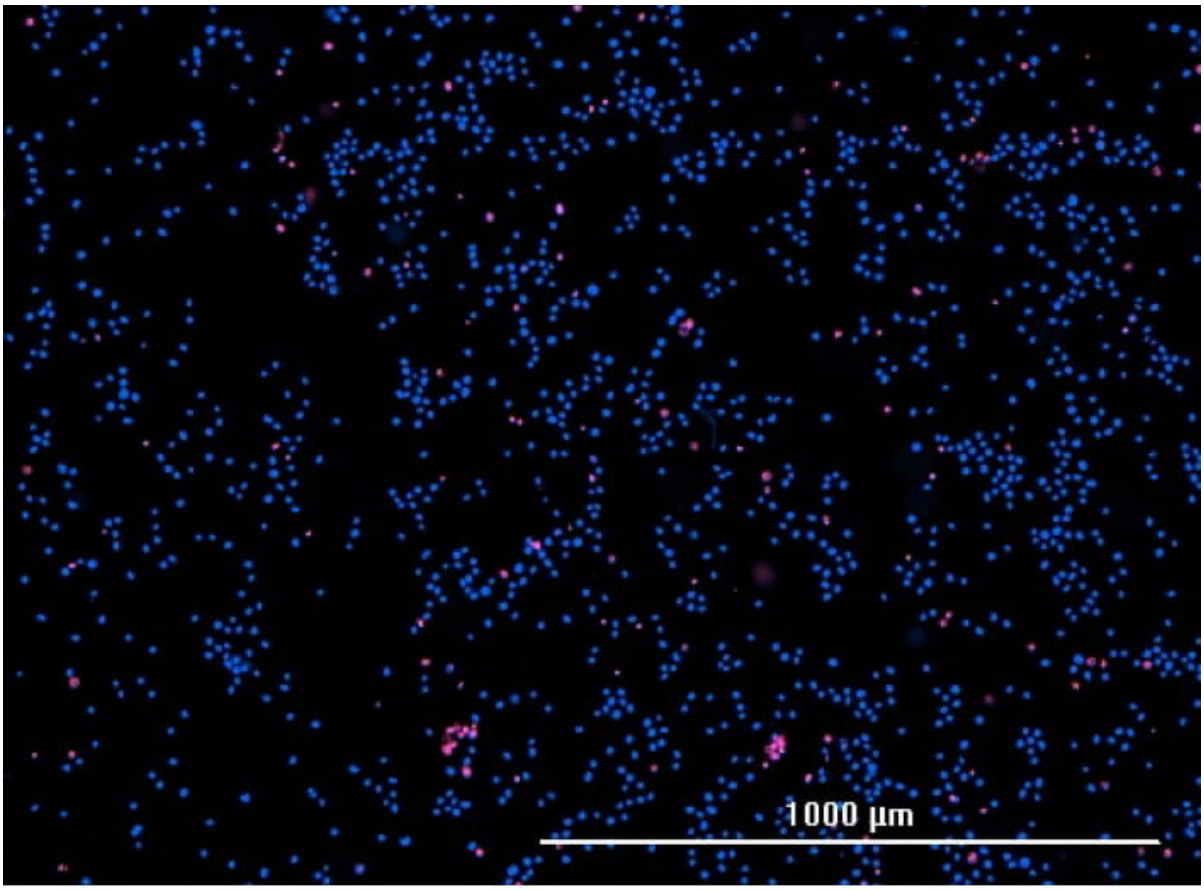
# Cocktail proves toxic to leukemia cells

