*
Diagnosis of pre-T1D prior to overt hyperglycemia requires proof of impaired metabolism via lengthy oral glucose tolerance tests, creating a need to identify additional biomarkers involved in metabolism and/or immune dysregulation. Insulin-like growth factors (IGFs) have been suggested to protect against T1D via impacts on the pancreas and immune system, although it remained unclear if IGFs were deficient in pre-T1D. I showed that serum IGF1 and IGF2 levels were diminished in autoantibody positive (AAb+) subjects at high-risk of developing T1D as compared to low-risk first-degree relatives of T1D subjects without AAb. IGF1 levels also decreased over time in multiple AAb+ subjects and those who progressed to T1D. IGF1

has been implicated in promoting immune regulation, although there is limited understanding of the impacts of IGFs on human innate and adaptive immunity *in vivo*. I studied the immune profile of a family with a novel heterozygous splice variant in *IGF1R* (c.641-2A>G) and observed reduced IGF1R expression on peripheral blood mononuclear cells of those with the mutation. Although these subjects were unaffected by T1D, the mutation was associated with CD4+ T cell skewing toward Th1 and away from Th17 phenotype--a profile reported to be enriched in T1D. My findings suggest that IGFs may act as biomarkers of T1D progression and as immunomodulatory agents to augment CD4+ T cell regulation.

1. **Shapiro MR**, Wasserfall CH, McGrail SM, Posgai AL, Bacher R, Muir A, Haller MJ, Schatz DA, Wesley JD, von Herrath M, Hagopian WA, Speake C, Atkinson MA, Brusko TM. Insulin-Like Growth Factor Dysregulation Both Preceding and Following Type 1 Diabetes Diagnosis. Diabetes. 2020 Mar;69(3):413-423. doi: 10.2337/db19-0942. Epub 2019 Dec 11. PubMed PMID: 31826866; PubMed Central PMCID: PMC7034187.
2. **Shapiro MR**, Atkinson MA, Brusko TM. Pleiotropic roles of the insulin-like growth factor axis in type 1 diabetes. Curr Opin Endocrinol Diabetes Obes. 2019 Aug;26(4):188-194. doi: 10.1097/MED.0000000000000484. PubMed PMID: 31145130.
3. **Shapiro MR**, Foster TP, Perry DJ, Rosenfeld RG, Dauber A, McNichols JA, Muir A, Hwa V, Brusko TM, Jacobsen LM. A Novel Mutation in Insulin-Like Growth Factor-1 Receptor (c.641-2A>G) Is Associated with Impaired Growth, Hypoglycemia, and Modified Immune Phenotypes. Horm Res Paediatr. In Revision.

II. *Defining mechanisms by which the costimulatory molecule CD226 contributes to T1D.*

Type 1 diabetes (T1D) spontaneously develops in the non-obese diabetic (NOD) mouse from T cell-mediated destruction of the pancreatic islets. The costimulatory molecule CD226 is highly expressed on effector/memory CD8+ T cells, influencing both central and peripheral tolerance, and genetic polymorphisms in *CD226* have been associated with T1D susceptibility. We were the first to develop and characterize a NOD model with knockout (KO) of *Cd226*, hypothesizing that this strain would show attenuated T1D by altering T cell activation. CD226 KO mice showed decreased T1D incidence and islet inflammation versus wild-type controls. I found that CD226 KO mice showed potential modulation of CD8+ T cell thymic selection, demonstrated by increased thymic CD8+ T cell output. I also detected attenuated peripheral CD8+ T cell activation, demonstrated by decreased memory CD8+ T cells in the pancreatic lymph nodes. Evidence of decreased CD8+ T cell receptor affinity for islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), an immunodominant T1D epitope, was observed in the pancreas of CD226 KO mice. These findings support future investigation of translational blockade of CD226 signaling in prevention of T1D and other autoimmune diseases.

1. **Shapiro MR**, Yeh W, Longfield JR, Gallagher J, Infante CM, Wellford S, Posgai AL, Atkinson MA, Campbell-Thompson M, Lieberman SM, Serreze DV, Geurts AM, Chen Y, Brusko TM. CD226 Deletion Reduces Type 1 Diabetes in the NOD Mouse by Impairing Thymocyte Development and Peripheral T Cell Activation. Front Immunol. 2020 Jun. In Review.

III. *Illustrating the contribution of intestinal epithelial cells to T1D pathogenesis in human organ donors*.

As non-traditional antigen-presenting cells, intestinal epithelial cells (IEC) have been shown to impact systemic immunity. Studies of the contribution of these cells to human T1D were made possible with access to fresh duodenal tissue from T1D and non-diabetic controls from nPOD. During the summer prior to and an additional research rotation during my graduate program, I worked in the laboratory of Dr. Shannon Wallet, processing these precious samples under the guidance of Dr. Christina Graves. I stimulated T cells with supernatants from T1D and control intestinal epithelial cells and found that the diabetic milieu induced expansion of effector CD8+ (Tc1) T cells and inhibited expansion of bona-fide suppressive Tregs. This work supports the notion that IECs may contribute to adaptive immune dysfunction in T1D.

