BIOGRAPHICAL SKETCH

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NAME: Miller, Brian C

eRA COMMONS USER NAME (credential, e.g., agency login): bcmiller16

POSITION TITLE: Assistant Professor, Department of Medicine, Division of Oncology

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
Princeton University, Princeton, NJ	BA	06/2003	Molecular Biology
Washington University in St. Louis, St. Louis, MO	PhD	05/2011	Immunology
Washington University in St. Louis, St. Louis, MO	MD	05/2011	Medicine
Duke University Hospital, Durham, NC	Internship	06/2012	Medical Intern
Duke University Hospital, Durham, NC	Residency	06/2014	Medical Resident
Dana-Farber Cancer Institute, Boston, MA	Fellowship	06/2018	Medical Oncology

A. Personal Statement

My long-term research goal is to understand the complex interaction of the immune system with cancer cells, with the aim of identifying novel targets for cancer immunotherapy. In preparation for this path, I obtained my PhD in immunology in the laboratory of Dr. Herbert “Skip” W. Virgin, studying the functions of autophagy genes in lymphocyte survival and osteoclast function. I pursued my interest in oncology through my residency and fellowship at the Dana-Farber Cancer Institute. In my post-doctoral work, I studied the mechanisms by which anti-PD-1 therapy augments the anti-tumor immune response. Working with Drs. Arlene H. Sharpe, an expert in T cell immunology and PD-1 biology, and W. Nicholas Haining, an expert in T cell exhaustion and systems immunology, my work from these labs identified the subset of exhausted $CD8^+$ T cells that responds to anti-PD-1 therapy and controls tumor growth long-term.

My translational research lab at the University of North Carolina at Chapel Hill is now studying how different tumor resistance mutations subvert the immune response against the tumor. We hypothesize that a deep understanding of the immune microenvironment of resistant tumors will be required to identify rational immunotherapy combinations that will overcome resistance, targeting specific treatments to unique patients based on their tumor mutations. Our data suggest that unique populations of immunosuppressive myeloid cells contribute to resistance mediated by specific tumor mutations.

I have received excellent mentoring throughout my training and have been fortunate to coach trainees under my supervision in the lab and the clinic. I have worked with young graduate students and post-docs, providing career advice and teaching about experimental design and the scientific method. I mentored two technicians in my post-doctoral years who have gone on to matriculate in medical school and graduate school. I am honored to have earned multiple teaching awards at Duke and Harvard for my mentorship of medical residents and students.

Ongoing and recently completed projects that I would like to highlight include:
Burroughs Wellcome Career Award for Medical Scientists
Miller (PI)
2022-2027
Targeting Myeloid Cells as a Personalized Immunotherapy Approach to Cancer

1K08CA248960 (National Cancer Institute)
Miller (PI)
2020-2025
Targeting Unique Myeloid Populations to Overcome Anti-PD-1 Resistance Conferred by Specific Cancer Mutations

KL2/CMeRIT Award
Bedella, MA and Rutkove, S (PI)
2018-2020
Dissecting Mechanisms of Action and Acquired Resistance to Anti-PD-1 Therapy

B. Positions and Honors

Positions and Employment

2021-	Assistant Professor, University of North Carolina at Chapel Hill
2018-2021	Physician, Dana-Farber Cancer Institute
2018-2021	Instructor in Medicine, Harvard Medical School
2014-2018	Hematology/Oncology Fellow, Dana-Farber Cancer Institute/MGH Cancer Center
2012-2014	Resident in Internal Medicine, Duke University Hospital
2011-2012	Intern in Internal Medicine, Duke University Hospital

Professional Memberships

2016-	Member, Society for Immunotherapy of Cancer
2015-	Member, American Association for Cancer Research
2015-2018	Member in Training, American Society of Clinical Oncology
2010-	Member, Alpha Omega Alpha Honor Medical Society
2002-	Member, Phi Beta Kappa Society

Other Experience

2018-2021	Lecturer, Oncology Fellowship Lecture Series, Dana-Farber Cancer Institute
2018-2021	Resident Tutor, Leverett Undergraduate House, Harvard University
2018-2019	Leader, Broad Immuno-oncology Initiative, Broad Institute
2016-2021	Leader, Single-Cell Working Group, Broad Institute
2014	Assistant Chief Resident, Duke University Hospital
2005-2006	Teaching Assistant, medical student physiology course, Washington University in St. Louis School of Medicine

