# BIOGRAPHICAL SKETCH

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NAME: Sant'Angelo, Derek

eRA COMMONS USERNAME (credential, e.g., agency login): santangd

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) | END DATE MM/YYYY | FIELD OF STUDY |
|---|---|---|---|
| University of Michigan, Ann Arbor, MI | BS | 05/1986 | Cellular and Molecular Biology |
| Rutgers, The State University of NJ, New Brunswick, NJ | MS | 05/1989 | MICROBIOLOGY |
| Rutgers, The State University of NJ, New Brunswick, NJ | PHD | 01/1993 | MOLECULAR GENETICS |

## A. Personal Statement

I have been studying the development and function of T cells for more than twenty years. During this time, I have consistently published high impact papers in the field. Our current work primarily focuses on the transcriptional control of T cell effector functions. In particular, my lab made the breakthrough discovery that PLZF controls the development of the effector function of innate T cells, such as iNKT cells. My lab has continued to study the impact of PLZF on immune system function and the molecular mechanisms that control PLZF expression. We showed that TCR signaling during development directs PLZF low NKT cells in the adipose resident lineage. These cells help maintain the non-inflammatory environment in the adipose, protecting against obesity. Furthermore, we have identified a protein partner of PLZF that regulates its function and we have shown that PLZF controls basophil function. Based on discrete expression of PLZF-like BTB-ZF transcription factors, we have identified a new type of regulatory T cell that is required for maintaining the integrity of the intestine. The full impact of these cells has for controlling disease is a new focus for the lab. Throughout my career I have successfully trained and mentored undergraduates, graduate students, postdoctoral and MD fellows. I have organized trainee research in progress meetings, journal clubs and have served on dozens of qualifying exam and theses committees. Additionally, I serve as Associate Director of the Rutgers Child Health Institute, the Head of the Division of Immunobiology, the Director of the Rutgers Cancer Institute Genome Editing Shared Resource, Chair of the Rutgers Biomedical Advisory Committee, and Chair of the Rutgers Research Advisory Committee and an active contributor to developing programs that address health disparities. My career so far, includes impactful scientific discoveries and meaningful contributions for the future of biomedical research and training.

Citations:


1. Krzyzanowska AK, Haynes Ii RAH, Kovalovsky D, Lin HC, Osorio L, Edelblum KL, Corcoran LM, Rabson AB, Denzin LK, **Sant'Angelo DB.** Zbtb20 identifies and controls a thymus-derived population of regulatory T cells that play a role in intestinal homeostasis. Sci Immunol. 2022 May 6;7(71):eabf3717. PubMed PMID: 35522722.
2. Darcy PW, Denzin LK, **Sant'Angelo DB.** YY1$^{lo}$ NKT cells are dedicated IL-10 producers. Sci Rep. 2020 Mar 3;10(1):3897. PubMed Central PMCID: PMC7054430.
3. Vieth JA, Das J, Ranaivoson FM, Comoletti D, Denzin LK, **Sant'Angelo DB**. TCRα-TCRβ pairing controls recognition of CD1d and directs the development of adipose NKT cells. Nat Immunol. 2017 Jan;18(1):36-44. PubMed PMID: 27869818.
4. Kovalovsky D, Uche OU, Eladad S, Hobbs RM, Yi W, Alonzo E, Chua K, Eidson M, Kim HJ, Im JS, Pandolfi PP, **Sant'Angelo DB**. The BTB-zinc finger transcriptional regulator PLZF controls the development of invariant natural killer T cell effector functions. Nat Immunol. 2008 Sep;9(9):1055-64. PubMed Central PMCID: PMC2662733.

