BIOGRAPHICAL SKETCH

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NAME: Brusko, Todd M.

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

POSITION TITLE: 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)*	Start Date MM/YYYY	Completion Date MM/YYYY	FIELD OF STUDY
University of Florida, Gainesville, FL	BS	08/1997	08/2001	Microbiology & Cell Science
University of Florida, Gainesville, FL	PhD	08/2002	08/2006	Immunology
University of Florida, Gainesville, FL	Postdoc	08/2006	11/2007	Immunology & Molecular Genetics
University of San Francisco, Diabetes Center, San Francisco, CA	Postdoc	09/2007	08/2010	Molecular Immunology & Cell Therapy

A. Personal Statement

As both the Scientific Director and a 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 published over 115 studies after 11 years as an investigator (current h-index of 43 and 8189 citations; Google Scholar) reporting on cellular immune defects in type 1 diabetes (T1D) and systemic lupus erythematosus (SLE), along with reports on the genetic and epigenetic basis of such defects. Our lab is currently investigating mechanisms of immune regulation related to regulatory T cell (Treg) biology, genotype:immunophenotype associations, the adaptive immune receptor repertoire, and peripheral immune system development spanning the first decade of life. Equally important to my research productivity has been my involvement as a research mentor. I have continually hosted 3-5 undergraduate students per year, including prestigious University Scholars and a Goldwater Scholarship recipients. I have also had the opportunity to directly mentor seven PhD and MD/PhD students, including two T32 supported pre-doctoral candidates, three F-awardees, a Peds Endo fellow (now Assist Prof.), as well as five postdoctoral fellows supported by the JDRF, ADA, and HIRN. As a PI and MPI of multiple federal and foundation grants, I have senior leadership experience to manage **Project 3** and **Core A**. As evidence, I current chair the ADA Immunolology, Immunogenetics and Transplantation working group, co-direct the NIH TrialNet collaborative mechanistic studies panel (CMSP), and have held positions in the JDRF Biomarker Working Group, TEDDY Immune Markers Committee, and HIRN Trans-Network Committee. I direct the UF Human Immunophenotyping and single cell analysis core within the UF Department of Pathology and oversee immune studies in nPOD. Collectively, my integration in numerous national and international organizations involed in T1D research positions me to oversee Project 3 and Core A of this **P01**.

Ongoing and recently completed projects that I would like to highlight include:
UG3DK122638/in UH3 Phase
Stabler (PI), Role: MPI
08/01/19-07/31/24
Engineering a Human Microphysiological System for the Characterization of Islet-Immune Interactions

U54AI142766
Atkinson (PI), Role: Co-Investigator Project-001; Project Lead Project-002; Co-Investigator Project-003

09/14/18-06/30/22
A 3D Tissue Map of the Human Lymphatic System

P01 AI42288
Atkinson (PI), Role: mPI Project 2
06/30/18-05/31/23
Immune function and the progression to type 1 diabetes

2019PG-T1D011
Brusko (PI)
10/01/18–09/30/21
T cell receptor sequencing in type 1 diabetes - biomarker discovery and technology development

2018PG-T1D071
Brusko (PI)
04/01/18-03/31/21
Human Atlas of Neonatal Development and Early-Life Immunity

R01 DK106191
Brusko (PI)
04/01/16-02/28/21
The CD226 and TIGIT costimulatory axis in type 1 diabetes

Citations:

1. Shapiro MR, Yeh WI, Longfield JR, Gallagher J, Infante CM, Wellford S, Posgai AL, Atkinson MA, Campbell-Thompson M, Lieberman SM, Serreze DV, Geurts AM, Chen YG, **Brusko TM**. CD226 Deletion Reduces Type 1 Diabetes in the NOD Mouse by Impairing Thymocyte Development and Peripheral T Cell Activation. Front Immunol. 2020 Sep 4;11:2180. PMCID: PMC7500101.
2. Perry DJ, Wasserfall CH, Oram RA, Williams MD, Posgai A, Muir AB, Haller MJ, Schatz DA, Wallet MA, Mathews CE, Atkinson MA, **Brusko TM**. Application of a Genetic Risk Score to Racially Diverse Type 1 Diabetes Populations Demonstrates the Need for Diversity in Risk-Modeling. Sci Rep. 2018 Mar 14;8(1):4529. PMCID: PMC5852207.
3. Yeh WI, Seay HR, Newby B, Posgai AL, Moniz FB, Michels A, Mathews CE, Bluestone JA, **Brusko TM**. Avidity and Bystander Suppressive Capacity of Human Regulatory T Cells Expressing *De Novo* Autoreactive T-Cell Receptors in Type 1 Diabetes. Front Immunol. 2017 Oct 26;8:1313.PMCID: PMC5662552.
4. Seay HR, Yusko E, Rothweiler SJ, Zhang L, Posgai AL, Campbell-Thompson M, Vignali M, Emerson RO, Kaddis JS, Ko D, Nakayama M, Smith MJ, Cambier JC, Pugliese A, Atkinson MA, Robins HS, **Brusko TM**. Tissue distribution and clonal diversity of the T and B cell repertoire in type 1 diabetes. JCI Insight. 2016 Dec 8;1(20):e88242. PMCID: PMC5135280.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2020 – 2021	NIH The Environmental Determinants of Diabetes in the Young (TEDDY). Immune Mechanisms Cmt.
2017 – 2020	University of Florida Term Professorship
2016 – Present	Associate Professor, Department of Pathology, Immunology and Laboratory Medicine, College of Medicine, University of Florida, Gainesville, FL
2014 – 2021	Member, NIH TrialNet. Collaborative Mechanistic Studies Panel (Scientific Co-chair); Ancillary studies presentations and publications (PPS) subcommittee review 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	Elected UF faculty senate counsel
2013 – 2021	JDRF Biomarker Working Group, Committee member; ADA Research Grant Review

	Committee (RGCR) Member
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).
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
2010 – 2016	Assistant Professor, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, College of Medicine, Gainesville, FL
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.
2008 – Present	Journal reviewer selected: *Science Translational Medicine*, *PNAS, 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, Molecular Therapy, Cytotherapy, New England Journal of Medicine.* F1000 associate faculty member. *Frontiers in Immunology* - Assoc. Editor.
2007 – Present	Member, American Association for the Advancement of Sciences
2007 – Present	Federation of Clinical Immunology Societies (Immunology of Diabetes Society)
2007 – 2010	Post-Doctoral Fellow, University of California, San Francisco (UCSF), San Francisco, CA
2002 – Present	Member, American Diabetes Association
2002 – 2006	Graduate Student, Department of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, FL
2000 – 2002	Laboratory Technician and Undergraduate Research, Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL
1998 – 2000	Laboratory Technician and Teaching Assistant, Department of Natural Sciences, St. Petersburg College, St. Petersburg, FL

Honors

2021	University of Florida, College of Medicine Teaching Award
2017	University of Florida, College of Medicine Teaching Award
2015	Science Foundation Ireland. SFI/EI Technology Innovation Development Award (TIDA)
2013	Pfizer Aspire Young Investigator Award Recipient
2011	JDRF Career Development Award Recipient
2010	JDRF Early Career Investigator Travel Award
2010	JDRF Transition Award Recipient
2009	FOCIS Meeting -- National Institutes of Health and JDRF travel awards
2008	Midwinter Conference of Immunologists – JDRF Travel Award Recipient
2007	FOCIS Meeting--National Institutes of Health Travel Award Recipient
2005	Graduate Fellowship for Outstanding Research Award
2001	Elected to the Golden Key Honor Society

