BIOGRAPHICAL SKETCH

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NAME: Shirley Zhang

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

POSITION TITLE: Research Associate

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
New York University New York, NY	B.A.	05/2009	Biochemistry
University of Pennsylvania Philadelphia, PA	Ph.D.	08/2014	Immunology
University of Pennsylvania Philadelphia, PA	Postdoctoral Training	Present	Neurobiology Chronobiology

A. Personal Statement

My long-term interest is to understand how molecular and cellular processes result in higher-level biological phenomena such as behavior. My research experience and academic training have provided me with an excellent background in multiple biological disciplines including molecular biology, developmental biology, and immunology. As an undergraduate, I had the opportunity of working in the laboratory of Dr. Nicholas Geacintov at New York University where I examined the efficiency of nucleotide excision repair in the removal of polycyclic aromatic hydrocarbons intercalated in double stranded DNA. Under the mentoring of Drs. Georg Wondrak and Donna Zhang at the University of Arizona, I examined how cells respond to oxidative stress. I learned many molecular techniques, including tissue culture, quantitative PCR, and immunoblotting, all of which I was able to perform independently by time I finished my undergraduate degree. These early experiences resulted in co-authorship on three publications and my exposure to the “high” of being the first person in the world to know something.

Although tissue culture work was interesting and informative about the ability of the cells, I wanted to work with an organism model to understand how cells interact with other cell types within the body. I did my graduate work in the field of developmental immunology under the guidance of Dr. Avinash Bhandoola at the University of Pennsylvania. My doctoral research focused on understanding progenitor cell trafficking into the thymus under physiologic conditions as well as after irradiation in a mouse model. During this time, I developed an assay to measure in vivo progenitor cell trafficking and I published two first author papers, coauthored two other papers, and wrote a review. I also presented my work at the international ThymUS conference (2012) as a plenary talk. During these experiences, I learned many different techniques that I have applied to my postdoctoral work ranging from working with an animal model to molecular biology to flow cytometry and cell sorting.

For my postdoctoral training, I joined the laboratory of Dr. Amita Sehgal, an internationally recognized leader in the field of circadian rhythms and behavior. I built on my previous training in cell to tissue interactions by moving into a *Drosophila* system, which allows more genetic manipulation, to address questions of how circadian rhythms can effect cellular and molecular processes. Conceptually, I have built up my knowledge of chronobiology and have written a book chapter review of the literature entitled “Circadian rhythms and disease.” Technically, I have learned how to genetically manipulate *Drosophila* and adapt various molecular and cellular

assays such as flow cytometry to *Drosophila* tissues. I have presented an early version of my work at the Cold Spring Harbor Drosophila Neurobiology meeting (2015). I have published three first author papers during this period: a descriptive paper showing that the fecal microbiome is unperturbed by sleep deprivation and two mechanistic paper demonstrating that a circadian rhythm in blood-brain barrier regulates xenobiotic efflux from the brain. I have also co-authored several papers and a review on peripheral rhythms.

I am currently expanding my training in the Sehgal lab to examine the relationship between blood-brain barrier and behavior and also developing collaborations with Dr. Sigrid Veasey to study sleep in a mouse model. My goal as an independent investigator is to study the temporal gating of the blood-brain in health and disease.

In the third year of my postdoctoral fellowship, I took 6 weeks of maternity leave followed by a few months of 4-day weeks due to childcare scheduling restraints. In total, I lost approximately 8 weeks of time in the lab. During this period, I had significantly reduced productivity despite coordinating with technicians and collaborators to continue various aspects of my projects. This disruption temporarily delayed my postdoctoral development and publications.