October 31 2019, by Mike Williams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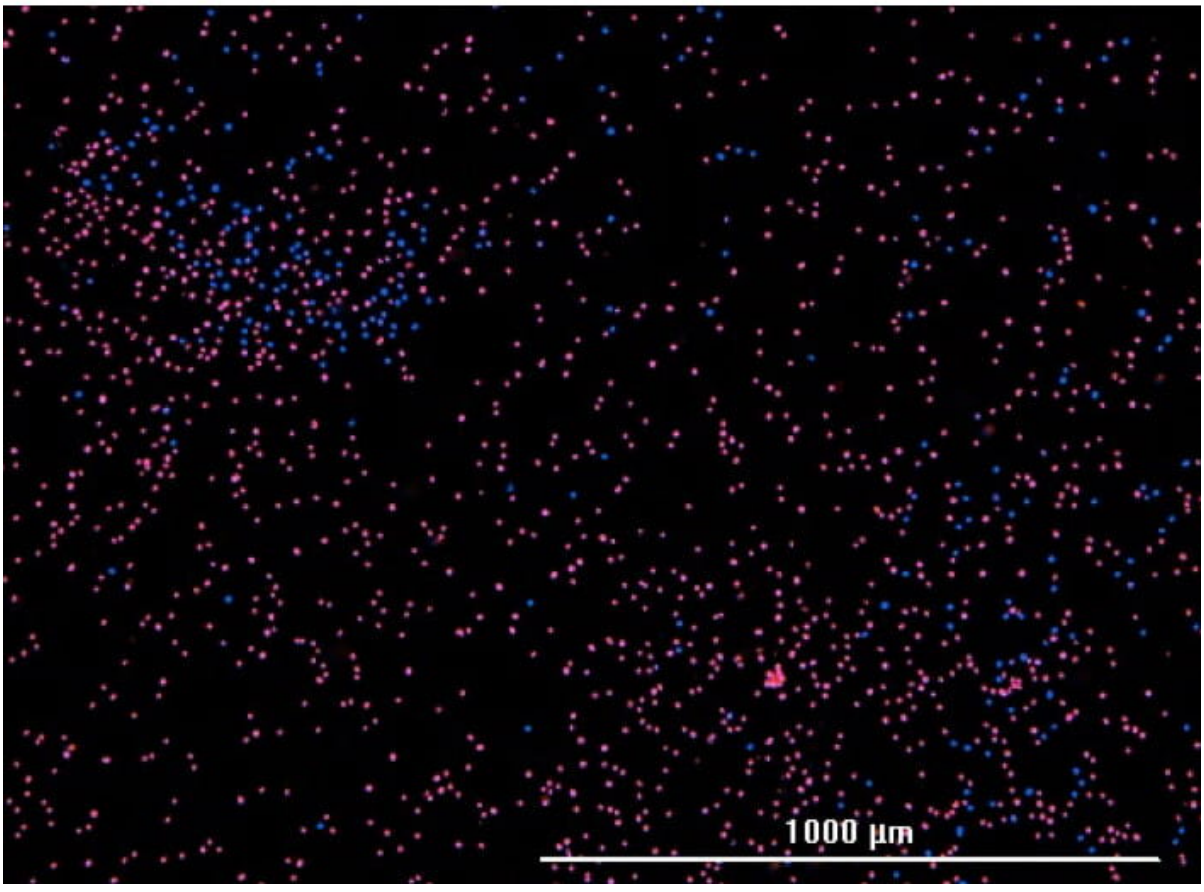
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Microscope images taken at Rice show acute myeloid leukemia cells before (top) and after treatment with a combination of a mitocan cancer drug and a glycolytic inhibitor at concentrations lower than what was necessary to kill healthy cells. Two dyes were used to stain the cells: Blue dye stained all of the cancer cells while a red dye stained only dead cells, which show up as purple in the bottom image. Click on the image for a larger version. Credit: Kirienko Lab

A combination of drugs that affect mitochondria—the power plants inside cells—may become the best weapons yet to fight acute myeloid leukemia, according to Rice University researchers.

A study led by Rice bioscientist Natasha Kirienko and postdoctoral researcher Svetlana Panina found that mitocans, anti-cancer drugs that target mitochondria, are particularly adept at killing leukemia cells, especially when combined with a glycolytic inhibitor, while leaving healthy blood cells in the same sample largely unaffected.

Their open access paper, a collaboration with the University of Texas MD Anderson Cancer Center, appears in the Nature journal *Cell Death & Disease*. The research could lead to new ways to personalize treatment for patients with leukemia.

"We started with the idea of finding an underlying connection between types of cancer and their sensitivity to specific kinds of chemotherapeutics, mitochondria-targeting drugs," Kirienko said. "Our bioinformatic analysis, which included 60 cell lines from nine different cancer types, showed that leukemia cells are particularly sensitive to mitochondrial damage."

The researchers exposed the cell lines to multiple known mitocan molecules. They found low doses of a mitocan/glycolytic inhibitor cocktail killed all of the leukemia cell lines they tested at concentrations lower than what was necessary to kill healthy cells. Conversely, they reported that solid tumor cells, like ovarian cancers, proved highly resistant to mitocans. Glioblastoma cells were sensitive to mitocans, but unfortunately more resistant than healthy blood cells.

In their best experimental results, 86% of targeted leukemia cells were killed, compared to only 30% of healthy blood cells. "A number of drugs currently used in the clinic have some cancer preference, but here we're talking about a five-fold difference in survival," Kirienko said.

