Healing kidneys with nanotechnology

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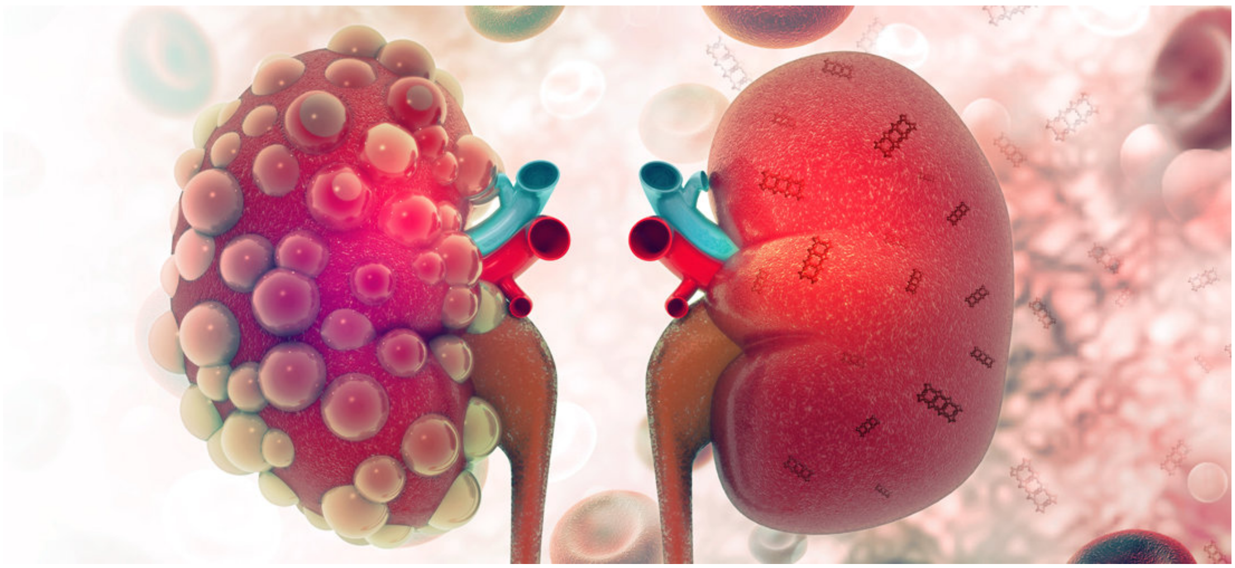


The illustration shows a diseased kidney on the left and a healthy kidney on the right, after rectangular DNA nanostructures migrated and accumulated in the kidney, acting to alleviate damage due to oxidative stress. Credit: Shireen Dooling

Each year, there are some 13.3 million new cases of acute kidney injury (AKI), a serious affliction. Formerly known as acute renal failure, the ailment produces a rapid buildup of nitrogenous wastes and decreases urine output, usually within hours or days of disease onset. Severe complications often ensue.

AKI is responsible for 1.7 million deaths annually. Protecting healthy kidneys from harm and treating those already injured remains a significant challenge for modern medicine.

In new research appearing in the journal *Nature Biomedical Engineering*, Hao Yan and his colleagues at the University of Wisconsin-Madison and in China describe a new method for treating and preventing AKI. Their technique involves the use of tiny, self-assembling forms measuring just billionths of a meter in diameter.

The triangular, tubular and rectangular shapes are designed and built using a method known as DNA origami. Here, the base pairing properties of DNA's four nucleotides are used to engineer and fabricate DNA origami nanostructures (DONs), which self-assemble and preferentially accumulate in kidneys.

"The interdisciplinary collaboration between nanomedicine and the in-vivo imaging team led by professor Weibo Cai at the University of Wisconsin-Madison and the DNA nanotechnology team has led to a novel application—applying DNA origami nanostructures to treat acute kidney injury," Yan says. "This represents a new horizon for DNA nanotechnology research."

Experiments described in the new study—conducted in mice as well as human embryonic kidney cells—suggest that DONs act as a rapid and active kidney protectant and may also alleviate symptoms of AKI. The distribution of DONs was examined with positron emission tomography (PET). Results showed that the rectangular nanostructures were particularly successful, protecting the kidneys from harm as effectively as the leading drug therapy and alleviating a leading source of AKI known as oxidative stress.

The study is the first to explore the distribution of DNA nanostructures in a living system by means of quantitative imaging with PET and paves the way for a host of new therapeutic approaches for the treatment of AKI as well as other renal diseases.