a. **Zhang SL,** Wang X, Manna S, Zlotoff DA, Bryson JL, Blazar BR, and Bhandoola A. “Chemokine treatment rescues profound T-lineage progenitor homing defect after bone marrow transplant conditioning in mice.” ***Blood****.* 2014. Jul 10;124(2):296-304.
b. **Zhang SL**, Bai L, Goel N, Bailey A, Jang CJ, Bushman FD, Meerlo P, Dinges DF, Sehgal A. “Human and rat gut microbiome composition is maintained following sleep restriction.” ***Proc Natl Acad Sci USA****.* 2017. Feb 21;114(8): E1564-E1571.
c. **Zhang SL**, Yue Z, Arnold DM, Artiushin G, Sehgal A. “A circadian clock in the blood-brain barrier regulates xenobiotic efflux.” ***Cell***. 2018 Mar 22;173(1):130-139.
d. **Zhang SL**, Lahens NF, Yue Z, Arnold DM, Pakstis PP, Fellheimer HS, Schwarz JE, and Sehgal A. “A circadian clock regulates efflux by the BBB in mammals.” ***Nature Communications.*** 2021 Jan 27;12(1):617.

B. Positions and Honors

Positions and Employment:

2020-present	Research Associate, Amita Sehgal Lab, HHMI/University of Pennsylvania
2014-2020	Postdoctoral fellow, Amita Sehgal Lab, HHMI/University of Pennsylvania
2009-2013	Graduate Student, Avinash Bhandoola Lab, University of Pennsylvania
2008	Summer Research Fellow, Max Costa Lab, New York University
2007	Integrated Micro/Nano Summer Undergraduate Research Experience (IM-SURE) Fellow, Abraham Lee Lab, University of California Irvine
2006-2009	Undergraduate Research Assistant, Nicholas Geacintov Lab, New York University

Other experiences:

2019-2020	Chronobiology planning committee, University of Pennsylvania
2016-2017	Lecturer BiBB 240, Biological Basis of Behavior, University of Pennsylvania

Academic and Professional Honors

2019	Featured Speaker, University of Pennsylvania Chronobiology Symposium
2017	Featured Speaker, University of Pennsylvania Chronobiology Symposium
2012	Featured Speaker, ThymUS International Conference
2007	NYU Dean’s Undergraduate Research Fund Award
2006	Integrated Micro/Nano Summer Undergraduate Research Experience Fellowship

C. Contributions to Science

1. My early contributions to science elucidated the molecular mechanisms of the cellular responses to oxidative stress, which is important in the understanding of cancer prevention and treatment. Primarily, I studied the cellular antioxidant and anti-inflammatory responses. The transcription factor nrf2 binds to the antioxidant response element in the promoter region to activate many antioxidant genes. I found that nrf2 localization within the cell is dependent on Keap1, which suppresses nrf2 through sequestration in the cytoplasm. We also showed that while promoting nrf2 activity is beneficial in preventing cancer; eliciting an antioxidant response in transformed cancer cells promotes their resistance to chemotherapy. The results of these studies suggests that compounds that inhibit nrf2 induction (or promote Keap1) should be used concurrently with chemotherapy to achieve more effective cancer treatment outcomes. I also contributed to the identification of a novel protein regulator of oncogenic Ras that functions to decrease the inflammatory response to oxidative stress.

a. Sun Z, Zhang S, Chan, JY, and Zhang DD. “Keap1 controls postinduction repression of the nrf2-mediated antioxidant response by escorting nuclear export of nrf2.” *Molec and Cell Bio*. 2007. Sep 27(18):6334-49. PubMed PMID: 17636022
b. Wang XJ, Sun Z, Villeneuve NF, Zhang S, Zhao F, Li Y, Chen W, Yi X, Zheng W, Wondrak GT, Wong PK, Zhang DD. “Nrf2 enhances resistance of cancer cells to chemotherapeutic drugs, the dark side of Nrf2. *Carcinogenesis*.” 2008 Jun;29(6):1235-43. PubMed PMID: 18413364
c. Wondrak GT, Cabello CM, Villeneuve NF, Zhang S, Ley S, Li Y, Sun Z, Zhang DD. “Cinnamoyl-based Nrf2-activators targeting human skin cell photo-oxidative stress.” *Free Radic Biol Med.* 2008 Aug 15;45(4):385-95. PubMed PMID: 18482591
d. Gus-Brautbar Y, Johnson D, Zhang L, Sun H, Wang P, Zhang S, Zhang L, and Chen YH. “The anti-inflammatory TIPE2 is an inhibitor of the oncogenic Ras.” Mol Cell. 2012. Mar 9;45(5):610-8. PubMed PMID: 22326055

