

# Kidney News

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## Kidney Circadian Clock Affects Metabolic Processes, Drug Pharmacokinetics



Many of the body's processes follow a natural daily rhythm, or circadian clock, that is based on regular light-dark cycles that correspond to day and night. A circadian clock in the kidneys plays an important role in maintaining balance throughout the body, and alterations to the clock can

influence metabolism in both health and disease. For example, in individuals who take medications, the kidney's circadian clock may control the process of drug elimination and therefore influence the duration of a drug's action and the effectiveness of the therapy. The findings are published in the *Journal of the American Society of Nephrology* (Nikolaeva S et al. *J Am Soc Nephrol.* 2016 Apr 7. pii: ASN.2015091055).

The body's circadian clock can have a range of influences, from determining when a person experiences peak cognitive performance to the timing of acute medical events such as strokes and heart attacks. The clock even enables maximum expression of genes at appropriate times of the day, allowing individuals to adapt to the earth's rotation. Research has also shown that it can change as people age, so, for example, the brain signals the body to sleep earlier in the evening and to awaken earlier in the morning.

In the kidneys, physiologic processes

such as sodium reabsorption, renal blood flow, and glomerular filtration follow a daily rhythm, and coordination of the timing of these processes allows the kidney to anticipate changes in metabolic and physiological demands throughout a 24-hour cycle. Results from animal and human studies indicate that circadian disruption and sleep deprivation can have detrimental effects on the kidneys.

In the *JASN* study, a team led by Dmitri Firsov, PhD, and Natsuko Tokonami, PhD, of the Department of Pharmacology and Toxicology at the University of Lausanne in Switzerland, blocked kidney cells' expression of *Bmal1*, a gene critically involved in the circadian clock system, and found that the clock is responsible for the temporal adaptation of kidney function to the light and dark phases of the day that correspond to activity and rest.

"Since urine formation and excretion by the kidney is one of the most easily detectable rhythmic processes—we are forming and excreting much more urine during the day—we had hypothesized

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## ASN, KHI Announce New Initiatives at White House Organ Summit

By Rachel Meyer

On June 13, 2016, ASN and the Kidney Health Initiative (KHI)—the society's public-private partnership with the US Food and Drug Administration—participated in a summit the White House convened to address the shortage of organs available for

transplantation. The White House Organ Summit brought together a wide variety of stakeholders committed to building on the Obama administration's efforts to improve outcomes for individuals waiting for organ transplants and support for living organ donors.

Approximately 100,000 Americans are on the waitlist for a kidney transplant alone, and 13 die every day waiting for their name to be called. ASN engaged in dialogue with the White House regarding challenges to transplantation and new kidney therapeutics prior to the summit for several months, and was invited to unveil initiatives in support of the summit's goals.

ASN announced three initiatives at the summit: the first \$7 million toward a kidney disease XPRIZE, commitment to

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## Kidney Circadian Clock

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that at least a part of this rhythmicity is dependent on the circadian clock mechanism,” Tokonami said.

The researchers also performed experiments that combined functional, transcriptomic, and metabolomic analyses in mice with inducible conditional knockout of *BMAL1* (the mouse version of *Bmal1*) in renal tubular cells. Blocking *BMAL1* in adult mice did not produce obvious abnormalities in sodium, potassium, or water handling in the kidneys, but there were significant changes in the expression of

genes related to metabolic pathways. Furthermore, kidneys from knockout mice exhibited changes indicative of altered mitochondrial function, an effect that could have a range of impacts on diverse functions within cells. The animals’ blood also contained altered levels of various amino acids, lipids, and other components, with significant increases in plasma urea and creatinine. The investigators’ partial analysis covered less than 5% of the total number of metabolites found in plasma, but even this restricted approach identified more than 50 metabolites that are differentially represented in the plasma of knockout mice.

The investigators noted that the animals’ kidneys had a reduced capacity to secrete the diuretic furosemide, paralleled

by an approximate 80% decrease in expression of SLC22a8, a member of the organic anion transporter family of proteins that is known to mediate the excretion of many drugs.

“We’ve shown that the circadian clock in the kidney plays an important role in different metabolic and homeostatic processes at both the intrarenal and systemic levels and is involved in drug disposition,” Firsov said. The findings related to SLC22a8 suggest that by controlling the process of drug elimination, the kidney’s circadian clock may control how long a drug remains active, and therefore its effectiveness.