1. Graves CL, Li J, LaPato M, **Shapiro MR**, Glover SC, Wallet MA, Wallet SM. Intestinal Epithelial Cell Regulation of Adaptive Immune Dysfunction in Human Type 1 Diabetes. Front Immunol. 2017 Jan 10;7:679. doi: 10.3389/fimmu.2016.00679. eCollection 2016. PubMed PMID: 28119693; PubMed Central PMCID: PMC5222791.

IV. *Identification and phenotypic description of novel regulators of B cell activation.*

Although metabolic dysregulation is considered the primary cause of type 2 diabetes (T2D), inflammation has been shown to promote insulin resistance. As an undergraduate student, I led a mouse study determining the role of B cells in the development of obesity-associated insulin resistance, under the guidance of Dr. Wenxia Song. I created a novel mouse model of B cell lipid accumulation through B cell-specific KO of CGI-58 (BKO), a gene necessary for triglyceride hydrolysis. I found that BKO mice with obesity induced by high fat diet showed signs of autoimmunity, as evidenced by an increased number of rapidly proliferating germinal center B cells, as well as splenomegaly. I also found that BKO mice had an increased number of splenic germinal centers, another indication of inflammation when observed in non-immunized mice. My work suggests that fat accumulation concomitant with insulin resistance can intrinsically impair B cell development, leading to inflammation and development of T2D. Additionally, I collaborated with a graduate student in the lab to show that germinal center formation was increased in the spleens of mice that had actin-binding protein 1, a negative regulator of B cell signaling, knocked out.

1. Seeley-Fallen MK, Liu LJ, **Shapiro MR**, Onabajo OO, Palaniyandi S, Zhu X, Tan TH, Upadhyaya A, Song W. Actin-binding protein 1 links B-cell antigen receptors to negative signaling pathways. Proc Natl Acad Sci U S A. 2014 Jul 8;111(27):9881-6. doi: 10.1073/pnas.1321971111. Epub 2014 Jun 23. PubMed PMID: 24958882; PubMed Central PMCID: PMC4103327.

V. *Demonstrating rescue of stress-induced immune phenotypes by corticotropin-releasing factor blockade.*

Hypothalamic-pituitary-adrenal axis dysregulation is a characteristic of many diseases, with excess stress hormones like glucocorticoids even playing a potential role in diabetes. Drugs targeting this axis have had concerning side effects due to poor specificity. Thus, the Golde lab developed a blocking antibody against corticotropin-releasing factor (CRF), an upstream hormone that promotes glucocorticoid production and release. Chronic stress has been shown to decrease splenic mass due to loss of B cells and T cells, despite increases in percentages of some inflammatory cell subsets. In collaboration with the Golde lab, I demonstrated in mice undergoing chronic stress that treatment with the anti-CRF antibody reversed many of the stress-induced immune phenotypes in comparison to an isotype control. Specifically, the antibody-treated mice had higher splenic cellularity, increased numbers of B and T cells, and decreased percentages of NK cells and inflammatory monocytes. These findings suggest that CRF blockade may restore a healthy immune profile during stress.

1. Futch HS, McFarland KN, Moore BD, Kuhn MZ, Giasson BI, Ladd TB, Scott KA, **Shapiro MR**, Nosacka RL, Goodwin MS, Ran Y, Cruz PE, Ryu DH, Croft CL, Levites Y, Janus C, Chakrabarty P, Judge AR, Brusko TM, de Kloet AD, Krause EG, Golde TE. An anti-CRF antibody suppresses the HPA axis and reverses stress-induced phenotypes. J Exp Med. 2019 Nov 4;216(11):2479-2491. doi: 10.1084/jem.20190430. Epub 2019 Aug 29. PubMed PMID: 31467037; PubMed Central PMCID: PMC6829597.

D. Additional Information: Research Support and Scholastic Performance

YEAR	COURSE TITLE	GRADE	YEAR	COURSE TITLE	GRADE
2015	Fundamentals of Biomedical Science	A	2016	Advanced Research	S
2015	Research/Professional Development	S	2017	Immunology/Microbiology Journal Club	A
2015	Laboratory Rotation 1	S	2017	Advanced Research	S
2015	Laboratory Rotation 2	S	2017	Immunology/Microbiology Grant Writing	A
2015	First Year Journal Club	S	2017	Immunotherapy	A
2016	Laboratory Rotation 3	S	2017	Autoimmunity	A
2016	Infectious Diseases	A	2017	Mucosal Immunology	A
2016	Principles of Immunology	A	2018	Informatics for Pathology – Unix, Python	A
2016	Responsible Conduct of Biomedical Res	S	2018	Immunology/Microbiology Journal Club	A
2016	Innate Immunology	A	2018	Doctoral Research	S
2016	B Cell Development	A	2019	Immunology/Microbiology Journal Club	A
2016	T Cell Immunity	A	2019	Doctoral Research	S
2016	Immunology/Microbiology Journal Club	A	2020	Doctoral Research	S