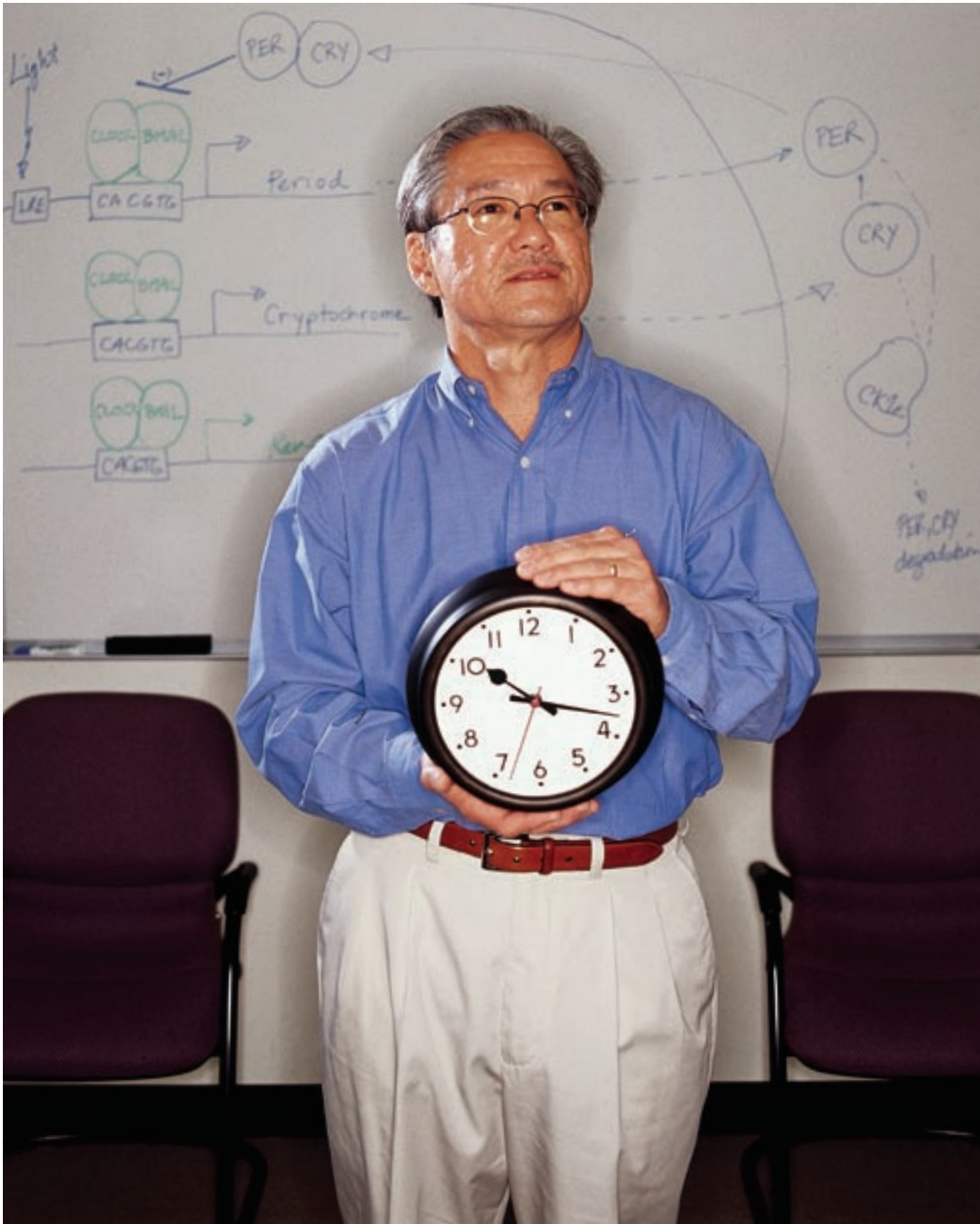


Cancer and the Clock

A molecular mechanism explains why sensitivity to anticancer drugs changes with the time of day.

BELOW — JOSEPH TAKAHASHI RESEARCHES THE GENETIC AND MOLECULAR BASIS OF CIRCADIAN RHYTHMS AND THE BODY'S "INTERNAL CLOCKS."



