BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Brusko, Todd M.

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

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 Florida, Gainesville, FL	B.S	08/2001	Microbiology & Cell Science
University of Florida, Gainesville, FL	Ph.D.	08/2006	Immunology
University of Florida, Gainesville, FL	Postdoc	11/2007	Immunology & Molecular Genetics
University of San Francisco, Diabetes Center, San Francisco, CA	Postdoc	08/2010	Molecular Immunology & Cell Therapy

A. Personal Statement

As an Associate Professor within the Diabetes Institute at the University of Florida, the research interests of my lab are centrally themed around understanding the mechanisms by which the immune system maintains a state of control, often referred to as immunological tolerance. A portion of my lab is dedicated to understanding the genes controlling this process as well as identifying the mechanisms at play in individuals who develop immune-mediated diseases. As evidence of this, I have previously published over 90 studies reporting cellular immune defects in patients with type 1 diabetes (T1D) and systemic lupus erythematosus (SLE), along with the genetic and epigenetic basis for such defects. Our lab is currently investigating mechanisms of immune regulation related to Treg cell biology, genotype:immunophenotype associations, the adaptive immune repertoire, and interactions between the innate and adaptive immune system.

B. Positions and Honors

Positions and Employment

1998-2000 Laboratory Technician and Teaching Assistant, Department of Natural Sciences, St. Petersburg College, St. Petersburg, FL

2000-2001 Laboratory Technician and Undergraduate Research, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL

2001-2002 Laboratory Technician, Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL

2002-2006 Graduate Student, Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL

2010-2016 Assistant Professor, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, College of Medicine, Gainesville, FL

2016- Associate Professor, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, College of Medicine, Gainesville, FL

Other Experience and Professional Memberships

2002- Member, American Diabetes Association

2007- Member, American Association for the Advancement of Sciences

2007- Federation of Clinical Immunology Societies (Immunology of Diabetes Society)

2008- Journal reviewer selected: *PNAS, USA, Journal of Clinical Investigation, Diabetes, Diabetes Care, Clinical Experimental Immunology, Journal of Immunology, BMC Immunology, Journal of Pediatrics, Cytotherapy, Cell Transplantation, Diabetes/Metabolism Research and Reviews, Journal of Visualized Experiments (JoVE), Nature Publishing Group- Molecular Therapy, Cytotherapy, New England Journal of Medicine.* F1000 associate faculty member.

2010-2014 JDRF Medical Science Review Committee (MSRC) member. Reviewed the Autoimmunity Center Consortiums, strategic grant review committees, and training award applications, which include Advanced Postdoctoral Fellowships (APFs), Postdoctoral Fellowships (PFs), Career Development Awards and Early Career Patient Oriented Diabetes Research Award.

2011 NIH RFA-DK-10-012 Type 1 Diabetes Impact Award (DP3)-scientific review panel

2011 Thrasher Research Fund for Children's Medical Research Grant Ad Hoc Reviewer

2012 NIH NIDDK-RFA-DK-11-024. "Small Business Innovative Research to Develop New Methods and Technologies able to Identify Individuals at risk of developing Type 1 Diabetes (T1D) (R43)". SBIR study section reviewer; French National Research Agency. "Blanc" program specialized reviewer. B7-IT. Committee SVSE 1; Israel Science Foundation. ISF-JDRF Joint Program in Type 1 Diabetes Research. Ad hoc reviewer; NIH NIDDK. Special emphasis panel review committee member. RFA-DK-11-019 entitled, "Function of Type 1 Diabetes Genes (DP3). (June 28-29, 2012); American Diabetes Association–Abstract reviewer (Immunology).

