OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026)

BIOGRAPHICAL SKETCH

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NAME: Yamazaki, Shin

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

POSITION TITLE: Research Professor

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 |
| --- | --- | --- | --- |
| 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 overall goal of my research program is to understand the fundamental properties and organization of the

circadian system and to investigate the link between disruption of the circadian system and poor health (e.g.

cancer, obesity, neurological disorders and mortality). As a postdoctoral fellow at Mitsubishi Kasei Institute for Life Sciences, I learned the technique of in vivo multi-unit neural activity recording from the suprachiasmatic nucleus (SCN) of freely behaving animals. When I became a post-doc at the University of Virginia, I applied this method to tau mutant hamsters and examined how tau mutation affects circadian and ultradian rhythms. As a post-doc, I became skilled in performing numerous survival surgeries, including telemetry implantation, brain micro-lesion, and ocular enucleation. As a research scientist 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. I was also instrumental in discovering that the timing of food availability affects the phase of the clock in the liver. As a PI, I have continued to investigate many aspects of the circadian system, including how the SCN and extra-SCN pacemakers are coupled and control behavioral and physiological circadian rhythms.

With its anatomical locus unknown and its outputs not expressed under normal physiological conditions, the food entrainable oscillator (FEO) is a “black box” mystery. My lab has shown that the FEO is functional in mice lacking all three paralogs of the *Period* gene (this disables their canonical circadian system). These mice are a novel and unique tool for revitalizing the search for the FEO. My lab has also shown that timed palatable meals or running wheel access reveals novel circadian behavior rhythms in these mice lacking functional circadian clocks. Using an open-source operant feeding device, the Feeding Experimentation Device version 3 (FED3), our lab recently had a surprising discovery that daily food anticipation is encoded on a light-entrainable extra-SCN circadian oscillator.

Ongoing and recently completed projects that I would like to highlight include:

Ongoing Research Support

1R01NS114527-01A1 Yamazaki (PI) 09/15/20-06/30/25

NIH/NINDS

Neural Circuitry and functional significance of extra-SCN pacemakers

The major goal of this project is to identify the neural circuitry and physiological roles of the methamphetamine-sensitive circadian oscillator.

Role: PI

IOS-1931115 Yamazaki (PI) 05/01/20-04/30/26 (no cost extension)

NSF/IOS

Revealing the Palatable Meal-Inducible Circadian Oscillator

The major goal of this project is to define the functional significance of the newly discovered palatable-meal inducible circadian oscillator.

Role: PI

Completed Projects

R01NS106657 Takahashi (PI) 09/25/17-07/31/22

NIH/NINDS

Cell-type-specific analysis of the suprachiasmatic nucleus

This project uses a new generation of conditional PER2::LUCIFERASE reporters to study genetically identified neuronal cell types in the suprachiasmatic nucleus.

Role: Co-Investigator

R21 NS099809 Yamazaki (PI) 09/01/16-08/31/19

NIH/NINDS

Identification of the anatomical locus for the food-entrainable circadian oscillator

The major goal of this project is to identify the anatomical locus of the food-entrainable oscillator.

Role: PI

Citations:

* 1. Ehichioya DE, Taufique SKT, Farah S, **Yamazaki S** (2023) A time memory engram embedded in a light-entrainable circadian clock. ***Curr Biol.*** 33(23):5233-5239.e3. doi: 10.1016/j.cub.2023.10.027. *PMID: 37951213*
  2. **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*
  3. 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*
  4. Ehichioya DE, Taufique SKT, Magaña I, Farah S, Obata Y, **Yamazaki S** (2023) Gut microbiota depletion minimally affects the daily voluntary wheel running activity and food anticipatory activity in female and male C57BL/6J mice. ***Front Physiol.***14:1299474. doi: 10.3389/fphys.2023.1299474. *PMCID: PMC10722266*

**B. Positions, Scientific Appointments, 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

2013-2019 Research Associate Professor of Neuroscience, UT Southwestern Medical Center, Dallas TX

2019-present Research Professor of Neuroscience, UT 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*

2013-present Section Editor, *PLoS ONE*

2018-present Associate Editor, *Frontiers in Molecular Neuroscience*

2020 ZRG1-ICN-B-02M, NIH Special Emphasis Panel, ad hoc reviewer

2022-2024 Members-at-Large, Board Directors, Society for Research on Biological Rhythms

**2023 ZRG1 ICN-B (04), NIH Special Emphasis Panel, ad hoc reviewer**

**2023 NSF Neural Systems- modulation, ad hoc reviewer**

**C. Contributions 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 and 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.
2. **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*
3. **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*
4. 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*
5. 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*
6. **Discovered circadian clocks in the peripheral organs of mammals:** When I was a senior researcher, I collaborated with Professor Hajime Tei to develop the first rodent model for monitoring 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 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.
   1. **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*
   2. **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*
   3. 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*
   4. 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]
7. **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.
   1. 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*
   2. 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*
   3. **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*
   4. 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*
8. **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.
9. 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*
10. 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*
11. Pendergast JS, Friday RC, **Yamazaki S** (2010) Photic entrainment of Periodmutant mice is predicted from their Phase Response Curves. ***J Neurosci*** 30 (36):12179-84. *PMCID: PMC2943870*
12. Pendergast JS, Niswender KD, **Yamazaki S** (2012) Tissue-specific function of Period3 in circadian rhythmicity. ***PLoS ONE*** 7(1): e30254. *PMCID: PMC3256228*
13. **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.
14. 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*
15. 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*
16. Izumo M, Johnson CH, **Yamazaki S** (2003) Circadian gene expression in mammalian fibroblasts revealed by real-time luminescence reporting: temperature compensation and damping. ***Proc Natl Acad Sci USA*** 100: 16089-16094. PMCID: PMC307697
17. Reyes BA, Pendergast JS, **Yamazaki S** (2008) Mammalian Peripheral Circadian Oscillators are Temperature Compensated. ***J Biol Rhythms*** 23:95-98. PMCID: PMC2365757

**Complete List of Published Work (includes 82 peer-reviewed primary research publications):**

[My Bibliography - NCBI (nih.gov)](https://www.ncbi.nlm.nih.gov/sites/myncbi/shin.yamazaki.1/bibliography/41154531/public/?sortby=pubDate&sdirection=descending)