BIOGRAPHICAL SKETCH

NAME: Yamazaki, Shin

eRA COMMONS USER NAME: SHIN.YAMAZAKI

POSITION TITLE: Research Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
Tamagawa University, Tokyo, Japan	B. Agr.	03/1986	Agriculture
Tamagawa University, Tokyo, Japan	M. Bio. Res.	03/1988	Agricultural Science
Tamagawa University, Tokyo, Japan	Ph.D.	03/1992	Agricultural Science
Mitsubishi Kasei Inst. of Life Sci., Tokyo, Japan	Postdoctoral	04/1992	Neuroscience
Tokyo Metro. Inst. for Neuroscience, Tokyo, Japan	Postdoctoral	07/1993	Neuroscience
University of Virginia, Charlottesville VA	Postdoctoral	04/1994	Chronobiology

A. Personal Statement

The goal of this proposal is to determine the anatomical locus of the food-entrainable oscillator (FEO). I will use luminescence real-time gene reporting and whole brain microscopy to complete this project. I have been an active researcher studying circadian rhythms for over 25 years. As a postdoctoral fellow at the University of Virginia, I developed the technology for real-time monitoring of circadian gene expression and discovered that mammalian peripheral tissues contain self-sustained circadian oscillators. This discovery laid the groundwork for my studies investigating the organization of the circadian system and how an experimental protocol that approximates chronic jet-lag or shift-work disrupts the phase relationship among circadian clocks. As a PI, I have continued to investigate the organization of the circadian system using real-time gene expression monitoring.

With their anatomical loci unknown and their outputs not expressed under normal physiological conditions, the FEO and methamphetamine-sensitive circadian oscillator (MASCO) are “black box” mysteries. My lab has shown that the FEO and MASCO are functional in mice lacking all three paralogs of the *Period* gene (their canonical circadian system is disabled). These mice are a novel and unique tool for revitalizing the search for the FEO and MASCO. My expertise in time-lapse brain imaging led to my position as Director of the Imaging Facility in the Department of Neuroscience at UT Southwestern, and to my collaboration with the UT Southwestern Whole Brain Microscopy Facility. This project is the culmination of my circadian expertise and data and toolsets collected over 25 years. My lab, in collaboration with the UT Southwestern Whole Brain Microscopy Facility, is ideally positioned to discover the locus of the FEO. By combining circadian mouse models, which I have characterized, with cutting-edge whole brain imaging technology, we will elucidate the neural substrate(s) of food anticipatory activity.

a. **Yamazaki S**, Numano R, Abe M, Hida A, Takahashi RI, Ueda M, Block GD, Sakaki Y, Menaker M, Tei H (2000) Resetting central and peripheral circadian oscillators in transgenic rats. ***Science*** 288 (5466): 682-685. *PMCID: PMC1635489*

b. Pendergast JS, Oda GA, Niswender KD, **Yamazaki S** (2012) Period determination in the food-entrainable and methamphetamine-sensitive circadian oscillator(s). ***Proc Natl Acad Sci U S A.*** 109 (35): 14218-14223. *PMCID: PMC3435193*

c. Pendergast JS, **Yamazaki S** (2013) The complex relationship between the light-entrainable and methamphetamine-sensitive circadian oscillators: evidence from behavioral studies of Period-mutant mice. ***Eur J Neurosci*** 38 (7): 3044-3053. *PMCID: PMC3899104*
d. Pendergast JS, **Yamazaki S** (2014) Effects of light, food, and methamphetamine on the circadian activity rhythm in mice. ***Physiol Behav*** 128: 92-98. *PMID: 24530262*

B. Positions and Honors

Positions and Employment

1996-2002 Research Scientist, Department of Biology, University of Virginia, Charlottesville, VA
2002-2006 Research Assistant Professor of Biological Sciences, Vanderbilt University, Nashville, TN
2006-2013 Research Associate Professor of Biological Sciences, Vanderbilt University, Nashville TN
2013-present Research Associate Professor of Neuroscience, University of Texas Southwestern Medical Center, Dallas TX
2013-present Director of Neuroscience Imaging Laboratory, University of Texas Southwestern Medical Center, Dallas TX

Other Experience and Professional Memberships

1990-2010 Member, The Japanese Society for Comparative Physiology and Biochemistry
1994-present Member, Society for Neuroscience
1996-present Member, Society for Research on Biological Rhythms
2000-2002 Center Investigator, NSF Center for Biological Timing, Charlottesville, VA
2006 NIH Peer Review Committee: Biological Rhythms and Sleep, ad hoc reviewer
2006-2013 Member of the Vanderbilt Kennedy Center for Research on Human Development, Nashville, TN
2008-2011 Scientist Member of the Institutional Animal Care and Use Committee, Vanderbilt University
2008-2013 Academic Editor, *PLoS ONE*
2009-present Review Editor, *Frontiers in Molecular Neuroscience*
2013-present Section Editor, *PLoS ONE*