2013-2015 JDRF Biomarker Working Group, Committee member; ADA Research Grant Review Committee (RGCR) Member

2014 Helmsley T1D Exchange Living Biobank Scientific Advisory Board Steering Committee Participant; R&D Challenge Fund, The Guy's & St Thomas' Charity, South London and the Maudsley Charity, the Medical Research Counsel and the Welcome Trust. King's College London. Ad Hoc Grant Reviewer: Help a Diabetic Child Foundation, Advisory Board Member; Diabetes UK. Special Emphasis Panel for the Prevention and Treatment of Type 1 Diabetes Ad hoc grant reviewer; Coordinator for the Center for Immunology and Transplantation

2014 Member, NIH TrialNet Biomarkers and Mechanisms Steering Panel

2015 Science Foundation Ireland. SFI/EI Technology Innovation Development Award (TIDA)

2015 Peer review panel. Ad Hoc Grant Reviewer. August 2015.

2016- NIH Type 1 Diabetes TrialNet: Ancillary studies presentations and publications (PPS) subcommittee review member

Honors

2001 Elected to the Golden Key Honor Society

2005 Graduate Fellowship for Outstanding Research Award

2007 FOCIS Meeting--National Institutes of Health Travel Award Recipient

2008 Midwinter Conference of Immunologists – JDRF Travel Award Recipient

2009 FOCIS Meeting -- National Institutes of Health and JDRF travel awards

2010 JDRF Early Career Investigator Travel Award

2010 JDRF Transition Award Recipient

2011 JDRF Career Development Award Recipient

2013 Pfizer Aspire Young Investigator Award Recipient

2014 Elected UF faculty senate counsel

2017 University of Florida, College of Medicine Teaching Award

2017-2020 University of Florida, College of Medicine Term Professorship

C. Contributions to Science

1. Understanding Immunoregulatory defects in T1D: These publications were among the first to describe defective immune suppression, cellular plasticity (IFNγ and IL-17 production) within the Treg compartment, as well as quantify the frequency of FOXP3$^+$ Tregs in circulation of patients with T1D. Through analysis of Helios, the unique epigenetic methylation profile of natural Tregs at the Treg-Specific Demethylated Region (TSDR), and transcriptional profiles of IFNγ^+ Tregs, we identified the costimulatory molecule CD226 as a key surface marker of cytokine producing cells within the human CD4$^+$CD127$^{-/lo}$CD25$^+$ T cell population. This line of investigation has led to a career centrally focused on understanding the mechanisms that lead to a breakdown in peripheral immune tolerance in individuals with T1D. From this and related publications, I have generated a reputation as an expert in Tregs and immune regulation resulting in multiple highly cited review articles. Moreover, these studies aided in generating a current paradigm that bolstering Treg activity and/or stability may provide a means to attenuate T effector cell activity during the pathogenesis of T1D.
   a. Brusko, T. M., C. H. Wasserfall, M. J. Clare-Salzler, D. A. Schatz, and M. A. Atkinson. Functional defects and the influence of age on the frequency of CD4+CD25+ T-cells in type 1 diabetes. *Diabetes.* 2005 May:54:1407-1414. (PMID: 15855327; 390 citations)
   b. Brusko T.M., C. Wasserfall, K. McGrail, R. Schatz, HL Viener, D. Schatz, M. Haller, J. Rockell, P. Gottlieb, M. Clare-Salzler, and M. Atkinson. No Alterations in the Frequency of FOXP3$^+$ Regulatory T Cells in Type 1 Diabetes*. Diabetes*. 2007 Mar;56(3):604-12. (PMID: 17327427; 244 citations)
   c. McClymont S.A., Putnam A.L., Lee M.R., Esensten J.H., Liu W., Baron U., Olek S., Bluestone J.A., and Brusko

T.M. Plasticity of Human Regulatory T Cells in Healthy Subjects and Patients with Type 1 Diabetes. *J Immunol.* 2011;186(7);3918-26. (PMID: 21368230; 332 citations)

d. Seay H.R., Yusko E., Rothweiler S.J., Zhang L., Posgai A.L., Campbell-Thompson M., Vignali M., Emerson R.O., Kaddis J.S., Ko D., Nakayama M., Smith M.J., Cambier J.C., Pugliese A., Atkinson M.A., Robins H.S., Brusko T.M. Tissue distribution and clonal diversity of the T and B cell repertoire in type 1 diabetes. *JCI Insight*. 2016 Dec:1(20):e88242. (PMID: 27942583; 44 citations)