MATTHEW GILSON

ONCOLOGISTS HAVE LONG THOUGHT that cancer treatments tend to be more effective at certain times of day. Now, researchers have discovered a molecular mechanism that explains this sensitivity. In experiments with mice, they found that the body's internal biological clock affects the survival of immune cells targeted by the anticancer drug cyclophosphamide (CY).

Initial experiments with normal mice, performed by Marina P. Antoch during her tenure in the lab of Joseph S. Takahashi, an HHMI investigator at Northwestern University, confirmed that animals treated with CY in late afternoon survived better than those whose treatments were initiated early in the morning. Antoch extended these original findings—by examining the mechanism for this difference—after she moved to Cleveland, Ohio, and established a research program in the department of

cancer biology at the Cleveland Clinic's Lerner Research Institute.

Antoch and her colleagues used genetically altered mice that lacked specific components of the body's internal clock. "Defects in *Clock* or *Bmal1* genes, which essentially damp the cycles of the internal clock," she reasoned, "may produce a very different effect when compared to defects in *Cryptochrome* gene, which, in contrast, 'jams' the circadian clock at the most active point in its cycle."

The researchers discovered that *Clock*-mutant and *Bmal1*-knockout mice showed high sensitivity to CY at any time it was administered—as if it were always at optimal times of day. In contrast, the *Cryptochrome*-knockout mice showed more resistance to the drug at all times than did normal mice. When the Antoch team analyzed the knockout animals' immune-system B cells, they found that

the presence or absence of functional *Clock* and *Bmal1* genes determined their sensitivity to CY.

"This is not some vague metabolic difference between day and night," says Takahashi. "This is a tangible difference in the immune system that influences sensitivity" to certain anticancer drugs. The researchers' findings were published in the March 1, 2005, issue of the *Proceedings of the National Academy of Sciences*.

The results may well extend to the effects of other anticancer drugs, as well as to radiation therapy, and may provide a rationale for adjusting the timing of chemotherapy to make it less toxic. And, Antoch says, "they provide a rationale for developing drugs that can enhance the therapeutic index through the modulation of the circadian clock." ■

- Dennis Meredith -

A HEALTHY INTERNAL CLOCK KEEPS WEIGHT OFF

Staying up late, skipping meals, and snacking constantly resulted in weight gain, fatty livers, and high cholesterol levels for an unlucky group of mice whose internal biological clocks were genetically disrupted.

Researchers at Northwestern University—including HHMI investigator Joseph Takahashi—have identified wide-ranging molecular and behavioral changes in mice that have a faulty circadian system. In people, similar changes in body fat and metabolic activity are known as metabolic

syndrome, which can lead to cardiovascular disease and type 2 diabetes.

The study suggests a surprising new angle for understanding and eventually preventing and treating obesity and related disorders in people. "Timing is critical to keep the metabolic symphony in tune," says researcher Joseph Bass, corresponding author on the paper. The work was published on April 21, 2005, in *Science Express*, which provides rapid electronic publication of select articles from the journal *Science*.

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JOSEPH TAKAHASHI



Early to Bed, Early to Rise

Researchers investigate a rare sleep syndrome.

A FEW OF US WHO CONSISTENTLY NOD OFF EARLY AND THEN wake up wide-eyed long before dawn can blame a newly found mutant gene. This odd "time-shift" trait—called familial advanced sleep phase syndrome (FASPS)—was recently studied in one affected family by neurologist Louis J. Ptáček, an HHMI investigator, and his colleague Ying-Hui Fu at the University of California, San Francisco.

The sleep-shifting mutation they found is in "a gene that was not previously shown in mammals to be a circadian rhythm gene," Ptáček explained.

In earlier research, Ptáček and his colleagues discovered an entirely different gene that causes a similar clock shift. Both

arise because of so-called point mutations in the genes. This means that altering a single base pair in the gene's long DNA chain is enough to change a person's sleep behavior.

It's not clear how the mutant gene works to shift people's sleep time, their circadian rhythm, Ptáček says. Further studies may unravel some of the fundamental mysteries of how circadian rhythms are established and maintained in creatures that have evolved along very different paths.

The paper was published in the March 31, 2005, issue of the journal *Nature*. The lead author was Ying Xu, a member of the team in San Francisco. Other team members are at the University of Vermont and the University of Utah. ■

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