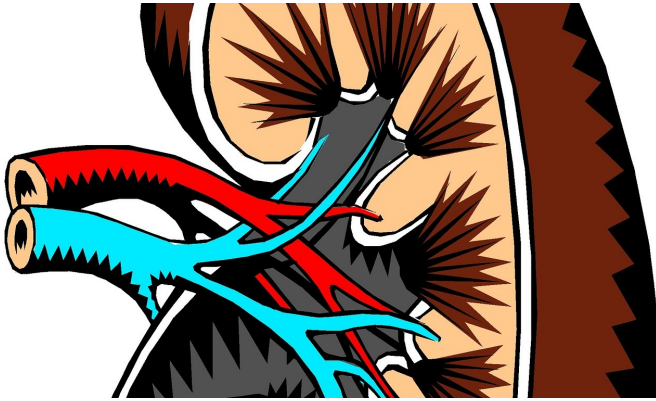


New compound stops progressive kidney disease in its tracks

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Progressive kidney diseases, whether caused by obesity, hypertension, diabetes, or rare genetic mutations, often have the same outcome: The cells responsible for filtering the blood are destroyed. Reporting today in *Science*, a team led by researchers from the Broad Institute of MIT and Harvard, Brigham and Women's Hospital, and Harvard Medical School describes a new approach to prevent death in these essential kidney cells. Studying multiple animal models of kidney disease, the team discovered a compound that can impede loss of the filtration cells and restore kidney function. The work, inspired by an investigation into a genetic form of the condition, has the potential to affect therapeutic research for millions of people suffering from progressive kidney diseases.

"We're ultimately trying to create a drug that can protect these critical filtration cells in the [kidney](#)," said senior author Anna Greka, an institute member at Broad, associate physician at Brigham and Women's Hospital, and assistant professor at Harvard Medical School. "We attacked the problem from the biology of the genetic disease, and we think we've actually found what might be a shared pathway for kidney failure—and a potential way to

treat it."

Treatment options for kidney disease are few and far between, and the last 40 years have seen virtually no progress in new drug development. Patients who receive a transplant often experience complications, and the majority of patients eventually die on dialysis. Of note, the cost of dialysis care in the United States is 50 billion dollars per year, which dwarfs the entire NIH budget.

In order to address this, Greka and her colleagues began their investigation with a rare genetic type of kidney disease, and, using a [rat model](#), set out to understand the genes, proteins, and pathways involved in the organ's deterioration. The [kidney damage](#) is characterized by loss of the filtration cells, or "podocytes," which normally keep essential proteins in the blood and filter out toxins. When these cells are destroyed, proteins from the blood start spilling out into the urine, a symptom called proteinuria.

Previous work indicated that the genetic mutations in this disease activate a protein called Rac1. Greka's team revealed that Rac1 then activates a protein called TRPC5 in a damaging feedback loop. In diseased kidneys, TRPC5 causes an influx of calcium ions into the podocyte, eventually destroying it. The researchers designed and tested a variety of compounds to find one that could block this process, and identified a small molecule they called AC1903 (named after Anna Greka and co-author Corey Hopkins of the University of Nebraska Medical Center College of Pharmacy) that looked promising.

In a genetic rat model of progressive kidney disease, AC1903 protected the kidney's filtration cells. Even when animals began treatment at advanced stages of the disease, AC1903 was able to prevent further podocyte loss and suppress proteinuria, indicating restored [kidney function](#).

"We could literally count the podocytes and see that the [cells](#) were preserved with this treatment," said Greka. "We learned from the genetics, identified the pathway, and then targeted that cellular biology."

But the team didn't stop there. The researchers predicted that the TRPC5 mechanism might play a similar role in other types of progressive kidney disease—even if, in those cases, the damaging feedback loop was kickstarted from chronic disorders such as high blood pressure, rather than a specific genetic mutation.

The team tested AC1903 in a rat model of kidney disease caused by hypertension and saw the same results: The treatment preserved kidney podocytes and prevented the organs from failing, even in advanced disease.

The results suggest that TRPC5 channels are activated by a variety of kidney stressors, and that TRPC5 inhibitors may be able to broadly prevent a breakdown of the kidney filter. These compounds may form the basis for much-needed, mechanistically based therapies for progressive kidney diseases.

"Even after we see this rip-roaring, terrible disease that just wreaks havoc on the kidneys, we were able to prevent further damage in these rat models," said Greka. "Of course, we now need to test TRPC5 inhibitors in clinical studies in patients, but the results are very exciting. The field has waited a very long time—decades, really—for a genetically-inspired, mechanism-based therapy. I'm delighted that our team has contributed to this finally approaching a reality."

More information: Y. Zhou et al., "A small-molecule inhibitor of TRPC5 ion channels suppresses progressive kidney disease in animal models," *Science* (2017).

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