2. Efforts to translate bench research into clinical therapies for patients with T1D: The publications below and an authored FDA pharmacology and toxicology IND application outlined a novel FACS-based and GMP-compatible method to isolate and grow Tregs from patients with T1D. This work resulted in a phase I safety trial in patients with recent-onset T1D in the laboratory of Dr. Jeffrey Bluestone at UCSF (NCT01210664). This work is now the basis for a planned follow-up phase IIb trial conducted with Caladrius Biosciences, Inc. We are also planning an additional phase I trial using autologous umbilical cord blood-derived Tregs as a cellular therapeutic in pediatric patients with recent-onset T1D (Drs. Brusko and Haller as Co-PIs).

   a. Putnam A.L., *Brusko T.M., Lee M.R., Liu W., Szot G.L., Ghosh T., Atkinson M.A., and Bluestone J.A.. Expansion of Human Regulatory T Cells from Patients with Type 1 Diabetes. *Diabetes*, 2009 Mar;58(3):652-62. Epub 2008 Dec 15. *Co-first author. (PMCID: PMC2646064; 181 citations)

   b. Seay H.R., Putnam A.L., Cserny J., Posgai A.L., Rosenau E.H., Wingard J.R., Kraus M., Lares A.P., Brown H.L., Brown K.S., Balavage K.T., Peters L., Bushdorf A., Atkinson M.A., Bluestone J.A., Haller M.J., Brusko T.M. Expansion of human Tregs from cryopreserved umbilical cord blood for GMP-compliant autologous adoptive cell transfer therapy. *Cell – Mol Ther Methods Clin Dev.* 2016 Dec 24;4:178-191. (PMID: 28345003; 27 citations)

   We were the first to demonstrate that TCR gene transfer could redirect the specificity of human Tregs. We showed that high-affinity TCR could elicit Treg activation in the context of HLA-A*02-01. We also visualized Treg activity following adoptive transfer by live animal *in vivo* imaging. The technologies developed through this project now enable the overexpression or knockdown of candidate susceptibility genes facilitating functional studies in autoantigen-specific human T cells. Moreover, these studies support future TCR and chimeric antigen receptor (CAR)-directed Treg therapies as a potential treatment modality for T1D.

   c. Brusko, T.M., Koya, R.C., Zhu, S, Lee, M.R., Putnam, A.L., McClymont, S.A., Nishimura, M.I., Han, S., Chang, L., Atkinson, M.A., Ribas, A., and Bluestone, J.A. Human antigen-specific regulatory T cells generated by T cell receptor gene transfer. PLoS ONE. 5(7): e11726. doi:10.1371/journal.pone.0011726. (PMCID: PMC2908680; 105 citations)

   I have actively participated in five clinical intervention trials. These multi-year trials require the integrated efforts of physicians, basic scientists, and clinical trial staff within the UFDI and larger TrialNet clinical networks. The study noted below support the notion of a long-term commitment to identify pathway targets for therapy as well as providing an increased understanding of therapeutic mechanism of action(s).

   d. Haller M.J., Gitelman S.E., Gottlieb P.A., Michels A.W., Rosenthal S.M., Shuster J.J., Zou B., Brusko T.M., Hulme M.A., Wasserfall C.H., Mathews C.E., Atkinson M.A., and Schatz D.A.. ATG and G-CSF Preserves Beta Cell Function in Established Type 1 Diabetes. *J. Clin. Invest.* Jan. 2, 2015;125(1):448–455. (PMID: 25500887; 39 citations)

3. Efforts to characterize costimulation and IL-2 receptor biology: We identified a key role for the soluble form of the IL-2RA (sCD25) in Treg and conventional T cell activity. Moreover, these studies led to key genotype:phenotype associations highlighting the critical role the IL-2 axis plays in maintaining the activity of Tregs. This work also led to a seminal study published by Lowe et al. Nat. Genetics, 2007 (Brusko second author) conducted in collaboration with Drs. John Todd and Linda Wicker. This path of investigation has resulted in a long-term interest within my laboratory investigating how genetic susceptibility variants impact both innate and adaptive immune activity. Current investigations include immune studies of genetic susceptibility at PTPN22 and the costimulatory molecule CD226.