C. Contribution to Science

1. **Pioneered in vivo measurements of SCN circadian rhythms:** As a postdoctoral fellow, I wanted to understand how individual SCN neurons are coupled together to drive the robust circadian locomotor activity rhythm. To address this question, I measured electrical activity, intracellular calcium, ATP, cAMP and neuropeptides from the suprachiasmatic nucleus (SCN) in rodents. I developed the surgical and technical approaches for measuring multi-unit activity (MUA) from freely-behaving animals and used this technique to demonstrate that locomotor activity feeds back and alters neural activity in the SCN. I shared my approach with other labs (researchers at Osaka University, Meiji University, Leiden University Medical Center, and Kent State University) that now use this technique to study in vivo electrical activity rhythms in the SCN.

   a. **Yamazaki S**, Ishida Y, Inouye ST (1994) Circadian rhythms of adenosine triphosphate contents in the suprachiasmatic nucleus, anterior hypothalamic area and caudate putamen of the rat--negative correlation with electrical activity. ***Brain Res*** 664 (1-2): 237-240. *PMID: 7895035*
   b. **Yamazaki S**, Kerbeshian MC, Hocker CG, Block GD, Menaker M (1998) Rhythmic properties of the hamster suprachiasmatic nucleus in vivo. ***J Neurosci*** 18 (24): 10709-10723. *PMID: 9852606*
   c. Vansteensel MJ, **Yamazaki S**, Albus H, Deboer T, Block GD, Meijer JH (2003) Dissociation between circadian Per1 and neuronal and behavioral rhythms following a shifted environmental cycle. ***Curr Biol*** 13 (17): 1538-1542. *PMID: 12956957*
   d. Nakamura W, **Yamazaki S**, Nakamura TJ, Shirakawa T, Block GD, Takumi T (2008) In vivo monitoring of circadian timing in freely moving mice. ***Curr Biol*** 18 (5): 381-385. *PMID: 18334203*

2. **Discovered circadian clocks in the peripheral organs of mammals:** During my time as a senior researcher, I collaborated with Professor Hajime Tei to develop the first rodent model for monitoring the circadian gene expression rhythm using bioluminescence. Using this technique, we discovered the existence of circadian clocks in the peripheral organs of mammals. This discovery was paradigm-shifting; we came to

view the mammalian circadian system as a multi-oscillatory system, rather than a system controlled by one pacemaker structure in the SCN. I have shared detailed information about luminescence imaging and photon-counting with more than 20 labs. In collaboration with Dr. David Ferster (Actimetrics Inc.), we developed a turntable apparatus for recording luminescence. This device, the LumiCycle, is now commercially available and used by 150 labs in 17 countries.

a. **Yamazaki S**, Numano R, Abe M, Hida A, Takahashi RI, Ueda M, Block GD, Sakaki Y, Menaker M, Tei H (2000) Resetting central and peripheral circadian oscillators in transgenic rats. ***Science*** 288 (5466): 682-685. *PMCID: PMC1635489*
b. **Yamazaki S**, Straume M, Tei H, Sakaki Y, Menaker M, Block GD (2002) Effects of aging on central and peripheral mammalian clocks. ***Proc Natl Acad Sci USA*** 99 (16): 10801-10806. *PMCID: PMC125050*
c. Yoo S-H, **Yamazaki S**, Lowrey PL, Shimomura K, Ko CH, Buhr ED, Siepka SM, Hong H-K, Oh WJ, Yoo OJ, Menaker M, Takahashi JS (2004) PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. ***Proc Natl Acad Sci USA*** 101 (15):5 339-5346. *PMCID: PMC397382*
d. Patent: US7659387 B1"Transgenic mammals introduced a Period 1 promoter that confers rhythmical expression." (granted on February 9th, 2010 by United States Patent Trademark Office) [http://www.google.com/patents/US7659387]

3. **Discovered that disorganization of circadian clocks leads to disease:** After discovering that the mammalian circadian system is a multi-oscillator network, I investigated the organization (or phase relationship) of these clocks. I developed a method for generating phase maps, by preparing acute tissue explants and measuring circadian gene bioluminescence rhythms. Using this technique, I have shown how the system changes during jet-lag, shift-work, ontogeny, and aging. In addition, I found that some tissue clocks respond to specific environmental cues independent of the SCN (e.g. the liver clock is shifted by restricted feeding and high-fat diet). Together these studies have defined the multi-oscillator hierarchy of the mammalian circadian system that is finely tuned to the environment.