## B. Positions, Scientific Appointments and Honors

### Positions and Scientific Appointments

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|---|---|
| 2021 - | Editorial Board Member, Critical Reviews in Immunology |
| 2020 - | Chair, Program Steering Committee, Memorial Sloan-Kettering Cancer Center/City College of New York Partnership for Cancer Research, Training and Community Outreach U54, New York, NY |
| 2016 - 2020 | Member Program Steering Committee, Memorial Sloan-Kettering Cancer Center/City College of New York Partnership for Cancer Research, Training and Community Outreach U54, New York, NY |
| 2015 - | Associate Director for Basic Science, Rutgers Child Health Institute of NJ, New Brunswick, NJ |
| 2014 - | Professor, Rutgers Robert Wood Johnson Medical School, Department of Pediatrics, Pharmacology and Biomedical Engineering, New Brunswick, NJ |
| 2013 - 2017 | Member, Cellular and Molecular Immunology Study Section (CMIb), NIH NIAID |
| 2011 - | Head, Division of Immunobiology, Dept. of Pediatrics, Rutgers, RWJ Medical School, New Brunswick, NJ |
| 2011 - 2014 | Associate Professor, Rutgers, Robert Wood Johnson Medical School, New Brunswick, NJ |
| 2011 - 2014 | Associate Editor, The Journal of Immunology |
| 2009 - 2019 | External Advisory Committee Member Research Centers in Minority Institutions (RCMI) for the Study of the Cellular and Molecular Basis of Development, The City College of New York, Harlem, New York, NY |
| 2009 - 2013 | Scientific Reviewer (ad hoc) Cellular and Molecular Immunology Study Section (CMIb), NIH NIAID |
| 2008 - | Associate Editor, Immunology Section, BioMed Central |
| 2005 - 2011 | Associate Member, Memorial Sloan-Kettering Cancer Center, New York, NY |
| 2005 - 2011 | Associate Professor, Weill Cornell Graduate School of Medical Sciences, New York, NY |
| 2004 - 2007 | Scientific Reviewer (ad hoc), Innate Immunity and Inflammation Study Section, NIH NAIAD |
| 2004 - 2005 | Scientific Reviewer, National Science Foundation |
| 2003 - 2006 | Scientific Reviewer, NIDDKD Program Project Grants, NIH |
| 2003 - 2005 | Scientific Reviewer Section of Immunobiology (IMB) (ad hoc), NIH NIAID |
| 2001 - 2008 | Editorial Board, BioMed Central: Immunology |
| 2001 - 2004 | Member MSKCC IACUC, Memorial Sloan-Kettering, New York, NY |
| 2001 - 2003 | Scientific Reviewer, Prostate Cancer Research Program U.S. Army Medical Research |
| 1999 - | Scientific Reviewer, Immunity, The Journal of Experimental Medicine, The Journal of Immunology, Current Biology, The Scandinavian Journal of Immunology, Nature Reviews - Immunology, Tissue Antigens, European Journal of Immunology, PNAS, Nature Immunology, Scientific Reports, Nature Communications, Gene Therapy, eLIFE, Plos ONE, Science |
| 1998 - 2005 | Assistant Member, Memorial Sloan-Kettering Cancer Center, New York, NY |
| 1998 - 2005 | Assistant Professor, Weill Cornell Graduate School of Medical Sciences, New York, NY |
| 1996 - 1998 | Associate Research Scientist, Yale School of Medicine, New Haven, CT |
| 1993 - 1996 | Research Associate, HHMI at Yale Medical School, New Haven, CT |

### Honors

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|---|---|
| 2016 | New Jersey Health Foundation's Excellence in Research Award, New Jersey Health Foundation |
| 2012 | Harold L. Paz, M.D. Endowed Professor of Developmental Biology, Rutgers RWJ Medical School |
| 1999 | Tow Foundation Awardee, Tow Foundation 1999-2003 |
| 1999 | Rudin Family Foundation Awardee, May and Samuel Rudin Family Foundation 1999-2011 |
| 1993 | Howard Hughes Medical Institute, Howard Hughes Medical Institute Fellowship 1993-1998 |
| 1991 | Summer Fellowship Award, Department of Microbiology, Rutgers University 1991-1992 |

## C. Contribution to Science

1. As a postdoctoral fellow with Charlie Janeway in the Immunobiology section at the Yale University School of Medicine, I initiated studies on T cell development that serve as the foundation for my current efforts. My first studies uncovered the basic rules for the interaction of the TCR with its MHCII ligands. We predicted that a pocket formed by CDR3a/b would define specificity by interacting with a key amino acid residue of the antigenic peptide. We went on to show how positive selection on self-peptides defines the mature TCR repertoire. These studies were the first to directly measure how the pre-selection repertoire is molded into the mature TCR repertoire. These efforts, which directly quantify TCR usage by single thymocytes, were key for showing how positive selection can enrich for particular TCR specificities. This approach was then used to "map" the phenotypic pathway travelled by developing thymocytes. These influential studies are still used as the basis for analysis of T cell development.