“In normal light-dark conditions and on a normal diet, these kidney-specific conditional *Bmal1* knockout mice exhibit

an intriguing phenotype that includes dramatic changes in gene expression affecting, among other things, pharmacokinetic pathways,” said Michelle Gumz, PhD, who was not involved with the research and is an Assistant Professor in the Division of Nephrology, Hypertension and Renal Transplantation within the University of Florida’s Department of Medicine. Her laboratory is investigating the role of the circadian clock in the kidney, with a focus on sodium transport regulation. “These findings have important implications for our understanding of how chronotherapy may affect renal function and drug efficacy. It will be very interesting to determine the effect of a modified diet or light cycle on fluid and electrolyte handling in this novel knockout mouse model.” ●

## New Initiatives

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developing a roadmap to achieve the goal of creating a bio-artificial or bioengineered alternative to dialysis, and a partnership with the US Department of Veterans Affairs called the Kidney Innovation Initiative.

Onstage at the White House, ASN announced its commitment of the first \$7 million toward a kidney disease prize competition, in partnership with the XPRIZE Foundation.

“With more than 450,000 Americans and millions of people around the world suffering from kidney failure who depend on dialysis to live, ASN is committed to finding a superior alternative that improves their lives and today announced its pledge of the first \$7 million toward a possible XPRIZE competition to achieve that goal,” said ASN President Raymond C. Harris, MD, FASN.

Developed in partnership with the XPRIZE Foundation, the kidney disease prize competition would incentivize the development of a novel wearable or implantable device that replaces kidney func-

tion and improves patient quality of life.

The Medicare program entitles every American suffering from kidney failure—regardless of age—to lifesaving dialysis at a cost of nearly \$35 billion annually, more than the National Institutes of Health’s total budget. Despite this commitment to care for patients with kidney diseases, little innovation in the field of kidney treatment has occurred for decades.

“ASN believes a prize competition has the power to catalyze the radical degree of change patients deserve and to ignite the science that is poised to develop life-changing solutions,” Harris said.

Michelle A. Josephson, MD, FASN, former chair of the ASN Transplant Advisory Group, made the kidney disease XPRIZE announcement on behalf of ASN.

“It was wonderful to see the White House recognize the problem of kidney failure, the large number of people affected by kidney failure, and that treatments need innovation and improvement,” Josephson said. “As excellent as our interventions are, they are not good enough; we really need improvements in the dialysis field.”

Following a morning of panel discussions and other announcements of com-

mitments to advance the goals of increasing access to transplantation, participants divided into breakout groups—including one group focused on innovation opportunities. In that discussion, XPRIZE emerged as “really the subject of the roundtable with members of the FDA, CMS, and some of the other scientific agencies there, talking about the best way to get this implemented and to move things forward,” recounted ASN Public Policy Board Chair John R. Sedor, MD, FASN.

“We also focused on kidney diseases under-recognized, as research in kidney diseases has been underinvested, and we asked the White House to help us raise awareness about the problem kidney disease is for patients across the country and in fact, worldwide,” Sedor said.

In addition to pledging the first \$7 million for the kidney disease XPRIZE, ASN announced the Kidney Innovation Initiative—a partnership with the US Department of Veterans Affairs (VA) that challenges innovators worldwide to compete in developing technology resources that improve quality of life and outcomes for people with kidney diseases and those anticipating a kidney transplant.

Also at the summit, KHI committed to initiate the development of a roadmap that will describe scientific, technical, and regulatory milestones needed to achieve the goal of creating a bio-artificial or bioengineered alternative to dialysis as renal replacement therapy. The roadmap will consider challenges to development, provide “state of the art” expectations for entrepreneurs and other technology developers, and spur innovation in producing functioning kidney replacements by engaging stakeholders, identifying research priorities to alleviate critical knowledge gaps, and advancing the science of alternatives to dialysis.

The White House asked participating organizations, companies, and other stakeholders to report back on progress concerning the goals and announcements set at the summit in 6 months.

“We think this is a very positive step that the White House has identified kidney disease broadly as an issue which is very important for the country’s health. We are delighted that they took the time and energy to put together this conference, and we’re hoping this is just the beginning of a much larger initiative,” Sedor said. ●

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