   a. Lowe C.E., Cooper J.D., Brusko T.M., Walker N.M., Smyth D.J., Bailey R., Bourget K., Plagnol V., Field S., Atkinson M., Clayton D.G., Wicker L.S., Todd J.A. Large-scale genetic fine mapping and genotype-phenotype associations implicate polymorphism in the IL2RA region in type 1 diabetes. *Nat Genet*. 2007 Sep; 39(9):1074-1082. (PMID: 17676041; 441 citations)

   b. Brusko, T.M., C. Wasserfall, C.H., Hulme M., Cabrera R., Schatz D., and M.A. Atkinson. Influence of Membrane CD25 Stability on T Lymphocyte Activity: Implications for Immunoregulation. *PLoS ONE*. 2009 Nov 24;4(11):e7980. (PMCID: PMD2775921; 56 citations)

   c. Fuhrman C.A., Yeh W., Seay H.R., Saikumar Lakshmi P., Chopra G., Zhang L., Perry D.J., McClymont S.A., Yadav M., Lopez M-C., Baker H.V., Zhang Y., Li Y., Whitley M., Schack D., Atkinson M.A., Bluestone J.A., and Brusko T.M. Divergent phenotypes of human regulatory T cells expressing the receptors TIGIT and CD226. *Journal of Immunology*. 2015 May 20. (PMID: 25994968; 92 citations)

4. Participation in team science efforts and consortiums (e.g., Human Islet Research Network) focused on advancing

the understanding and treatment of T1D: I actively participate in a number of "team science" efforts. Most notably, my laboratory serves as a core lymphocyte-processing site for the JDRF-sponsored nPOD program. Our laboratory provides advanced cellular phenotyping and FACS-based cell sorting support on fresh donor tissue in a program funded by the Helmsley Charitable Trust and the George Eisenbarth Award for Team Science. In this role, we helped to create the Autoimmunity Working Group to coordinate sample collection and distribution to nPOD approved investigators interested in understanding antigen-specific T cell responses in T1D. I have also been a member of two additional JDRF autoimmunity consortium center grants (umbilical cord blood (UF) and Collaborative Center for Cell Therapy (CCCT-UCSF). Finally, our lab participates in NIH sponsored TrialNet biomarker ancillary studies, as well as two P01 (Atkinson, PD and Anderson, PD); all with the goal of driving discovery and translation in T1D.

5. Development of novel assays to assess immune metabolism in T1D and SLE: My laboratory has pioneered assays to monitor innate and adaptive immune metabolism in autoimmune diseases including T1D and SLE. These efforts include participation in the JDRF Biomarkers Working Group and a recently awarded U01 (Pugliese, PD), where my laboratory will monitor the impact of low-dose IL-2 on T cell metabolism.
   a. Y. Yin, SC. Choi, Z. Xu, D.J. Perry, H.R. Seay, B.P. Croker[1], E.S. Sobel, TM Brusko, and L. Morel. Normalization of $CD4^+$ T Cell Metabolism Reverses Lupus. *Sci. Trans Med*. 2015 Feb 11;7(274):274ra18. (PMID: 25673763; 276 citations)
   b. Choi, S.C.; Titov, A.A.; Abboud, G.; Seay, H.R.; Brusko, T.M.; Roopenian, D.C.; Salek-Ardakani, S.; Morel, L. Inhibition of glucose metabolism selectively targets autoreactive follicular helper T cells. *Nature Commun*. 2018 Oct 22;9(1):4369. (PMID: 30348969; 29 citations)

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/47367280/?sort=date&direction=ascending

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

Ongoing Research Support

1UG3DK122638-01 Stabler (PI) 08/01/2019 – 07/31/2024
NIH
Engineering a Human Microphysiological System for the Characterization of Islet-Immune Interactions
We will develop an islet-immune chip for functional studies and accelerated testing of therapeutics for T1D.
Role: mPI