2. T cell development occurs throughout the lifetime of an individual; however, the numbers of naïve T cells emerging from the thymus decreases with age, leaving patients susceptible to diseases if peripheral T cells become depleted. During my PhD, I sought to understand the molecular mechanisms of hematopoietic precursor migration to the thymus under homeostatic conditions and after bone marrow transplant. Thymus-dependent T cell reconstitution depends on hematopoietic progenitors developing in the bone marrow, migration into the thymus via the circulation, and differentiation in the thymus. I developed an assay in a mouse model to quantify the very low numbers of progenitors that home to the thymus under steady state conditions and found that thymic recovery after BMT is limited by the number of rare progenitors entering the thymus, contrary to the previous dogma of the field. After irradiation, chemokine ligands important for homing were absent on the endothelial cells of the thymus. By restoring chemokine signaling in the progenitor cells, I could rescue the homing defect after BMT and improve T cell reconstitution. BMT doctors are now running a clinical trial to determine whether the stimulation of chemokine receptors prior to transplant will improve T cell numbers in patients. My contribution to the field of progenitor trafficking to the thymus also includes a comprehensive review of the literature describing the current state of the field, which was published as a book chapter alongside other chapters written by experts in the field of T cell development.

a. Zhang SL*, Zlotoff DA*, De Obaldia ME, Hess PR, Todd S, Logan TD, and Bhandoola A. “Delivery of progenitors to the thymus limits T-lineage reconstitution after bone marrow transplantation.” *Blood*. 2011. Aug 18;118(7):1962-70. PubMed PMID: 21659540
b. Zhang SL, Wang X, Manna S, Zlotoff DA, Bryson JL, Blazar BR, and Bhandoola A. “Chemokine treatment rescues profound T-lineage progenitor homing defect after bone marrow transplant conditioning in mice.” *Blood.* 2014. Jul 10;124(2):296-304. PubMed PMID: 24876562
c. Zhang SL and Bhandoola A. “Trafficking to the thymus.” *Current Topics in Microbiology and Immunology.* 2014; 373:87-111. PubMed PMID: 23624945
d. Sultana DA, Zhang SL, Todd SP, and Bhandoola A. “Expression of functional P-selectin glycoprotein ligand 1 on hematopoietic progenitors is developmentally regulated.” *J Immunol*. 2012 May 1;188(9):4385-93. PubMed PMID: 22461691

3. During my postdoctoral research, I studied the relationship between sleep and peripheral tissues. Loss of sleep is associated with metabolic diseases such as obesity and diabetes, cardiovascular disorders, and

neurological and cognitive impairments. Shifts in gut microbiome composition have also been associated with the same pathologies; thus, I examined the microbiome following days of several days of sleep restrictions in rats and humans to find that the microbiome is largely resistant to changes during sleep restriction. This work was published in *PNAS*. In addition, I found that loss of sleep increased the level of endocytosis at the *Drosophila* blood-brain barrier, further illuminating sleep as important for movement of molecules between the brain and the periphery. My contribution to the field also includes a *Trends In Neuroscience* review of the current literature.

a. Zhang SL, Bai L, Goel N, Bailey A, Jang CJ, Bushman FD, Meerlo P, Dinges DF, Sehgal A. “Human and rat gut microbiome composition is maintained following sleep restriction.” *Proc Natl Acad Sci USA.* 2017. Feb 21;114(8): E1564-E1571. PubMed PMID: 28179566
b. Artiushin G, Zhang SL, Tricoire H, Sehgal A. Endocytosis at the Drosophila blood-brain barrier as a function for sleep. Elife. 2018 Nov 26;7. PubMed PMID: 30475209
c. Cuddapah VA, Zhang SL, Sehgal A. Regulation of the Blood-Brain Barrier by Circadian Rhythms and Sleep. *Trends Neurosci*. 2019 Jul;42(7):500-510. Review. PubMed PMID: 31253251

