BIOGRAPHICAL SKETCH

NAME: Brusko, Todd M.

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

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Florida, Gainesville, FL	B.S	08/2001	Microbiology and Cell Science
University of Florida, Gainesville, FL	Ph.D.	08/2006	Immunology
University of Florida, Gainesville, FL	Postdoc	11/2007	Immunology and Molecular Genetics
University of San Francisco, Diabetes Center, San Francisco, CA	Postdoc	08/2010	Molecular Immunology and Cell Therapy

A. Personal Statement

I am currently appointed as an Associate Professor within the Diabetes Institute at the University of Florida (UFDI), College of Medicine. I am also a founding member and COO for a biomaterials-based vaccine development company, OneVax, LLC. The research interests of my academic 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 impact of genetic risk variants on the function of immune subsets in autoimmune diseases. As evidence of this, I have published over 60 studies reporting on both innate and adaptive immune defects in patients with type 1 diabetes (T1D) and systemic lupus erythematosus (SLE), and have investigated the molecular basis of such defects.

My laboratory has been actively involved in a number of studies investigating how regulatory T cells (Tregs) become phenotypically unstable and lose suppressive activity in T1D. We have extended this work to develop methods to expand Tregs for adoptive cell therapies currently in clinical trials. Our laboratory is currently exploring detailed pathways of T cell co-stimulation, specificity, and nanoparticle conjugation to augment Treg action. In addition to our own research projects, my lab oversees the advanced cytometry and cell-sorting facility within the Center for Immunology and Transplantation (CIT). Access to human samples from the UFDI clinical network and the JDRF Network for Pancreatic Organ donors with Diabetes (nPOD) program provides a unique opportunity to address the pathogenesis of T1D. These clinical samples are being leveraged for biomarker development work to understand the repertoire driving T1D pathogenesis.

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. Served to review the Autoimmunity Center Consortiums, strategic grant review committees, and training award applications, which include Advanced Postdoctoral Fellowships (APFs), Postdoctoral Fellowships (PFs), Career Development Awards (CDAs) and Early Career Patient Oriented Diabetes Research Award (ECPDRs).
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; American Diabetes Association 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. Reviewer for the 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 of the 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
2017-2020 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 serve as an effective 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; 201 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; 124 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; 170 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)

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).

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; 46 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; 219 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; 19 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; 17 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; 32 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

Ongoing Research Support

R01 DK106191 Brusko (PI) 04/01/16-03/31/20
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 disease.
Role: PI

P01 AI42288 Atkinson (PI) 07/01/13-06/30/18
NIH/NIAID
Immune function and the progression to type 1 diabetes
This is a program project investigating the relationship between genetic susceptibility for IDD and various immune functions.
Role: Co-Investigator, 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 type 1 diabetes. The Brusko laboratory will supply Tregs from the nPOD program for this project.
Role: Co-Investigator

AGR DTD 05/01/2017/R43AI131850 Marshall (PI) 03/17/17-03/16/18

OneVax/NIH
Biomaterial-based delivery of Interleukin-2 to Regulatory T Cells for the amelioration of Type 1 Diabetes
The objective of this phase I proposal is to conduct pre-clinical physiochemical and biological *in vitro* characterization of the nanoparticle-Treg conjugate therapy, and to determine its capacity to prevent diabetic onset in the therapeutically relevant non-obese diabetic mouse model.
Role: PI-Subcontract

AGR00004849 Haller (PI) 06/01/16-11/30/17
Cord Blood Registry
Clinical Trial Planning Grant for Treg Therapy in Type I Diabetes
This is a research agreement to complete the planning activities associated with the development of clinical trial for Treg Therapy in Type 1 Diabetes
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
The central goal of this proposal is functional characterization of the cell types, epigenetic mechanisms and biological pathways disrupted by non-coding T1D risk variants
Role: Co-Investigator

DP3 DK110845 Michels (PI) 08/02/16-07/31/19
UC Denver/NIH
Insulin Specific T and B cells in Type 1 Diabetes
The goals are to propose to identify biomarkers of disease progression and ultimately aid in T1D prevention with enhanced understanding of disease pathogenesis.
Role: Co-Investigator

R01 AI045050 Morel (PI) 05/01/13-04/30/18
Characterization of SLE-susceptibility loci on mouse chromosome 1
The project proposes to functionally characterize the Sle1 cluster of SLE-susceptibility genes, including Sle1a1 and Sle1c2 in T cells.
Role: Co-Investigator

UC4 DK104194 Mathews (PI) 12/01/14-11/30/19
NIH
Genetic regulation of human beta cell destruction
Our goal is to create an innovative platform to study how Type 1 Diabetes genetic risk factors precipitate autoimmunity leading to the loss of insulin producing cells.
Role: Co-Investigator

664215/2015PG-T1D052 Pugliese (PI) 01/01/15-12/31/17
Univ. of Miami/Helmsley Trust/JDRF
The George S. Eisenbarth nPOD Award for Team Science
The goal of the project is to conduct coordinated studies to optimize knowledge gained from donor tissues collected through the Network for Pancreatic Organ donors with Diabetes Program. The Brusko portion of the grant supports efforts within the flow cytometry and cell isolation core laboratories.
Role: Co-Investigator; PI, UF Sub-contract

Completed Research Support

2-2012-280 Brusko (PI) 05/01/12-04/30/17
JDRF Career Development Award
Investigating human autoreative T cells in humanized mice
The major goals of this project are is to stop and/or reverse the immune system attack that is responsible for pancreatic beta cell destruction in type 1 diabetes.
Role: PI