    a. **Sant'Angelo DB,** Waterbury G, Preston-Hurlburt P, Yoon ST, Medzhitov R, Hong SC, Janeway CA Jr. The specificity and orientation of a TCR to its peptide-MHC class II ligands. Immunity. 1996 Apr;4(4):367-76. PubMed PMID: 8612131.
    b. **Sant'Angelo DB**, Waterbury PG, Cohen BE, Martin WD, Van Kaer L, Hayday AC, Janeway CA Jr. The imprint of intrathymic self-peptides on the mature T cell receptor repertoire. Immunity. 1997 Oct;7(4):517-24. PubMed PMID: 9354472.
    c. **Sant'Angelo DB**, Lucas B, Waterbury PG, Cohen B, Brabb T, Goverman J, Germain RN, Janeway CA Jr. A molecular map of T cell development. Immunity. 1998 Aug;9(2):179-86. PubMed PMID: 9729038.
    d. **Sant'Angelo DB,** Janeway CA Jr. Negative selection of thymocytes expressing the D10 TCR. Proc Natl Acad Sci U S A. 2002 May 14;99(10):6931-6. PubMed Central PMCID: PMC124506.

2. As an early-stage independent investigator, we continued studies of the specificity of TCR-ligand interactions during T cell development. Of particular interest were studies showing that the conserved MHC tertiary structure was not sufficient for productive interactions with TCRs. We also published one of the first papers to show that TCRs could be retrovirally introduced into HSC such that positive selection was supported and fully functional T cells would develop. These studies, with our collaborator Michel Sadelain, led to taking advantage of miR-181a to suppress transgenic TCR expression to enable production of self-reactive T cells for potentiation immunotherapy. Collaborative work also led to the finding that altered T cell development led to altered functions of naïve T cells, work that indicated that the naïve T cell pool was heterogenous and needed to be studied at the level of single cells.

    a. Blander JM, **Sant'Angelo DB**, Metz D, Kim SW, Flavell RA, Bottomly K, Janeway CA Jr. A pool of central memory-like CD4 T cells contains effector memory precursors. J Immunol. 2003 Mar 15;170(6):2940-8. PubMed PMID: 12626545.
    b. Kim HJ, Guo D, **Sant'Angelo DB**. Coevolution of TCR-MHC interactions: conserved MHC tertiary structure is not sufficient for interactions with the TCR. Proc Natl Acad Sci U S A. 2005 May 17;102(20):7263-7. PubMed Central PMCID: PMC1091755.
    c. Stolzer AL, Sadelain M, **Sant'Angelo DB**. Fulminant experimental autoimmune encephalo-myelitis induced by retrovirally mediated TCR gene transfer. Eur J Immunol. 2005 Jun;35(6):1822-30. PubMed PMID: 15909313.
    d. Papapetrou EP, Kovalovsky D, Beloeil L, **Sant'angelo D**, Sadelain M. Harnessing endogenous miR-181a to segregate transgenic antigen receptor expression in developing versus post-thymic T cells in murine hematopoietic chimeras. J Clin Invest. 2009 Jan;119(1):157-68. PubMed Central PMCID: PMC2613472.

3. Throughout my career, I have been associated with work related to MHCII antigen presentation. Typically, as a collaborator, I assisted with studies that have helped define a fundamental role for the MHCII-like protein, HLA-DO in modulating the self-peptide and antigenic peptide repertoire in subtle but highly biologically relevant ways.

a. Denzin LK, **Sant'Angelo DB**, Hammond C, Surman MJ, Cresswell P. Negative regulation by HLA-DO of MHC class II-restricted antigen processing. Science. 1997 Oct 3;278(5335):106-9. PubMed PMID: 9311912.

