

# Novel drug acts in unique way to protect against kidney injury

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New research reveals the mechanism by which an experimental drug can protect the kidneys from sudden damage, called acute kidney injury (AKI). The findings, which appear in an upcoming issue of the *Journal of the American Society of Nephrology* (JASN), show how the drug may be able to save many lives and cut medical costs related to the condition.

AKI, which affects millions of people worldwide and increases the risk of developing [chronic kidney disease](#) and dying early, is most often caused by reduced or blocked blood flow to the kidney (called ischemia). This can occur in many clinical situations, including shock, trauma, sepsis, heart attack, and during heart surgery. Taking high potency statins to [lower cholesterol](#) is also linked with an increased risk for AKI. Unfortunately, there are no approved drugs that reduce the incidence or severity of AKI.

Ischemia damages cells' mitochondria, which make a form of energy called ATP that keeps cells alive and functioning. When mitochondria are damaged by ischemia, cells have a limited ability to regenerate ATP when blood flow is later restored. This causes cell death and inflammation.

In studies designed to investigate potential [drug targets](#) for AKI, Alexander Birk, PhD, Shaoyi Liu, MD, and Hazel Szeto, MD, PhD (Weill Cornell Medical College) and their colleagues recently reported that a novel agent called SS-31 (also known as Bendavia™) can accelerate ATP recovery after ischemia and reduce AKI, but its

mechanism of action remained unclear. Their latest research—which uses chemical, biochemical, and [structural biology](#) approaches—shows that Bendavia helps protect a unique fatty compound, or phospholipid (called cardiolipin), on the inner mitochondrial membrane that is critical in the pathway that leads to ATP production. Cardiolipin helps form the foldings of the inner mitochondrial membrane that are studded with protein complexes involved in ATP production. The loss of cardiolipin during ischemia causes mitochondria to lose their membrane folding and reduce their ability to produce ATP. Using a method called transmission electron microscopy, the researchers were able to confirm that treatment with Bendavia prior to kidney ischemia dramatically preserved mitochondrial membrane foldings and accelerated ATP recovery to protect cell structure and function.

"Recent studies have shown that AKI has more than doubled since 2000, causing nearly 39,000 deaths in 2009 alone. The discovery of a therapeutic agent that can minimize AKI will have enormous medical and economic impact," said Dr. Szeto. "Bendavia is a first-in-class [mitochondria](#) protective agent that holds promise in preventing not only AKI, but also ischemia-related injury in multiple organs," she added. Bendavia is currently being evaluated in several phase 2 clinical trials in the United States and Europe for heart and kidney disease.

In an accompanying editorial, Andrew Hall, PhD (University of Zurich, in Switzerland) wrote, "It seems clear that SS-31 can ameliorate adverse changes in mitochondrial structure and function in ischemic AKI, with the result that tubular cell structure and overall kidney function are better preserved."

**More information:** The article, entitled "Cardiolipin as a Novel Target to Re-Energize Ischemic Mitochondria," will appear online on July 11, 2013, [doi: 10.1681/ASN.2012121216](https://doi.org/10.1681/ASN.2012121216).

The editorial, entitled "Maintaining Mitochondrial Morphology in AKI:

Looks Matter," will appear online on July 11, 2013, [doi: 10.1681/ASN.2013050519](https://doi.org/10.1681/ASN.2013050519).

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