2019PG-T1D011 Brusko (PI) 10/01/2018 – 09/30/2021
Helmsley Charitable Trust
T cell receptor sequencing in type 1 diabetes - biomarker discovery and technology development
We will use cutting-edge sequencing technologies and computer algorithms to generate an in-depth molecular profile of immune cell subsets, from blood and organ donor tissues, involved in the development of T1D in order to design novel approaches to disease prediction, prevention and therapeutic intervention.
Role: PI

3-SRA-2019-793-S-B Brusko (PI) 06/01/2019 – 05/31/2022
JDRF
Single cell sequencing for islet-reactive T cell clonotype and transcript signatures
This grant seeks to establish robust assays to detect and characterize autoreactive T cells from peripheral blood as potential biomarkers of T1D for future testing in autoantibody positive subjects with pre-T1D.
Role: PI

U54 HL142766 Atkinson (PI) 09/14/18 – 06/30/22
NIH
A 3D Tissue Map of the Human Lymphatic System
The goal of this proposal is to develop 3D tissue maps of normal organs, across the human life span, to provide insights and improve our understanding of the immune system structure and function, including the trafficking of white blood cells and the immune surveillance mechanisms toward combating infectious insults.
Role: mPI, Project 2

2018PG-T1D071 Brusko (PI) 04/01/18 – 03/31/21
Helmsley Charitable Trust
Human Atlas of Neonatal Development and Early-Life Immunity
The goal is to characterize immune system development, ultimately leading to novel interventional strategies.

Role: PI

R01 GM126089 Zhou (PI) 01/01/2018 – 12/31/2021
NIH
An Imputation-Consistency Algorithm for Biomedical Complex Data Analysis
This project aims to develop effective, and highly efficient algorithms for complex data analysis to improve accuracy of biomarker identification from ‘omics data and the development of precision medicine.
Role: Co-Investigator

2018PG-T1D053 Atkinson (PI) 01/01/18-12/31/20
Helmsley Charitable Trust
Collaborative Type 1 Diabetes Research Project: The Network for Pancreatic Organ donors with Diabetes (nPOD)
Pancreas collected from organ donors are assessed for metabolic activity, immune function, clinical history, β-cell biology, developmental biology, and new areas of research (e.g., single cell technologies, “omics”) allowing for major improvements in our understanding of the pathogenesis of T1D.
Role: Co-Investigator

T32 DK108736 Atkinson (PI) 09/01/17-08/31/22
NIH
Interdisciplinary Graduate Program in Type 1 Diabetes and Biomedical Engineering
Supports interdisciplinary co-mentoring of pre-doctoral students in bioengineering and T1D research.
Role: Co-Investigator

R01 DK106191 Brusko (PI) 04/01/16-02/28/21
NIH/NIDDK
The CD226 and TIGIT costimulatory axis in type 1 diabetes
The major goal of this project is to understand how these genes control immune checkpoints and result in a loss of tolerance to pancreatic β-cells in individuals who develop T1D.
Role: PI

P01 AI42288 Atkinson (PI) 06/30/18-5/31/23
NIH/NIAID
Immune function and the progression to type 1 diabetes
This program project investigates the relationship between genetic susceptibility for T1D and immune function.
Role: mPI, Project 2

P01 AI118688-01 Anderson (PI) 07/01/16-06/30/21
UCSF/NIH/NIDDK
Disruption of T cell tolerance in type 1 Diabetes
This grant seeks to understand the specificity and repertoire of autoreactive Tregs during the pathogenesis of T1D. The Brusko laboratory will supply Tregs from the nPOD program for this project.
Role: Co-Investigator

DP3DK111914 Marson (PI) 09/30/16-06/30/21
UCSF/NIH/NIDDK
Functional Interrogation of Non-Coding Type 1 Diabetes Risk Variants in Human Immune Cells and Beta Cells
Characterization of the cell types, epigenetic mechanisms and pathways disrupted by T1D risk variants
Role: Co-Investigator