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 TM,** Wasserfall CH, Clare-Salzler MJ, Schatz DA, Atkinson MA. Functional defects and the influence of age on the frequency of CD4+ CD25+ T-cells in type 1 diabetes. Diabetes. 2005 May;54(5):1407-14**.** (431 citations)
b. **Brusko T.M,** Wasserfall C, McGrail K, Schatz R, Viener HL, Schatz D, Haller M, Rockell J, Gottlieb P, Clare-Salzler M, Atkinson M. No alterations in the frequency of FOXP3+ regulatory T-cells in type 1 diabetes. Diabetes. 2007 Mar;56(3):604-12. (271 citations)
c. McClymont SA, Putnam AL, Lee MR, Esensten JH, Liu W, Hulme MA, Hoffmüller U, Baron U, Olek S, Bluestone JA, **Brusko TM**. Plasticity of human regulatory T cells in healthy subjects and patients with type 1 diabetes. J Immunol. 2011 Apr 1;186(7):3918-26. PMCID: PMC3091943 (410 citations)
d. Seay HR, Yusko E, Rothweiler SJ, Zhang L, Posgai AL, Campbell-Thompson M, Vignali M, Emerson RO, Kaddis JS, Ko D, Nakayama M, Smith MJ, Cambier JC, Pugliese A, Atkinson MA, Robins HS, **Brusko TM**. Tissue distribution and clonal diversity of the T and B cell repertoire in type 1 diabetes. JCI Insight. 2016 Dec 8;1(20):e88242. PMCID: PMC5135280; (72 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 AL, ***Brusko TM**, Lee MR, Liu W, Szot GL, Ghosh T, Atkinson MA, Bluestone JA. Expansion of human regulatory T-cells from patients with type 1 diabetes. Diabetes. 2009 Mar;58(3):652-62.. *Co-first author. PMCID: PMC2646064 (370 citations)
b. Seay HR, Putnam AL, Cserny J, Posgai AL, Rosenau EH, Wingard JR, Girard KF, Kraus M, Lares AP, Brown HL, Brown KS, Balavage KT, Peters LD, Bushdorf AN, Atkinson MA, Bluestone JA, Haller MJ, Brusko TM. Expansion of Human Tregs from Cryopreserved Umbilical Cord Blood for GMP-Compliant Autologous Adoptive Cell Transfer Therapy. Mol Ther Methods Clin Dev. 2016 Dec 24;4:178-191. PMCID: PMC5363324 (45 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 RC, Zhu S, Lee MR, Putnam AL, McClymont SA, Nishimura MI, Han S, Chang LJ, Atkinson MA, Ribas A, Bluestone JA. Human antigen-specific regulatory T cells generated by T cell receptor gene transfer. PLoS One. 2010 Jul 22;5(7):e11726. PMCID: PMC2908680 (140 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 MJ, Gitelman SE, Gottlieb PA, Michels AW, Rosenthal SM, Shuster JJ, Zou B, **Brusko TM**, Hulme MA, Wasserfall CH, Mathews CE, Atkinson MA, Schatz DA. Anti-thymocyte globulin/G-CSF treatment preserves β cell function in patients with established type 1 diabetes. J Clin Invest. 2015 Jan;125(1):448-55. PMCID: PMC4382237 (127 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 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 CE, Cooper JD, **Brusko T**, Walker NM, Smyth DJ, Bailey R, Bourget K, Plagnol V, Field S, Atkinson