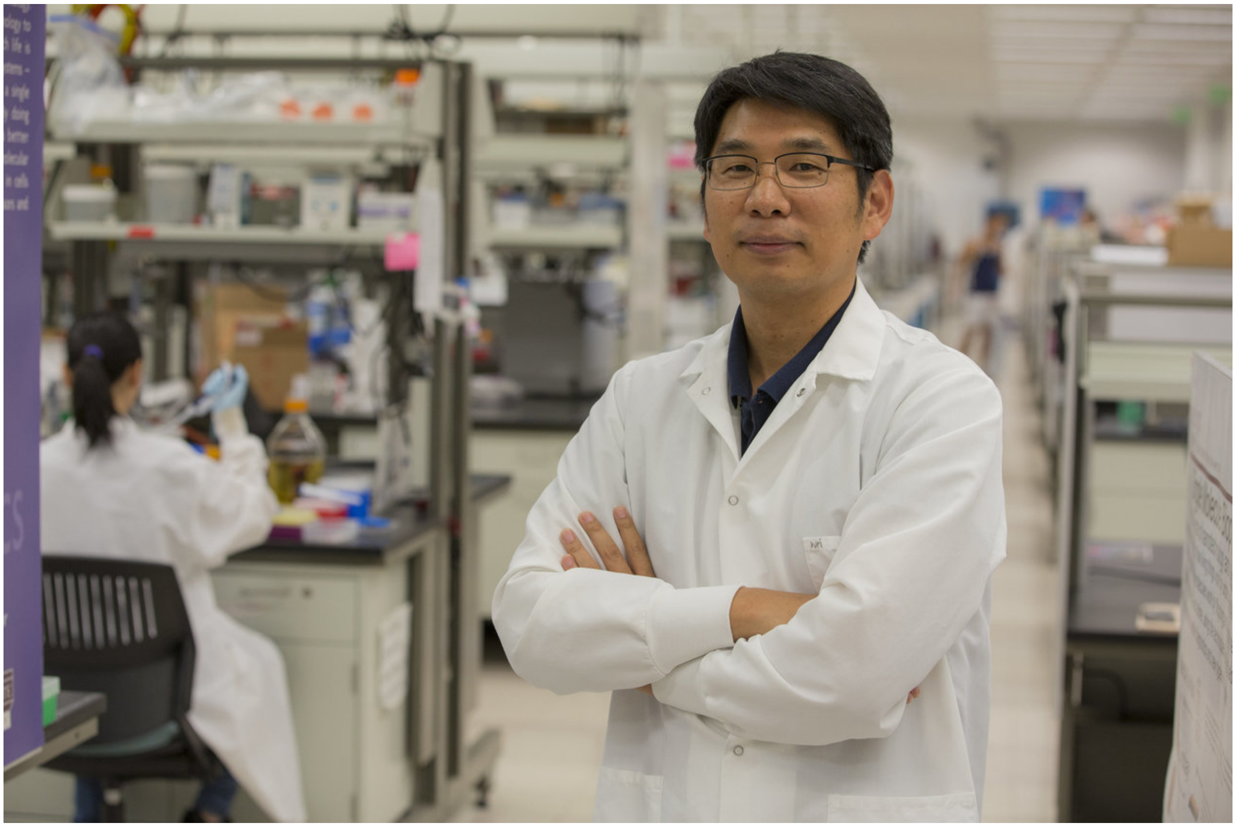
"This is an excellent example of team science, with multidisciplinary and multinational collaboration," Cai said. "The four research groups are located in different countries, but they communicate regularly and have synergistic expertise. The three equally-contributing first authors (Dawei Jiang, Zhilei Ge, Hyung-Jun Im) also have very different backgrounds, one in radiolabeling and imaging, one in DNA nanostructures, and the other in clinical nuclear medicine. Together, they drove the project forward."

Vital organ

Kidneys perform essential roles in body, removing waste and extra water from the blood to form urine. Urine then flows from the kidneys to the bladder through the ureters. Wastes in the blood are produced from the normal breakdown of active muscle and from foods, which the body requires for energy and self-repair.

Acute kidney injury can range considerably in severity. In advanced AKI, kidney transplantation is required as well as supportive therapies including rehydration and dialysis. Contrast-induced AKI, a common form of the illness, is caused by contrast agents sometimes used to improve the clarity of medical imaging. An anti-oxidant drug known as N-acetylcysteine (NAC) is used clinically to protect the kidneys from toxic assault during such procedures, but poor bioavailability of the drug in the kidneys can limit its effectiveness. (Currently, there is no known cure for AKI.)

