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From left to right: Michael Young, Jeffrey Hall, and Michael Rosbash.

CUHK; Gairdner Foundation; Gruber Foundation.

Timing is everything: U.S. trio earns Nobel for work on the body's biological clock

By [Gretchen Vogel](#), [Erik Stokstad](#) | Oct. 2, 2017, 5:50 AM

Discoveries about how organisms stay in sync with Earth's rhythm of day and night have won this year's Nobel Prize in Physiology or Medicine.

Jeffrey Hall and Michael Rosbash of Brandeis University in Waltham, Massachusetts, and Michael Young of The Rockefeller University in New York City share the prize equally for their work on how several genes work together to control the basic circadian clock, encoding proteins that build up during the night and are broken down during the day. These clocks are ticking inside plants, fungi, protozoa, and animals. In recent years, researchers have found that the clock is related not only to our sleep cycle, but also to metabolism and brain function.

Circadian, or daily, rhythms are "just as fundamental as respiration," says Charalambos Kyriacou, a molecular geneticist at the University of Leicester in the United Kingdom. "There isn't any aspect of biology

that circadian rhythms aren't important for. They are totally fundamental in a way that we didn't anticipate" before the discoveries honored today.

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The presence of a biological clock was already surmised in the 18th century. In 1729, French astronomer Jean Jacques d'Ortous de Mairan showed that mimosa leaves, which open at dawn and close at dusk, continued this cycle even when kept in darkness. But it wasn't until the 20th century that the idea of an internal clock—as opposed one that responds to external cues like light—was settled.

The genetic basis for a daily physiological cycle was first discovered in fruit flies in the 1970s. Seymour Benzer and Ronald Konopka at the California Institute of Technology in Pasadena created mutant flies that had abnormal biological clocks. One type had a broken clock—its patterns of activity became arrhythmic—whereas the others now had either a 19-hour or a 28-hour cycle. Benzer and Konopka showed the mutations all had hit the same gene, presumably in different ways. They and other researchers homed in on a gene called *period*.

Hall and Rosbash finally sequenced the gene in 1984, as did Young. Hall and Rosbash showed that its protein, called PER, rose and fell over 24 hours, peaking at night. They suspected the clock was driven by a feedback loop, with the protein PER interfering with the *period* gene. ("It makes you scratch your head and wonder if it's even possible," Young said in a [1985 news story in Science about the discovery](#).)

For the clock to work, PER had to get into the nucleus. Young figured out how that happened. In 1994, he and colleagues discovered a second clock gene, *timeless*, that allowed PER to enter the nucleus and stop *period* from making more. (Their paper was [published in Science](#).)

“ There isn't any aspect of biology that circadian rhythms aren't important for. They are totally fundamental. ”

Charalambos Kyriacou, University of Leicester

Researchers have since found half a dozen more genes that influence the cycle. For example, *period* and *timeless* are turned on by *clock*, discovered in 1997 by Joseph Takahashi, now at UT Southwestern in Dallas, Texas, and his colleagues. Within a year, this group discovered another key part of the feedback loop: When PER and TIM get into the nucleus, they **also curtail the activity of clock**.

Clock genes are extremely influential, affecting the activity of most other genes in the body in one way or another. Circadian mechanisms influence metabolism—how our body uses and stores energy—blood pressure, body temperature, inflammation, and brain function. Time of day can influence the effectiveness of drugs and their side effects. And mismatches between the clock and the environment, for instance as a result of jet lag or shift work, have been shown to play a role in mood disorders and even cancer risk.

"Since the seminal discoveries by the three laureates," the Nobel Assembly **said in its press release today**, "circadian biology has developed into a vast and highly dynamic research field, with implications for

our health and wellbeing." (An extensive discussion about the trio's work is available from the Nobel Assembly [here](#); watch a video of this morning's announcement [here](#).)

The award came as a complete surprise to one of the Nobelists. "You are kidding me," Rosbash said this morning after he was called and notified of the honor, Thomas Perlmann, the Nobel Committee's secretary, told journalists this morning.

The Nobel Prize comes with 9 million Swedish Kronor (\$1.1 million), which Hall, Rosbash, and Young will share. The amount went up from 8 million kronor last year, an increase of 12.5%.

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