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Joseph S. Takahashi Receives \$500,000 Gruber Neuroscience Prize for Pioneering Work on the Molecular and Genetic Basis of Circadian Rhythms in Mammals

Joseph S. Takahashi

May 9, 2019, New Haven, CT – Joseph S. Takahashi of the University of Texas Southwestern Medical Center is the recipient of the 2019 Gruber Neuroscience Prize. Takahashi, a Howard Hughes Medical Institute Investigator, is perhaps best known for his group’s discovery of the *Clock* gene in mice, which is a master regulator of circadian rhythms in mammals.

The prize, which includes a \$500,000 unrestricted cash award, will be presented to Takahashi on October 20 at the annual meeting of the Society for Neuroscience in Chicago, Illinois.

In search of the genetic basis of circadian rhythms, Takahashi’s group obtained mice with random genetic alterations and looked for any that displayed abnormal circadian behaviors. When given access to running wheels, mice use them at remarkably regular times each day; specifically, the type of mouse Takahashi’s group used in their studies run every 23.7 hours. Among hundreds of mice, the team noticed one that used the wheel on a 25-hour cycle instead, an indicator that there was something unusual about its circadian clock.

By breeding the mouse, they determined that its altered circadian behavior was genetic—a major milestone, but to make use of the finding, the group still needed to determine what gene was affected. This was no easy task in the 1990s, when the complete mouse genome was not known and DNA sequencing was much more laborious and costly than it is today. Ultimately, after ten members of the group spent three years working on the problem, they pinned down the gene that was altered in the abnormal mouse and named it *Clock*. When Takahashi’s group inserted DNA with a normal copy of the gene into the mutant mouse, the mouse’s running pattern was restored to normal, providing further evidence that the *Clock* gene dictates circadian rhythms in mice.

After identifying the *Clock* gene, the group built on work from others suggesting that it might be

expressed outside the brain by demonstrating that the circadian clock was expressed in cells throughout the body. Takahashi's lab also went on to discover *Clock*'s partner gene *Bmal1*; these genes contain the instructions for cells to make the proteins CLOCK and BMAL1, respectively. Working together, the CLOCK–BMAL1 complex affects the ways many other genes are used in a circadian rhythm-dependent fashion. One of the genes the complex regulates, the group found, is *Per1*, which is related to a gene that controls circadian rhythms in fruit flies.

But *Per1* is far from the only gene under *Clock*'s control—Takahashi's group has discovered that *Clock* is intertwined with an extensive list of biochemical pathways. It's even involved in metabolism, as the group found in collaboration with Northwestern University's Joseph Bass while investigating why mice with mutations in *Clock* become obese with age. Takahashi has reason to suspect that through its participation in metabolism, *Clock* may also influence longevity—a topic the group is now investigating.

Additional Information

In addition to the cash award, the recipient will receive a gold laureate pin and a citation that reads:

The Gruber Foundation proudly presents the 2019 Neuroscience Prize to Joseph S. Takahashi for his pioneering work on the molecular and genetic basis of circadian rhythms in mammals.

Takahashi has made groundbreaking discoveries in the neurobiology of circadian rhythms, including the isolation and cloning of the first mammalian circadian rhythm gene, known as the Clock gene. Using elegant genetic approaches in mammals, his research has elucidated the networks of genes and proteins that interact to drive the circadian clock system and the feedback loops that govern their expression. His use of innovative approaches to observe clock oscillations throughout the body in real time has revealed the broader impact of the circadian system in regulating the timing of cellular events in health and disease.

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Laureates of the Gruber Neuroscience Prize:

- **2018: Ann M. Graybiel, Okihide Hikosaka and Wolfram Schultz**, for pioneering work in the study of the structure, organization and functions of the basal ganglia
- **2017: Joshua Sanes**, for groundbreaking discoveries about synapses, transforming our understanding of how the human brain functions
- **2016: Mu-Ming Poo**, for his pioneering and inspiring work on synaptic plasticity
- **2015: Carla Shatz and Michael Greenberg**, for their elucidation of the molecular mechanisms through which neural activity controls wiring and plasticity of the brain
- **2014: Thomas Jessell**, for his pioneering work on the differentiation of spinal cord neurons and their wiring into networks
- **2013: Eve Marder**, for her contributions to understanding how circuit dynamics and behavior arise from the properties of component neurons and their synaptic connections
- **2012: Lily and Yuh Nung Jan**, for their fundamental contributions to molecular neurobiology
- **2011: Huda Y. Zoghbi**, for her pioneering work on revealing the genetic underpinnings of neurological disorders

- **2010: Robert H. Wurtz**, for pioneering work on neural bases of visual processing in primates
- **2009: Jeffrey C. Hall, Michael Rosbash, and Michael Young**, for revealing the gene-driven mechanism that controls rhythm in the nervous system
- **2008: John O'Keefe**, for discovering place cells, which led to important findings in cognitive neuroscience
- **2007: Shigetada Nakanishi**, for pioneering research into communication between nerve cells in the brain
- **2006: Masao Ito and Roger Nicoll**, for work on the molecular and cellular bases of memory and learning
- **2005: Masakazu Konishi and Eric Knudsen**, for work on the neural basis of sound localization
- **2004: Seymour Benzer**, for applying the tools of molecular biology and genetics to the fruit fly, *Drosophila*, and linking individual genes to their behavioral phenotypes

The Prize recipients are chosen by the Neuroscience Selection Advisory Board. Its members are:

Susan Amara, NIH/NIMH (Chair); **Frances Jensen**, University of Pennsylvania; **Tirin Moore**, Stanford University; **Anthony Phillips**, University of British Columbia; **Angela Roberts**, University of Cambridge; **Joshua Sanes**, Harvard University; and **Carla Shatz**, Stanford University.

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By agreement made in the spring of 2011 The Gruber Foundation has now been established at Yale University.

The Gruber International Prize Program honors individuals in the fields of Cosmology, Genetics and Neuroscience, whose groundbreaking work provides new models that inspire and enable fundamental shifts in knowledge and culture. The Selection Advisory Boards choose individuals whose contributions in their respective fields advance our knowledge and potentially have a profound impact on our lives.

The Neuroscience Prize honors scientists for major discoveries that have advanced the understanding of the nervous system.

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For more information on the Gruber Prizes, visit www.gruber.yale.edu, e-mail info@gruber.yale.edu or contact A. Sarah Hreha at +1 (203) 432-6231. By mail: The Gruber Foundation, Yale University, Office of Development, PO Box 2038, New Haven, CT 06521.

Media materials and additional background information on the Gruber Prizes can be found at our online newsroom: <https://gruber.yale.edu/news-media>