M, Clayton DG, Wicker LS, Todd JA. 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):1074-82. (491 citations)

b. **Brusko TM,** Wasserfall CH, Hulme MA, Cabrera R, Schatz D, Atkinson MA. Influence of membrane CD25 stability on T lymphocyte activity: implications for immunoregulation. PLoS One. 2009 Nov 24;4(11):e7980. PMCID: PMD2775921 (66 citations)

c. Fuhrman CA, Yeh WI, Seay HR, Saikumar Lakshmi P, Chopra G, Zhang L, Perry DJ, McClymont SA, Yadav M, Lopez MC, Baker HV, Zhang Y, Li Y, Whitley M, von Schack D, Atkinson MA, Bluestone JA, **Brusko TM**. Divergent Phenotypes of Human Regulatory T Cells Expressing the Receptors TIGIT and CD226. J Immunol. 2015 Jul 1;195(1):145-55. PMCID: PMC4475416 (148 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 Team Science Award. 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 Co-PI a collaborative program for immune system development with Dr. Donna Farber (Columbia University) entitled Human Atlas for Neonatal and Developmental Early Life – Immunity (HANDEL-I). Finally, our lab participates in NIH sponsored TrialNet studies, as well as two P01 (Atkinson, PD and Anderson, PD); and I am a Co-PI within the Human BioMolecular Atlas program (HuBMAP) under the NIH Director.

   a. HuBMAP Consortium. The human body at cellular resolution: the NIH Human Biomolecular Atlas Program. Nature. 2019 Oct;574(7777):187-192. PMCID: PMC6800388.

   b. Japp AS, Meng W, Rosenfeld AM, Perry DJ, Thirawatananond P, Bacher RL, Liu C, Gardner JS; HPAP Consortium, Atkinson MA, Kaestner KH, Brusko TM, Naji A, Luning Prak ET, Betts MR. TCR+ /BCR+ dual-expressing cells and their associated public BCR clonotype are not enriched in type 1 diabetes. Cell. 2021 Feb 4;184(3):827-839.e14. PMCID: PMC8016147.

   c. Poon MML, Rybkina K, Kato Y, Kubota M, Matsumoto R, Bloom NI, Zhang Z, Hastie KM, Grifoni A, Weiskopf D, Wells SB, Ural BB, Lam N, Szabo PA, Dogra P, Lee YS, Gray JI, Bradley MC, Brusko MA, Brusko TM, Saphire EO, Connors TJ, Sette A, Crotty S, Farber DL. SARS-CoV-2 infection generates tissue-localized immunological memory in humans. Sci Immunol. 2021 Nov 19;6(65):eabl9105. PMCID: PMC8626868.

   d. Poon MML, Byington E, Meng W, Kubota M, Matsumoto R, Grifoni A, Weiskopf D, Dogra P, Lam N, Szabo PA, Ural BB, Wells SB, Rosenfeld AM, Brusko MA, Brusko TM, Connors TJ, Sette A, Sims PA, Luning Prak ET, Shen Y, Farber DL. Heterogeneity of human anti-viral immunity shaped by virus, tissue, age, and sex. Cell Rep. 2021 Nov 30;37(9):110071.

5. Development of novel assays to assess immune metabolism in T1D and SLE: My laboratory helped 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 focused on T cell metabolism.

   a. Yin Y, Choi SC, Xu Z, Perry DJ, Seay H, Croker BP, Sobel ES, **Brusko TM**, MorelL. Normalization of CD4+ T cell metabolism reverses lupus. Sci Transl Med. 2015 Feb 11;7(274):274ra18. PMCID: PMC5292723 (391 citations)

   b. Choi SC, Titov AA, Abboud G, Seay HR, Brusko TM, Roopenian DC, Salek-Ardakani S, Morel L. Inhibition of glucose metabolism selectively targets autoreactive follicular helper T cells. Nat Commun. 2018 Oct 22;9(1):4369. PMCID: PMC6197193 (54 citations)

   c. Ahmed S, Cerosaletti K, James E, Long SA, Mannering S, Speake C, Nakayama M, Tree T, Roep BO, Herold KC, Brusko TM. Standardizing T-Cell Biomarkers in Type 1 Diabetes: Challenges and Recent Advances. Diabetes. 2019 Jul;68(7):1366-1379. PMCID: PMC6609980. (24 citations)

   d. 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. PMCID: PMC7034187. (13 Citations)

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