

## Experimental drug may prevent chemotherapy drug from damaging the heart

March 4 2020, by Deirdre Branley







Richard Kitsis. Credit: Albert Einstein College of Medicine

The commonly used chemotherapy drug doxorubicin can damage heart muscle, in some cases leading to severe or lethal heart failure. A new study led by Albert Einstein College of Medicine researchers and involving zebrafish and mice suggests that the experimental drug BAI1 can prevent doxorubicin from damaging the heart without lessening its anti-cancer properties. The study was published online in the journal *Nature Cancer*.

"In addition to providing a way to prevent <u>doxorubicin</u>-induced cardiotoxicity, a drug like BAI1 might allow oncologists to use doxorubicin at higher cumulative doses and in combinations with other cardiotoxic drugs to treat cancer more effectively," said co-study leader Richard N. Kitsis, M.D., professor of medicine and of <u>cell biology</u>, the Dr. Gerald and Myra Dorros Chair in Cardiovascular Disease, director of the Wilf Family Cardiovascular Research Institute at Einstein, and a cardiologist at Montefiore Health System.

## **Doxorubicin and Heart Damage**

The incidence of <u>heart damage</u> from doxorubicin is highest among certain groups of cancer patients: older adults, especially those with existing <u>heart</u> disease or risk factors for heart disease; children with hardto-treat cancers like sarcoma, who often require high doses of the drug; patients who receive multiple doses because of recurrent cancer; and those who have received other cardiotoxic treatments, such as radiation therapy.

In use since 1974, doxorubicin is believed to lead to loss of <u>heart muscle</u> cells through two distinct cell suicide pathways: apoptosis and necrosis.



A protein called BAX has long been known to play a role in apoptosis. In a <u>2012 study</u> in the *Proceedings of the National Academy of Sciences*, Dr. Kitsis' lab discovered that BAX also leads to necrosis. "So we had a single target—BAX—for blocking both types of cell death stemming from the use of doxorubicin," said Dr. Kitsis.

Dr. Kitsis teamed with Evripidis Gavathiotis, Ph.D., professor of biochemistry and of medicine at Einstein, to search for compounds that could inhibit BAX. Dr. Gavathiotis, in a 2008 paper in Nature, defined how BAX changes its shape to transform from a quiescent form to a lethal one, enabling his lab subsequently to discover small molecule activators and inhibitors of BAX. As reported in *Nature Chemical Biology* in 2019, the researchers developed several small molecules, including BAI1, which can bind to BAX and block its transformation.

## **Protecting Heart Muscle**

"In our new study, we show that BAI1 works by preventing BAX from converting to its active, lethal form," said Dr. Gavathiotis, a co-leader of the study. "This stops BAX from moving from the cytoplasm into the mitochondria—the cell's powerhouses—where BAX activates both apoptosis and necrosis."

The researchers used zebrafish and mice to test whether BAI1 can protect the heart against doxorubicin. Giving doxorubicin alone to the animals led to apoptosis and necrosis and caused heart damage. But the animals did not experience cardiotoxicity when doxorubicin and BAI1 were administered simultaneously. BAI1 also did not interfere with doxorubicin's ability to kill cancer cells in mouse models of breast cancer and acute myeloid leukemia.

The BAX inhibitor may also have wider applications. "It's not yet known, but heart damage resulting from some other <u>cancer</u> therapies is



also likely to be BAX-dependent, and therefore may also be preventable by BAI1," said first author Dulguun Amgalan, Ph.D., a postdoctoral fellow in Dr. Kitsis' lab. "BAI1 may also be able to reduce tissue damage caused by heart attack and stroke, both of which kill cells through apoptosis and necrosis."

Based on the prototype drug BAI1, the researchers continue to work on the development of BAX inhibitors and have plans to perform preclinical safety studies to enable testing in human trials.

**More information:** Dulguun Amgalan et al. A small-molecule allosteric inhibitor of BAX protects against doxorubicin-induced cardiomyopathy, *Nature Cancer* (2020). <u>DOI:</u> <u>10.1038/s43018-020-0039-1</u>

Provided by Albert Einstein College of Medicine

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