BIOGRAPHICAL SKETCH

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NAME: Steven J. Bensinger

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

POSITION TITLE: Associate Professor; Microbiology, Immunology and Molecular Genetics

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
Rice University. Houston, TX	BA	05/1990	Political Science
University of Pennsylvania School of Veterinary Medicine. Philadelphia, PA	VMD	05/1998	Veterinary Medicine
University of Pennsylvania School of Medicine. Philadelphia, PA	PhD	10/2003	Immunology
La Jolla Institute of Allergy and Immunology. San Diego, CA	Postdoctoral fellow	8/2005	Immunology/Apoptosis
University of California, Los Angeles	Postdoctoral fellow	6/2008	Lipid metabolism

A. Personal Statement

I have a long-standing interest in investigating the influence of lipid metabolism on cell growth, survival and function. My thesis work in the laboratories of Drs. Laurence A. Turka and Terri Laufer (University of Pennsylvania School of Medicine, Philadelphia, PA) examined the influence of PI3-kinase signaling in regulatory T cell development and function (Bensinger et al., JEM, 2001 PMCID: PMC2193499, Wu and Bensinger et al., Nat Med. 2003 PMCID: PMC2839903, Bensinger et al., JI 2004. PMCID: PMC2842445, Walsh et al., JCI 2006. PMCID: PMC1550279). My studies as a postdoctoral fellow in the laboratory of Dr. Peter Tontonoz (HHMI, University of California, Los Angeles) helped to define a previously unappreciated lipid metabolic checkpoint that directly implicated cellular sterol metabolism in controlling cell cycle progression and survival of lymphocytes during the generation of adaptive immunity (Bensinger et al., Cell 2008. PMCID: PMC2626438). In my current position as an associate professor in the Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine, University of California Los Angeles, I have built a team of scientist focused on interrogating the importance of metabolism on normal cells growth and function (York et al., Cell 2015**.** PMC4783382, Kidani et al., Nature Immunology 2013. PMCID: PMC3652626, Hong et al., JCI 2012. PMCID: PMC3248291, Wilson et al., Cell Host Microbe 2012. PMCID: PMC3359873.). In this application, we continue to elucidate that mechanisms by which fatty acid metabolism influences inflammation, and sepsis.

B. Positions and Honors

Positions and Employment

2008- Assistant Professor, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA.

2014- Co-director Metabolomics Core, University of California, Los Angeles, Los Angeles, CA.

2015- Associate Professor, Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA.

2015- Director Shared Resources, Jonsson Comprehensive Cancer Center, University of California, Los Angeles, Los Angeles, CA

Professional Memberships

2006- Member American Association of Immunologist
2015- Member American Association of Cancer Research
2016- Member American Society of Biochemistry and Molecular Biology

Honors

1996-1998 Dean's Scholarship (U. of Pennsylvania)- awarded for academic achievement.
1998 Leonard Pearson Award (U. of Pennsylvania)- awarded for outstanding research potential.
1998 J.P. Lippincott Award (U. of Pennsylvania)- awarded to valedictorian.
2011 Sontag Foundation Distinguished Scientist

C. Contributions to Science

1. Defining the influence of lipid metabolism in immune cell fate and function.
The adaptive immune system is endowed with the capacity to undergo rapid cell division in response to antigenic activation. During the height of the immune response, responding lymphocytes divide every 6-8 hours and a single clone might ultimately undergo 20 rounds of division. As such, the immune system provides a powerful model system for understanding the metabolic requirements of rapidly dividing and differentiating normal eukaryotic cells. Over the course of 10 years I have been actively engaged in determining the influence of central carbon and lipid metabolism in controlling components of immune cell function, including cellular energetics, cell cycle progression, survival and effector differentiation. In combination, our studies were the first to mechanistically describe the signal transduction and transcriptional pathways linking TCR to lipid anabolic metabolism. Our studies were also among the first to establish that perturbations in the ability of a leukocyte to undergo metabolic reprogramming during activation interferes with fate and function and CTL function. Finally, we have begun to mechanistically delineated how perturbations in metabolism influence tolerogenic programs, inflammation and innate immune cell function *in vitro* and *in vivo*.