Honors

2019	AACR Scholar-in-Training Award, travel award to attend AACR Conference on Tumor Immunology and Immunotherapy 2019
2019	AACR Scholar-in-Training Award, travel award to attend AACR Annual Meeting 2019
2018	Keystone Symposia Scholarship, travel award to Keystone conference
2017	Medical Oncology Board Certification, American Board of Internal Medicine
2017	AACR Scholar-in-Training Award, travel award to attend AACR Annual Meeting 2017
2017	Keystone Symposia Future of Science Fund Scholarship, travel award to Keystone conference
2015	Resident Teaching Award, awarded by the Harvard Medical School Class of 2015
2014	Internal Medicine Board Certification, American Board of Internal Medicine
2014	Duke Appleseed Teaching Award, awarded by the Duke Medical School Class of 2014
2012	Duke Appleseed Teaching Award, awarded by the Duke Medical School Class of 2012
2012	National American College of Physicians Associates Clinical Vignette Poster Winner
2012	North Carolina American College of Physicians Best Poster Award
2009	Stanley J Korsmeyer Young Investigator Award, Best Poster Award, Association of American Physicians
2005	The McGraw-Hill/Appleton & Lange Medical Student Book Award for academic achievement, Washington University in St. Louis School of Medicine
2003	Summa Cum Laude, Princeton University
2003	Phi Beta Kappa Society Prize for Academic Excellence, Princeton University

2003 Senior Thesis Prize in Molecular Biology, Princeton University
2003 Highest Graduating Honors, Department of Molecular Biology, Princeton University

C. Contributions to Science

1. **Defining the immunologic mechanisms by which tumors respond to anti-PD-1 therapy.** Using massively-parallel single-cell RNA-sequencing and multiparametric flow cytometry, I characterized the immune microenvironments of immunotherapy-sensitive tumors. Tumors with sensitizing mutations had increased infiltration by effector $CD8^+$ T cells and pro-inflammatory monocytes, suggesting that the mutations created an inflamed tumor microenvironment. Using these approaches, I defined a novel subpopulation of exhausted $CD8^+$ T cells in tumors, "progenitor exhausted" cells, that responds to anti-PD-1 treatment and is important for the long-term control of tumor growth. We used multiplex immunofluorescence to find this same population in human melanoma biopsy specimens and demonstrated that the presence of this population predicts duration of response to checkpoint blockade therapy. This work suggests that expanding the progenitor exhausted population may improve responses to checkpoint blockade.

a) **Miller BC[1]**, Sen DR[1], Al Abosy R, Bi K, Virkud YV, LaFleur MW, Yates KB, Lako A, Felt K, Naik GS, Manos M, Gjini E, Kuchroo JR, Ishizuka JJ, Collier JL, Griffin GK, Maleri S, Comstock DE, Weiss SA, Brown FD, Panda A, Zimmer MD, Manguso RT, Hodi FS, Rodig SJ, Sharpe AH, Haining WN. Functionally specialized subsets of exhausted $CD8^+$ T cells mediate tumor control and differentially respond to checkpoint blockade. *Nature Immunol*. 2019 Mar; 20(3):326-336.
    i. **[1]These two authors contributed equally to this manuscript.**
b) Ishizuka JJ, Manguso RT, Cheruiyot CK, Bi K, Panda A, Iracheta-Vellve A, **Miller BC**, Du PP, Yates KB, Dubrot J, Buchumenski I, Comstock DE, Brown FD, Ayer A, Kohnle IC, Pope HW, Zimmer MD, Sen DR, Lane-Reticker SK, Robitschek EJ, Griffin GK, Collins NB, Long AH, Doench JG, Kozono D, Levanon EY, Haining WN. Loss of ADAR1 in tumors overcomes resistance to immune checkpoint blockade. *Nature.* 2019 Jan; 565(7737):43-48.
c) Manguso RT, Pope HW, Zimmer MD, Brown FD, Yates KB, **Miller BC**, Collins NB, Bi K, LaFleur MW, Juneja VR, Weiss SA, Lo J, Fisher DE, Miao D, Van Allen E, Root DE, Sharpe AH, Doench JG, Haining WN. In vivo CRISPR screening identifies Ptpn2 as a cancer immunotherapy target. *Nature*. 2017 Jul 27; 547(7664):413-418.
d) LaFleur MW, Nguyen TH, Coxe MA, **Miller BC**, Yates KB, Gillis JE, Sen DR, Gaudiano EF, Al Abosy R, Freeman GJ, Haining WN, Sharpe AH. PTPN2 regulates the generation of exhausted $CD8^+$ T cell subpopulations and restrains tumor immunity. *Nature Immunol*. 2019 Oct; 20(10):1335-1347.

