Breakthroughs

Feinberg School of Medicine Research Office

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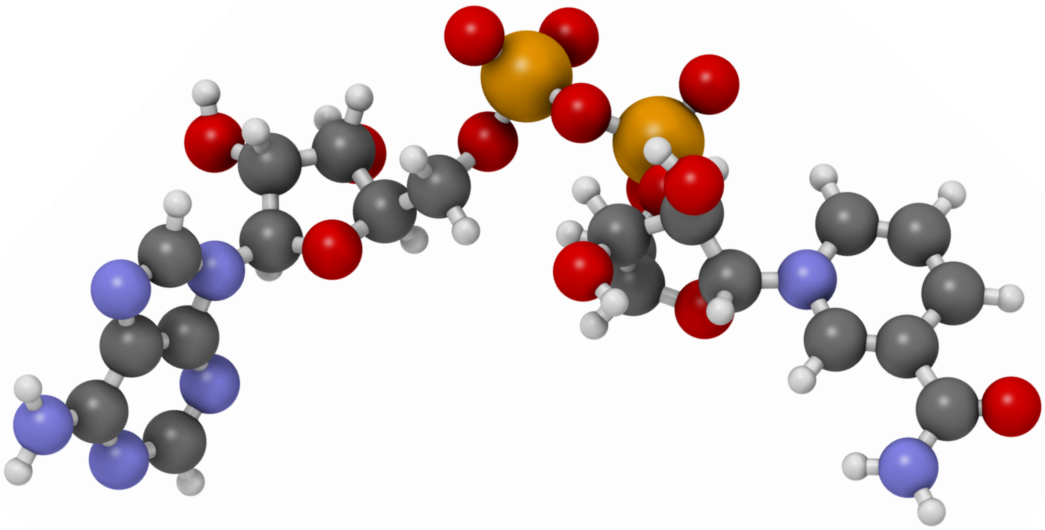

As part of his research on the body's circadian clocks, Joseph Bass, MD, PhD, is investigating the molecule NAD+, which is central to the mechanism that connects life span and aging to nutrition.

Uncovering Metabolism's Clockwork

"Timing is everything" may be an old cliché, but for Joseph Bass, MD, PhD, it's also a reflection of an emerging discovery in physiology: that the body's circadian clocks are in fact critical to driving a host of behaviors, processes and pathways — including those associated with several diseases and pathologies.

Bass, chief of Endocrinology, Metabolism and Molecular Medicine in the Department of Medicine, focuses his research on illuminating how the body's clocks regulate feeding behavior and glucose metabolism, and identifies how disruptions in that overarching circadian system play a role in metabolic disease. The goal of the research is to develop a deeper understanding of the clock and its mechanisms, which may eventually lead to novel therapies for widespread disorders like obesity and diabetes.

"The field of circadian time has been an area of excellence at Northwestern for more than 20 years," said Bass, also the Charles F. Kettering Professorship of Medicine and a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. "What we're trying to do now is take advantage of our know-how to identify new pathways and drugs for those pathways that could, for example, augment insulin secretion and improve diabetes."

It's long been known that the body possesses a master circadian clock, located in the brain, in the suprachiasmatic nucleus of the hypothalamus. But it wasn't until more recently, as the field of circadian time rapidly advanced, that it was discovered there are also distinct clocks residing in nearly every cell of the body.

The master clock — cued by internal factors and environmental signals like light — holds the rhythm across all the body's peripheral clocks, regulating behavior and biological processes throughout the 24-hour light-dark cycle. But when individual clocks fall out of tune with the master timekeeper, the breakdown in synchronization can contribute to a range of disorders, including diabetes.

"My focus has increasingly been drawn toward understanding the perspective of time as a variable in biochemical processes that determine our drive to eat — in turn affecting bodyweight — and regulate blood sugar control," Bass said.