a. Stokkan K-A, **Yamazaki S**, Tei H, Sakaki Y, Menaker M (2001) Entrainment of the circadian clock in the liver by feeding. ***Science*** 291(5503): 490-493. *PMID: 11161204*
b. Davidson AJ, **Yamazaki S**, Arble DM, Menaker M, Block GD (2008) Resetting of central and peripheral circadian oscillators in aged rats. ***Neurobiol Aging*** 29 (3): 471-477. *PMCID: PMC1635489*
c. **Yamazaki S**, Yoshikawa T, Biscoe EW, Numano R, Gallaspy LM, Soulsby S, Papadimas E, Pezuk P, Doyle SE, Tei H, Sakaki Y, Block GD, Menaker M (2009) Ontogeny of circadian organization in the rat. ***J Biol Rhythms*** 24 (1):55-63. *PMCID: PMC2665126*
d. Pendergast JS, Branecky KL, Yang W, Ellacott KL, Niswender KD, **Yamazaki S** (2013) High-fat diet acutely affects circadian organisation and eating behavior. ***Eur J Neurosci*** 37(8):1350-6. *PMCID: PMC3645495*

4. **Identified the function of each of three *Period* paralogs in mammals:** To determine if the three paralogs of the *Period* gene in mammals have redundant functions, my lab investigated circadian rhythms in single *Period*-deficient mice. We showed that each *Per* gene has a tissue-specific function. *Per1* is important for coupling cellular oscillators in the master pacemaker in the SCN, *Per2* is important for period determination in the SCN and some peripheral clocks, and *Per3* participates in timekeeping in some peripheral tissues.

a. Pendergast JS, Friday RC, **Yamazaki S** (2009) Endogenous rhythms in Period1 mutant suprachiasmatic nuclei in vitro do not represent circadian behavior. ***J Neurosci*** 29 (46):14681-14686. *PMCID: PMC2806308*
b. Pendergast JS, Friday RC, **Yamazaki S** (2010) Distinct functions of Period2 and Period3 in the mouse circadian system revealed by in vitro analysis. ***PLoS ONE*** 5(1):e8552. *PMCID: PMC2804141*
c. Pendergast JS, Friday RC, **Yamazaki S** (2010) Photic entrainment of Period mutant mice is predicted from their Phase Response Curves. ***J Neurosci*** 30 (36):12179-84. *PMCID: PMC2943870*
d. Pendergast JS, Niswender KD, **Yamazaki S** (2012) Tissue-specific function of Period3 in circadian rhythmicity. ***PLoS ONE*** 7(1): e30254. *PMCID: PMC3256228*

5. **Discovered the circadian clock and cell cycle are not connected in immortalized fibroblast and cancer cell lines:** Twenty-four hour fluctuations in cell division have been observed in numerous species, ranging from unicellular organisms to humans, suggesting that the circadian system is regulating cell cycle progression. In addition, multiple lines of evidence suggest that circadian dysregulation accompanies, or is a prerequisite for, cancer development and progression. I have used my expertise in luminescence recording to develop a novel approach for continuously monitoring the cell cycle rhythm in single cells using bioluminescence imaging. Using this method, my lab has recently shown that the circadian and cell cycles are uncoupled in immortalized rat-1 fibroblast and tumor-driven cell lines. Surprisingly, we found that the circadian rhythm was intact in these immortalized fibroblast and cancer cells. These data challenge the current dogma that the circadian clock gates cell mitosis and led to the provocative hypothesis that cancer cells achieve rapid cell division by disconnecting the circadian system from control of the cell cycle. If this hypothesis is supported, we will have an entirely new biological angle for generating cancer therapeutics by screening for compounds that "re-connect" the circadian and cell cycles in cancer cells and retard growth.

    a. Yeom M, Pendergast JS, Ohmiya Y, **Yamazaki S** (2010) Circadian-independent cell mitosis in immortalized fibroblasts. ***Proc Natl Acad Sci U S A*** 107 (21):9665-9670. *PMCID: PMC2906903*
    b. Pendergast JS, Yeom M, Reyes BA, Ohmiya Y, **Yamazaki S** (2010) Disconnected circadian and cell cycles in a tumor-driven cell line. ***Commun Integr Biol*** 3 (6): 536-539. *PMCID: PMC3038057*

Complete List of Published Work (64 peer-reviewed primary research publications):

http://www.ncbi.nlm.nih.gov/sites/myncbi/shin.yamazaki.1/bibliography/41154531/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

IOS-1146908 Yamazaki (PI) 03/01/12-02/29/16 (currently in no-cost extension)
NSF
Exploring the Interaction between Light- and Food-Entrainable Oscillators in the Mammalian Circadian System
The major goals of this project are (i) to identify genes that are important for timekeeping in the circadian clock that controls food anticipatory activity and the clock which controls methamphetamine-induced circadian behavior; and (ii) to investigate those circadian oscillators as components of the integrated circadian circuit.
Role: PI

Completed Projects

None in the past 3 years