a. York AG, Argus JP, Williams KJ, Brar G, Vergnes L, Gray EE, Zhen A, Wu NC, Yamada DH, Cunningham CR, Wilks MQ, Casero D, Gray D, Yu A, Brooks DG, Sun R, Kitchen SG, Wu T[1], Reue K, Stetson DB and **Bensinger SJ***.* Limiting cholesterol biosynthetic flux engages type I IFN signaling in a STING-dependent manner**.** *Cell*. 2015 Dec 17;163(7):1716-29 – PMC4783382
b. Kidani Y, Elsaesser H, Hock MB, Vergnes L, Williams KJ, Argus JP, Marbois BN, Komisopoulou E, Wilson EB, Osborne TF, Graeber TG, Reue K, Brooks DG, **Bensinger SJ**. The sterol regulatory element binding proteins are essential for the metabolic programming of effector T cells and adaptive immunity. *Nat Immunol*. 2013 May;14(5):489-99. PMCID: PMC3652626.
c. Hong C, Kidani Y, A-Gonzalez N, Phung T, Ito A, Rong X, Ericson K, Mikkola H, Beaven SW, Miller LS, Shao WH, Cohen PL, Castrillo A, Tontonoz P, **Bensinger SJ**. Coordinate regulation of neutrophil homeostasis by liver X receptors in mice. *J Clin Invest*. 2012 Jan 3;122(1):337-47. PMCID: PMC3248291
d. **Bensinger SJ**, Bradley MN, Joseph SB, Hausner MA, Shih R, Edwards PA, Jamieson BD and Tontonoz P. An LXR-dependent sterol-signaling pathway couples lymphocyte proliferation to metabolism in the acquired immune response. *Cell*. 2008 Jul 11;134(1):97-111. PMCID: PMC2626438

2. Lipid metabolism as a regulator of cancer growth and the cancer metabolic phenotype. It has long been appreciated that cellular metabolism is a physiologic regulator of neoplastic cell proliferation, viability, growth and behavior. Not surprisingly, understanding the molecular events underlying the metabolic programs of cancer cells is an area of significant interest in cancer research. We have been examining how transcriptional and biochemical regulation of cholesterol and fatty acid biosynthetic pathways influence cancer cell biology and tumor pathogenesis. Several years ago we helped to establish the SREBP–driven metabolic program is downstream of oncogenic signaling and is an important modulator of brain cancer cell survival and tumor growth.

a. Williams KJ, Argus JP, Zhu Y, Wilks MQ, Marbois BN, York AG, Kidani Y, Pourzia AL, Akhavan D, Lisiero DN, Komisopoulou E, Henkin AH, Soto H, Chamberlain BT, Vergnes L, Jung ME, Torres JZ, Liau LM, Christofk HR, Prins RM, Mischel PS, Reue K, Graeber TG, **Bensinger SJ**. An essential

requirement for the SCAP/SREBP signaling axis to protect cancer cells from lipotoxicity. *Cancer Res*. 2013 May 1;73(9):2850-2862. PMCID: PMC3919498

b. Akhavan D, Pourzia AL, Nourian AA, Williams KJ, Nathanson D, Babic I, Villa GR, Tanaka K, Nael A, Yang H, Dang J, Vinters HV, Yong WH, Flagg M, Tamanoi F, Sasayama T, James CD, Kornblum HI, Cloughesy TF, Cavenee WK, **Bensinger SJ*,** Mischel PS*.* De-repression of PDGFRβ transcription promotes acquired resistance to EGFR tyrosine kinase inhibitors in glioblastoma patients. *Cancer Discov.* 2013 Apr 23. PMCID: PMC3651754 * Co-corresponding authors