Bass, who joined Northwestern in 2000, arrived at an opportune time in the history of circadian clock discovery. Seminal work in the late 1990s by Fred Turek, PhD, professor of Neurology and Psychiatry and Behavioral Sciences, and Joseph Takahashi, PhD, a former professor of Neurology, for the first time pinpointed — and cloned — the genes that drive circadian function in mammals.

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Uncovering Metabolism's Clockwork

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"There was this intersection of critical developments at Northwestern that really opened the field," Bass said. "The collaborative environment then enabled me to join together my background in endocrine, metabolic and medical physiology with these powerful strategies from genetics to try to understand how the clock regulates behaviors and physiologic systems."

In a landmark paper published in *Science* in 2005, Bass, together with Turek and Takahashi, demonstrated that a misaligned biological clock impaired metabolism, increasing the prevalence of obesity and metabolic syndrome. In the study, mutant mice with a dysfunctional clock gene experienced a 35 percent increase in fat mass compared to wild-type mice.

"The paper was the first to provide genetic evidence that the clock system regulates both body weight and glucose metabolism; that was key," said Bass, who is also co-director of the Center for Diabetes and Metabolism and of the Comprehensive Metabolic Core.

Numerous breakthroughs in the metabolism-clock connection followed over the next 15 years of Bass' tenure at Northwestern. In *Nature* in 2010, Bass and his team first reported that beta-cells in the pancreas require a clock in order to produce insulin. In a subsequent study building upon those findings, Bass' laboratory, together with co-investigator Grant Barish, MD, used next-generation genome sequencing to pinpoint the precise set of genes in the pancreas that are controlled by the clock transcription factors. The findings were published in *Science* in 2015.

"Joe has really been a leader in establishing a very direct connection between the circadian clock and diabetes," said Barish, assistant professor of Medicine in the Division of Endocrinology, Metabolism, and Molecular Medicine. "Particularly in this most recent study, the discovery of the underlying regulatory mechanism by which the circadian clock controls the secretion of insulin — the principle hormone

Joseph Bass, MD, PhD, is the chief and Charles F. Kettering Professor of Endocrinology in the Department of Medicine at Feinberg.

responsible for glucose homeostasis — really cements a link between the clock and aspects of insulin, diabetes and related physiology."

The anticipation is that such fundamental discoveries may eventually inform the development of novel therapeutics for diabetes and other diseases. "While we're still very early in this, we know that some features of these circadian transcription factors are targetable and, to some extent, are amenable to pharmacologic manipulation," Barish said.

Bass' findings also have applications for the treatment of a wider range of disorders, as the body's metabolism of drugs is in part influenced by the circadian system, an area of study called chronopharmacology. For example, statins are largely administrated at night because the clock coordinates the synthesis of cholesterol to occur at night. "It's likely that this is just the tip of the iceberg, and that there are many other processes targeted with drugs that are controlled by the same clock mechanism," Bass said.

In ongoing research, Bass' laboratory is also striving to uncover how the clock helps regulate production of a key molecule called NAD+. The connection was first reported in a pair of papers Bass published in *Science* in 2009 and 2013, with first author Kathryn Ramsey, PhD, and first author Clara Peek, PhD, respectively, both research assistant professors of Medicine in the Division of Endocrinology, Metabolism, and Molecular Medicine.

"NAD+ has been shown to be central to the mechanism that connects life span and aging to nutrition. We're now trying to understand how it is that nutrition and clocks influence aging, and we think one of the ways this comes about is through the control of NAD+," Bass said. He is collaborating with colleagues in chemistry, including Milan Mrksich, PhD, professor of Cell and Molecular Biology, and Navdeep Chandel, PhD, David W. Cugell Professor of Medicine and of Cell and Molecular Biology, to address such questions.

"Interactions with other groups at Northwestern have enabled us to make key advances in our understanding of the clock and in how it's controlling other physiologic systems," Bass said. "Because of the history of discoveries here, we're now in a position to be on the ground floor in using genetic approaches to get at questions that have been asked for a long time in a more descriptive way."

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