

Study suggests drug intervention may prevent doxorubicin-induced cardiac injury

January 25 2021, by Emily Caldwell



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There could be an intervention on the horizon to help prevent heart damage caused by the common chemotherapy drug doxorubicin, new research suggests.

Scientists found that this chemo drug, used to treat many types of solid tumors and [blood cancers](#), is able to enter heart [cells](#) by hitchhiking on a specific type of protein that functions as a transporter to move a drug from the blood into [heart cells](#).

By introducing another [anti-cancer drug](#) in advance of the chemo, the researchers were able to block the transporter protein, effectively stopping the delivery of doxorubicin to those [cardiac cells](#). This added drug, nilotinib, has been previously found to inhibit activation of other, related transport proteins.

The current findings are based on lab experiments in [cell cultures](#) and mice. The researchers are continuing studies with hopes to start designing human trials of the drug intervention later in 2021.

"The proposed intervention strategy that we'd like to use in the clinic would be giving nilotinib before a chemotherapy treatment to restrict doxorubicin from accessing the heart," said first author Kevin Huang, who graduated in December from The Ohio State University with a Ph.D. in pharmaceutical sciences. "We have pretty solid preclinical evidence that this intervention strategy might work."

The study is published today in *Proceedings of the National Academy of Sciences*.

Doxorubicin has long been known for its potential to increase patients' risk for serious heart problems, with symptoms sometimes surfacing decades after chemo, but the mechanisms have been a mystery. The risk is dose-dependent—the more doses a patient receives, the higher the risk for cardiac dysfunction later in life that includes arrhythmia and a reduction in blood pumped with each contraction, a hallmark symptom of congestive heart failure.

Huang worked in the lab of senior study authors Shuiying Hu and Alex Sparreboom, faculty members in pharmaceuticals and pharmacology and members of the Ohio State Comprehensive Cancer Center's Translational Therapeutics program. This research and other studies targeting different transport proteins to prevent chemo-related nerve pain were also part of Huang's dissertation.

"Our lab works on the belief that drugs don't naturally or spontaneously diffuse into any cell they would like to. We hypothesize that there are specialized protein channels found on specific cells that will facilitate movement of internal or external compounds into the cell," Huang said.

For this work, the team focused on cardiomyocytes, cells composing the muscle behind the heart contractions that pump blood to the rest of the body. The researchers examined cardiomyocytes that were reprogrammed from skin cells donated by two groups of cancer patients who had been treated with doxorubicin—some who suffered cardiac dysfunction after chemo, and others who did not.

The scientists found that the gene responsible for production of the transport protein in question, called OCT3, was highly expressed in the cells derived from cancer patients who had experienced [heart](#) problems after treatment with doxorubicin.

"We used mouse models and engineered cell models to demonstrate

doxorubicin does transport through this protein channel, OCT3," Huang said. "We then looked prospectively into what this means from a therapy perspective."

Blocking OCT3 became the goal once researchers found that genetically modified mice lacking the OCT3 gene were protected from [heart damage](#) after receiving doxorubicin. Further studies showed that inhibiting OCT3 did not interfere with doxorubicin's effectiveness against cancer.

Hu and Sparreboom have specialized in a class of drugs called [tyrosine kinase inhibitors](#), which block specific enzymes related to many cell functions. Nilotinib, a chronic myeloid leukemia drug, is a tyrosine kinase inhibitor that is also known to act on OCT3.

Additional experiments showed that cardiac function was preserved in mice that were pretreated with nilotinib before receiving doxorubicin—and the pretreatment did not interfere with doxorubicin's ability to kill cancer cells.

The researchers plan to gather additional supporting evidence before pursuing a Phase 1 clinical trial testing the safety of two components of the proposed [drug](#) intervention in humans: blocking the function of the OCT3 transporter protein and demonstrating that inhibiting OCT3 in patients treated with [doxorubicin](#) protects those patients' hearts from chemo-induced injury.

More information: Kevin M. Huang et al., "Targeting OCT3 attenuates doxorubicin-induced cardiac injury," *PNAS* (2020). www.pnas.org/cgi/doi/10.1073/pnas.2020168118

Provided by The Ohio State University

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