Nanomedicine—the engineering of atoms or molecules at the nanoscale for biomedical applications—represents a new and exciting avenue of medical exploration and therapy. Recent research in the field has driven advances leading to improved imaging and therapeutics for a range of diseases, including AKI, though the use of nanomaterials within living systems in order to treat kidney disease has thus far been limited.



Hao Yan directs the Biodesign Center for Molecular Design and Biomimetics and is the Martin D. Glick Distinguished Professor in the School of Molecular Sciences at ASU. Credit: The Biodesign Institute at Arizona State University

The base-pairing properties of nucleic acids like DNA and RNA enable the design of tiny programmable structures of predictable shape and size, capable of performing a multitude of tasks. Further, these nanoarchitectures are desirable for use in living systems due to their stability, low toxicity, and low immunogenicity.

New designs

The current study marks the first investigation of DNA origami nanostructures within living organisms, using quantitative imaging to track their behavior. The PET imaging used in the study allowed for a quantitative and reliable real-time method to study the circulation of DONs in a living organism and to assess their physiological distribution. Rectangular DONs were identified as the most effective therapeutic to treat AKI in mice, based on the PET analysis.

Yan and his colleagues prepared a series of DONs and used radio labeling to study their behavior in mouse kidney, using PET imaging. The PET scans showed that the DONs had preferentially accumulated in the kidneys of healthy mice as well as those with induced AKI. Of the three shapes used in the experiments, the rectangular DONs provided the greatest benefit in terms of protection and therapy and were comparable in their effect to the drug NAC, considered the gold standard treatment for AKI.

Patients with kidney disease often have accompanying maladies, including a high incidence of cardiovascular disease and malignancy. Acute kidney illness may be induced through the process of oxidative stress, which results from an increase in oxygen-containing waste products known as reactive oxygen species, that cause damage to lipids, proteins and DNA. This can occur when the delicate balance of free radicals and anti-oxidant defenses becomes destabilized, causing inflammation and accelerating the progression of renal disease. (Foods and supplements rich in antioxidants act to protect cells from the harmful effects of reactive oxygen species.)

Safeguarding kidneys with DNA geometry

The protective and therapeutic effects of the DONs described in the new study are due to the ability of the nanostructures to scavenge reactive oxygen species, thereby insulating vulnerable cells from damage due to oxidative stress. This effect was studied in human embryonic kidney cell lines as well as in living mice. The accumulation of the nanostructures in both healthy and diseased kidneys provided an increased therapeutic effect compared with traditional AKI therapy. (DONs alleviated oxidative stress within 2 hours of incubation with affected kidney cells.)

Improvement in AKI kidney function—comparable with high-dose administration of the drug NAC— was observed following the introduction of nanostructures. Examination of stained tissue samples further confirmed the beneficial effects of the DONs in the kidney.

The authors propose several mechanisms to account for the persistence in the kidneys of properly folded origami nanostructures, including their resistance to digestive enzymes, avoidance of immune surveillance and low protein absorption.

Levels of serum creatinine and blood urea nitrogen (BUN) were used to assess renal function in mice. AKI mice treated with rectangular DONs displayed improved kidney excretory function comparable to mice receiving treatment using the mainline drug NAC.

Further, the team established the safety of rectangular DONs, evaluating their potential to elicit an immune response in mice by examining blood levels of interleukin-6 and tumor necrosis factor alpha. Results showed the DONs were non-immunogenetic and tissue staining of heart, liver, spleen lungs and kidney revealed their low toxicity in primary organs, making them attractive candidates for clinical use in humans.

Based on the effective scavenging of reactive oxygen species by DONs in both human kidney cell culture and living mouse kidney, the study concludes that the approach may indeed provide localized protection for kidneys from AKI and may even offer effective treatment for AKI-damaged kidneys or other renal disorders.

The successful proof-of-concept study expands the potential for a new breed of therapeutic programmable nanostructures, engineered to address far-flung medical challenges, from smart drug delivery to precisely targeted organ and tissue repair.

More information: Dawei Jiang et al, DNA origami nanostructures can exhibit preferential renal uptake and alleviate acute kidney injury, *Nature Biomedical Engineering* (2018). DOI: 10.1038/s41551-018-0317-8

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