PDA report, Andrew C. Liu, August 31, 2017

• Research Summary

I conducted my sabbatical as a visiting scientist with Dr. Douglas Green, Chair, Department of Immunology and Cancer Biology Program, St. Jude Children's Research Hospital, Memphis, TN. My research centers on circadian rhythms in behavior and physiology (including for example, the sleep/wake cycle, metabolism, heart rate, and blood pressure) in mammals. More specifically, we study how the circadian clock works in cells and in the organism at the biochemical, molecular and physiological levels. The research in my lab over the past several years (Zhang et al, Cell, 2009; Ramanathan et al, PLoS Genet, 2014), as well as from several other groups, led us to a new and emerging area in the field – the extensive crosstalk between the circadian clock and fundamentally important cellular and physiological functions. (In layman's term: on one hand, our endogenous clock regulates our sleep/wake cycle, and on the other hand, a good vs. a bad sleep/wake cycle will have very different impacts on our physiologies.) In the context of my sabbatical research, this crosstalk includes circadian immunity. Our findings suggest that the circadian clock regulates various immune functions, and conversely, immunity also regulates the clock function. To acquire new ideas and experimental approaches, I contacted Dr. Green at St Jude, a world-renowned immunologist and leading expert on cell death, and was granted an opportunity to conduct my sabbatical.

During my sabbatical at St Jude, I conducted myself both as a PI and as a postdoc, attending seminars, journal clubs and lab meetings, interacting with numerous PIs and postdocs both within the immunology department and from other departments on campus, and performing hands-on cell- and animal-based experiments. During my sabbatical, Dr. Swantje Liedmann, a postdoc fellow in the Green lab and an excellent researcher, served as my mentor! Through these activities, I was able to immerse myself full time in a new area and learned a great deal in this new discipline. Important outcomes from my experiments lie at two fronts: 1) we have successfully established methods to purify specific types of immune cells derived from our circadian clock reporter mice (only available in my lab at UoM, not at St Jude) and show that innate immune cells (including particularly macrophages and dendritic cells) have endogenous circadian clocks, and 2) we have successfully established CRISPR/Cas9-mediated genome editing approach to knock out genes in cells and in mice, which is allowing us to study how genes involved in immune functions (and any gene in any processes, for that matter) affect circadian timekeeping. Further, my expertise on circadian biology also allowed me to contribute directly to Dr. Green's research program. For example, I am collaborating with Dr. Brad Heckman, a postdoc fellow in his lab, on how disruption of sleep contributes to inflammation in the brain and neurodegeneration. It is important to point out that all these research activities are ongoing and we expect complete some experiments soon for publication. We expect our collaborations with Dr. Green will continue for years to come, which is exciting to my research and Dr. Green's research.

In summary, this full-time research opportunity has allowed me to work with experts in the immunology discipline, leverage the superb facilities at St Jude, perform key experiments aligned with research activities in my UoM lab, and obtain new data. We expect to complete some experiments and publish new data in peer reviewed journals. Going forward, we expect to submit new grants based on our new findings. These outcomes have directly benefited my research program, and by extension, also the biology department and the college.

I chose to do my PDA in Memphis because I have a young family to take care and I must be here with them and for them. Thus, the proposed PDA has allowed me to carry out full-time research activities in the city of Memphis, while maintaining close contact and mentoring of my research team members, and equally importantly, fulfilling my responsibility as a parent.

• Manuscripts

1. Gustafson CL, Parsley NC, Asimgil H, Lee H, Ahlbach C, Michael AK, Xu H, Williams OL, Davis TL, Liu AC, Partch CL (2017) A slow conformational switch in the BMAL1 transactivation domain modulates circadian rhythms, Molecular Cell 66: 447–457
2. Hughes ME… Liu AC… Hogenesch JB (2017) Guidelines for genome-scale analysis of biological rhythms, J. Biol Rhythms (In press).
3. Wible RS*, Ramanathan C*, Olesen KM, Sutter CH, Kensler TW, Liu AC, Sutter TR (2017), NRF2 integrates redox oscillations into the circadian clock function in hepatocytes. (Submitted)
4. Crone LB, Bloomer RJ, Butawan MB, Wyman J, Hill JL, Lee HW, Liu AC, McAllan L, Han JC and van der Merwe M (2017) Time restricted high fat diet feeding protects against adiposity, but not liver steatosis or adipose inflammation in mice. (Submitted)
5. Xu H, Kathale NK, Liu AC (2017) Synergy of BMAL1 C-terminal helical domains enables cellular circadian oscillation. (In prep)
6. Ramanathan C, Cao R, Lee C, Sonenberg N, Liu AC (2017) mTOR signaling links intracellular nutrient signaling to the mammalian circadian clock. In prep.
7. Shen Y, Wang W, Xu Z, Liu AC (2017) NF-kB signaling modifies the mammalian circadian clock through interactions with core clock proteins. (In prep)

• Grant Proposals

1. NIH-NINDS R01 renewal resubmission, Molecular, cellular, physiological mechanisms of the mammalian circadian clock. Resubmitted in July 2017 (role: MPI)
2. Memphis Research Investment Fund, Circadian regulation of blood pressure in diurnal Nile grass rats (role: lead PI)

• Talks Given

1. Invited talk, “Integration between the ticking circadian clock and cell physiology”, Dept. of Pathology and Laboratory Medicine, Center for Cancer Research, University of Tennessee Health Science Center, Memphis, TN
2. Invited talk, “Circadian integration with cell physiology”, Dept. of Physiology and Functional Genomics, University of Florida Medical Center, Gainesville, FL
3. Invited talk, “Circadian Clocks and Cell Physiology: Circle of Life” Dept. of Biological Sciences, Biocomplexity Institute, Virginia Tech, Blacksburg, VA

• Other Activities

1. February, NIH Cellular Signaling and Regulatory Systems (CSRS) study section, National Institutes of Health, Bethesda, MD
2. February, Reviewer for Faculty Research Grant (FRG), College of Arts and Sciences, U of Memphis
3. March, NIH-NIGMS, Maximizing Investigators' Research Award (MIRA) for Early Stage Investigators (R35) study section, National Institutes of Health, Bethesda, MD
4. April, visited Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, Meeting with collaborator Dr. John Hogenesch (9/22-9/23/2016) to discuss NIH grant renewal submission. The proposal was submitted on 7/5/2017
5. May, Rhythms in South Eastern Region (RISER), Middle Tennessee State University, Murfreesboro, TN
6. May, Lecture on circadian clock and biotechnology, for junior and senior high school students, White Station High School, Memphis
7. Established new collaborations with Dr. Yongqiang Feng (regulatory T cell expert at St Jude) and Dr. Gonghua Hung (dendritic cell expert at Shanghai Jiaotong University)