c. Guo D, Prins RM, Dang J, Kuga D, Iwanami A, Soto H, Lin KY, Huang TT, Akhavan D, Hock MB, Zhu S, Kofman AA, **Bensinger SJ**, Yong WH, Vinters HV, Horvath S, Watson AD, Kuhn JG, Robins HI, Mehta MP, Wen PY, DeAngelis LM, Prados MD, Mellinghoff IK, Cloughesy TF, Mischel PS. EGFR signaling through an AKT- SREBP1-dependent, rapamycin-resistant pathway sensitizes glioblastoma to antilipogenic therapy. *Sci Signal***.** ;2(101):ra82. PMCID: PMC2978002

d. Ahler E, Sullivan WJ, Cass A, Braas D, York AG, **Bensinger SJ**, Graeber TG, Christofk HR. Doxycycline alters metabolism and proliferation of human cell lines. *PLoS One*. 2013 May 31;8(5):e64561. doi: 10.1371/journal.pone.0064561. PMCID: PMC3669316

3. Examining the fate and function of CD4 regulatory T cells. Thymically derived CD4 regulatory T cells are important cellular players in enforcing self-tolerance and controlling autoimmune disease pathogenesis. Thus, understanding the molecular events underlying how these cells develop and persist in the periphery of immune system is an important objective for the immunology and rheumatologic communities. Early studies in my career were focused on defining key interactions in the thymus that led to the differentiation of Tregs and how these cells were maintained in the periphery.

a. **Bensinger SJ,** Bandeira A, Jordan MS, Caton AJ, Laufer TM. Major histocompatibility complex class II-positive cortical epithelium mediates the selection of CD4(+)25(+) immunoregulatory T cells. *J Exp Med.* 2001 Aug 20;194(4):427-38. PMCID: PMC2193499

b. Wu Z*, **Bensinger SJ*,** Zhang J, Chen C, Yuan X, Huang X, Markmann JF, Kassaee A, Rosengard BR, Hancock WW, Sayegh MH, Turka LA. Homeostatic proliferation is a barrier to transplantation tolerance. *Nat Med***.** 2004 Jan; 10(1): 87-92. * equal contribution PMCID: PMC2839903

c. **Bensinger SJ*,** Walsh PT*, Zhang J, Carroll M, Parsons R, Rathmell JC, Thompson CB, Burchill MA, Farrar MA, Turka LA. Distinct IL-2 receptor signaling pattern in CD4+CD25+ regulatory T cells**.** *J Immunol.* 2004 May 1;172 (9):5287-96. * equal contribution PMCID: PMC2842445

d. Walsh PT, Buckler JL, Zhang J, Gelman AE, Dalton NM, Taylor DK, **Bensinger SJ,** Hancock WW, Turka LA. PTEN inhibits IL-2 receptor-mediated expansion of CD4+ CD25+ Tregs. *J Clin Invest*. 2006 Sep;116(9):2521-31. PMCID: PMC1550279

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/steven.bensinger.1/bibliography/43443088/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01 AI122282 (Bensinger) 11/10/2015 – 10/31/2020
National Institute of Health
"Understanding the influence of SREBP signaling on CD4 T helper cell biology"
In this proposal, we test the hypothesis that the transcriptional regulation of cholesterol homeostasis plays a critical role in controlling Treg and Th17 subset differentiation and self-tolerance in MS-like disease.
Role: PI

R01 AI093768 (Bensinger) 4/1/2012 – 3/31/2017
National Institute of Health
"Determining the Impact of SREBP on Adaptive Immunity"

In this proposal, we test the hypothesis that the Sterol Response Element Binding Proteins (SREBP1 and 2), key transcriptional regulators of lipid biosynthesis and homeostasis, play a critical role in linking antigen receptor signaling with lipid metabolism, cell cycle progression and CD8 T cell fate/function.
Role: PI

R21 HL126556 (Bensinger) 09/17/2014-8/15/2016
National Institutes of Health
"Investigating the crosstalk between lipid metabolism and HIV"
In this grant, we test the hypothesis that sterol metabolism, controlled by the Sterol Response Element Binding Protein (SREBP2), regulates antiviral (HIV) responses in macrophage through the type I IFN responses.
Role: PI

Relevant Completed Research Support (past 3 years)
N/A