4. Biological rhythms regulate nearly every aspect of physiology and disruption of these rhythms results in increased risk of developing metabolic disease, respiratory disease, and cancer. The mechanisms by which molecular clocks contribute to disease are not entirely clear. I have contributed broad review of the literature on circadian rhythms and disease, which was published as a book chapter in *Emery and Rimoin’s Principles and Practice of Medical Genetics and Genomics*. In addition, I have collaborated with others to dissect the influence of the clock on lung rhythms during influenza, and on tumor growth.

a. Zhang SL and Sehgal A. “Circadian Rhythms and Disease.” *Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics* 7th edition. Nov 2018. Chapter 11.
b. Lee Y, Lahens NF, Zhang SL, Bedont J, Field JM, Sehgal A. “G1/S cell cycle regulators mediate effects of circadian dysregulation on tumor growth and provide targets for timed anticancer treatment.” PLoS Biol. 2019 Apr 30;17(4):e3000228. PubMed PMID: 31039152
c. Sengupta S, Tang SY, Devine J, Anderson ST, Nayak S, Zhang SL, Valenzuela A, Fisher DG, Grant GR, Lopez CB, and FitzGerald GA. “Circadian control of lung inflammation in influenza infection.” *Nature Communications*. 2019 Sep 11;10(1):4107. PubMed PMID: 31511530.
d. Lee Y, Fong SY, Shon J, Zhang SL, Brooks R, Lahens NF, Chen D, Dang CV, Field JM, Sehgal A. Time-of-day specificity of anticancer drugs may be mediated by circadian regulation of the cell cycle. Sci Adv. 2021 Feb;7(7). PubMed PMID: 33579708

5. Circadian rhythms are thought to modulate responses to external factors, but mechanisms that confer time-of-day differences in organismal responses to environmental insults/therapeutic treatments are poorly understood. Given the pervasive nature of circadian rhythms, it is generally thought that the response of an organism to drugs and therapies must also vary with time of day. The mechanisms suggested for such responses include rhythmic expression of molecular targets and/or rhythms in the responsiveness of the target tissue. Using *Drosophila* and mice as models, I found that peripheral clocks regulate a key function of the blood-brain barrier. I identified novel mechanism(s) of circadian regulation, which implies broad regulation of blood-brain communication and suggests changes to timing of brain-targeted therapeutics. These findings were published in *Cell* and *Nature Communications*.

a. Rhoades SD, Nayak K, Zhang SL, Sehgal A, and Weljie AM. "Circadian- and light-driven metabolic rhythms in Drosophila melanogaster." *J Biol Rhythms*. 2018 Jan 1:748730417753003. PubMed PMID: 29355066
b. Zhang SL, Yue Z, Arnold DM, Artiushin G, Sehgal A. “A circadian clock in the blood-brain barrier regulates xenobiotic efflux.” *Cell*. 2018 Mar 22;173(1):130-139. PubMed PMID: 29526461
c. Zhang SL, Lahens NF, Yue Z, Arnold DM, Pakstis PP, Fellheimer HS, Schwarz JE, and Sehgal A. “A circadian clock regulates efflux by the BBB in mammals.” *Nature Communications.* 2021 Jan 27;12(1):617. PubMed PMID: 33504784

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1NgT6YE31uhAV/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1K99HL147212-01 Zhang, Shirley (PI) 06/19 – 08/21
Determining the importance of temporal regulation of the blood-brain barrier
Role: PI

Completed Research Support

5T32 HL007713-22 Pack, Allan (PI) 03/15 - 03/17
Sleep and Chronobiology Training Grant
Role: Trainee