2. **Osteoclast cell secretion is regulated by autophagy proteins.** Proteins required for the formation of the autophagosome were initially identified in yeast, but in mammals these pathways have been co-opted for other purposes. I recognized a potential connection between autophagy and inherited Paget's disease of bone, in which 40-50% of patients have mutations in an important autophagy chaperone protein, p62. To this end, I formed a collaboration with Dr. Steven Teitelbaum's lab to study the functions of autophagy genes in osteoclasts. We discovered that the autophagic machinery is required for efficient bone degradation by osteoclasts. Importantly, we demonstrated that this machinery can be used for cell secretion in addition to degradation and identified a potential pathway to target in the prevention or treatment of osteoporosis and other bone diseases.

a) DeSelm CJ[1], **Miller BC**[1], Zou W, Beatty WL, van Meel H, Takahata Y, Klumperman J, Tooze SA, Teitelbaum SL, Virgin HW. Autophagy proteins regulate the secretory component of osteoclastic bone resorption. *Dev Cell.* 2011 Nov 15;21(5):966-74.
    i. **[1]These two authors contributed equally to this manuscript.**

3. **Autophagy genes are required for the survival and functions of B and T lymphocytes.** The majority of my graduate work focused on understanding the role of autophagy genes in lymphocytes. I used cre/flox technology and bone marrow chimeric mice to define the functions of essential autophagy genes in T and B lymphocytes. I identified a novel and essential function for the autophagy gene *Atg5* in B lymphocyte development. I also showed that these genes are required for the survival of peripheral T cells and used microarray analysis to identify a signature of mitochondrial regulation in these cells, which was confirmed by flow cytometry. This work suggests that dysregulation of mitochondria due to lack of autophagic degradation may contribute to the decreased survival of autophagy-deficient T cells. My research also contributed to

understanding the function of autophagy in invariant NKT cells in collaboration with Dr. Mitchell Kronenberg's lab.

a) **Miller BC**, Zhao Z, Stephenson LM, Cadwell K, Pua HH, Lee HK, Mizushima NN, Iwasaki A, He YW, Swat W, Virgin HW 4th. The autophagy gene ATG5 plays an essential role in B lymphocyte development. *Autophagy*. 2008 Apr 1;4(3):309-14.
b) Stephenson LM[1]**, Miller BC[1]**, Ng A, Eisenberg J, Zhao Z, Cadwell K, Graham DB, Mizushima NN, Xavier R, Virgin HW, Swat W. Identification of Atg5-dependent transcriptional changes and increases in mitochondrial mass in Atg5-deficient T lymphocytes. *Autophagy.* 2009 Jul;5(5):625-35.
    i. **[1]These two authors contributed equally to this manuscript.**
c) Pei B, Zhao M, **Miller BC**, Vela JL, Bruinsma MW, Virgin HW, Kronenberg M. Invariant NKT cells require autophagy to coordinate proliferation and survival signals during differentiation. *J Immunol.* 2015 Jun 15;194(12):5872-84.

4. **Macrophages use autophagy proteins for intracellular pathogen clearance.** By characterizing the role of the autophagy gene *Atg5* in macrophages, I contributed to research identifying a role for autophagy proteins in resistance to *Listeria monocytogenes* and *Toxoplasma gondii*. I also helped identify that *Atg5* is not required for coronavirus replication.

a) Zhao Z, Fux B, Goodwin M, Dunay IR, Strong D, **Miller BC**, Cadwell K, Delgado MA, Ponpuak M, Green KG, Schmidt RE, Mizushima N, Deretic V, Sibley LD, Virgin HW. Autophagosome-independent essential function for the autophagy protein Atg5 in cellular immunity to intracellular pathogens*. Cell Host Microbe.* 2008 Nov 13;4(5):458-69.
b) Zhao Z, Thackray LB, **Miller BC**, Lynn TM, Becker MM, Ward E, Mizushima NN, Denison MR, Virgin HW 4th. Coronavirus replication does not require the autophagy gene ATG5. *Autophagy*. 2007 Nov-Dec;3(6):581-5.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/brian.miller.4/bibliography/50445901/public/?sort=date&direction=ascending