b. Fallas JL, Tobin HM, Lou O, Guo D, **Sant'Angelo DB**, Denzin LK. Ectopic expression of HLA-DO in mouse dendritic cells diminishes MHC class II antigen presentation. J Immunol. 2004 Aug 1;173(3):1549-60. PubMed PMID: 15265882.

c. Denzin LK, **Sant'angelo DB**. Dipping into the cytosol to broaden the MHC class II peptide repertoire. Immunity. 2005 May;22(5):536-7. PubMed PMID: 15894271.

d. Yi W, Seth NP, Martillotti T, Wucherpfennig KW, **Sant'Angelo DB**, Denzin LK. Targeted regulation of self-peptide presentation prevents type I diabetes in mice without disrupting general immunocompetence. J Clin Invest. 2010 Apr;120(4):1324-36. PubMed Central PMCID: PMC2846047.

4. As an independent investigator I initiated studies of NKT cell development. Initial studies defined key developmental checkpoints and, most significantly, later studies discovered that PLZF (Zbtb16) is the lineage defining master regulator transcription factor that controls nearly all the innate-like functions of αβ NKT cells. These studies led to the discovery of a second innate like T cell lineage, the γδ NKT cell. Studies have also defined PLZF as a key factor for the regulation of regulatory NKT cells in the fat. PLZF, we reported, is also expressed in some myeloid lineage cells and that it controls basophil effector functions. We have published the only loss of function data concerning PLZF in humans, showing that multiple lineages of cells were directly dependent on PLZF for development. Most recently, we have shown that transcription factor YY1 is an essential co-factor for the function of PLZF.

   a. Darcy PW, Denzin LK, **Sant'Angelo DB**. $YY1^{lo}$ NKT cells are dedicated IL-10 producers. Sci Rep. 2020 Mar 3;10(1):3897. PubMed Central PMCID: PMC7054430.

   b. Zhang S, Vieth JA, Krzyzanowska A, Henry EK, Denzin LK, Siracusa MC, **Sant'Angelo DB**. The Transcription Factor PLZF Is Necessary for the Development and Function of Mouse Basophils. J Immunol. 2019 Sep 1;203(5):1230-1241. PubMed PMID: 31366712.

   c. Vieth JA, Das J, Ranaivoson FM, Comoletti D, Denzin LK, **Sant'Angelo DB**. TCRα-TCRβ pairing controls recognition of CD1d and directs the development of adipose NKT cells. Nat Immunol. 2017 Jan;18(1):36-44. PubMed PMID: 27869818.

   d. Kovalovsky D, Uche OU, Eladad S, Hobbs RM, Yi W, Alonzo E, Chua K, Eidson M, Kim HJ, Im JS, Pandolfi PP, **Sant'Angelo DB**. The BTB-zinc finger transcriptional regulator PLZF controls the development of invariant natural killer T cell effector functions. Nat Immunol. 2008 Sep;9(9):1055-64. PubMed Central PMCID: PMC2662733.

5. BTB-ZF transcription factors such as PLZF, ThPOK, Bcl6 and Zbtb32 serve as “master regulators” since for the function different types of T cells. In total, there are 49 BTB-ZF transcription factors, nearly all of which are expressed in the immune system. The function of just a handful have been studied. We have hypothesized that expression of a BTB-ZF gene in a discrete subpopulation of T cells is a means to identify new types of effector T cells. This approach led to the identification of Zbtb20 expressing T cells, which, we have shown are essential for the maintenance of intestinal integrity. The lab, therefore, is now working to understand the function of Zbtb20 T cells in the context of inflammatory bowel disease and other inflammatory diseases.

   a. Beaulieu AM, **Sant'Angelo DB**. The BTB-ZF family of transcription factors: key regulators of lineage commitment and effector function development in the immune system. J Immunol. 2011 Sep 15;187(6):2841-7. PubMed Central PMCID: PMC3170133.

   b. Krzyzanowska AK, Haynes Ii RAH, Kovalovsky D, Lin HC, Osorio L, Edelblum KL, Corcoran LM, Rabson AB, Denzin LK, **Sant'Angelo DB**. Zbtb20 identifies and controls a thymus-derived population of regulatory T cells that play a role in intestinal homeostasis. Sci Immunol. 2022 May 6;7(71):eabf3717. PubMed PMID: 35522722.