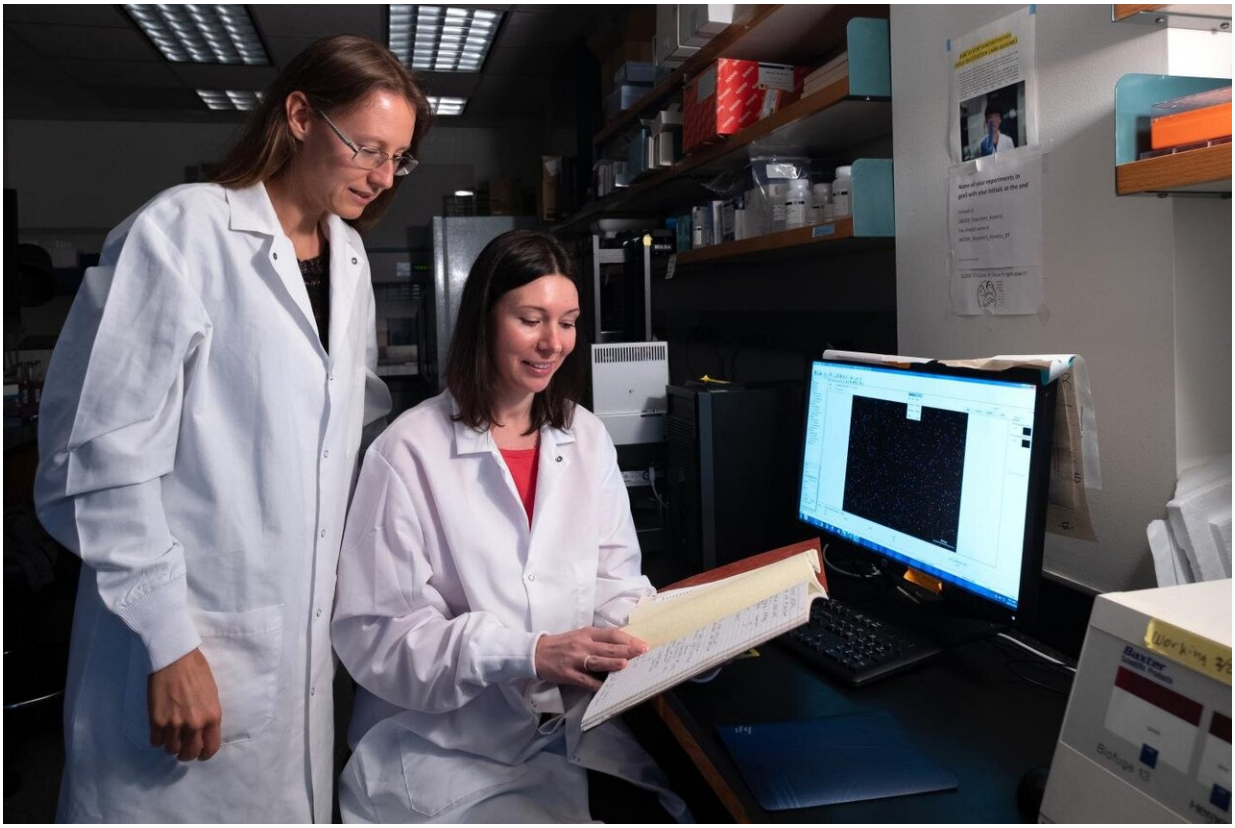
The researchers also showed a significant correlation between how efficiently mitochondria can turn energy from incoming oxygen into useful adenosine triphosphate (ATP) and how resistant they are to treatment.

"The more efficient they are, the more resistant they will be to mitochondria-targeting drugs," Kirienko said. "If this holds true, doctors can perform a relatively simple test of this specific parameter of mitochondrial health from a patient's sample and predict whether the treatment would be effective."

Panina said computational models led them to think the glycolysis pathway could be enlisted to help mitocans. "Glycolysis also provides ATP, so targeting that will decrease energy as well as block the precursor for energy production in mitochondria, which mitocans will exacerbate further," she said. "It led us to believe this combination would have a synergistic effect.

"Cancer cells are usually more metabolically active than normal cells, so we predicted that they be might be more sensitive to this combined

strike, and they are," Panina said.



Rice University bioscientists Natasha Kirienko, left, and Svetlana Panina found a cocktail of cancer-fighting mitocan molecules and a glycolytic inhibitor is effective at fighting acute myeloid leukemia. The discovery could lead to better personalized treatment of the disease. Credit: Jeff Fitlow/Rice University

Kirienko said a presentation of the research she and Panina gave at MD Anderson's recent Metabolism in Cancer Symposium drew a large response. "People were very interested, and they immediately started asking, 'Did you test my favorite drug or combination?' and 'Are you going to test it in a wider panel of cancers?'"

That work is well underway, Panina said. "We're currently doing high-throughput screening of these potential synergistic drug combinations against leukemia cells," she said. "We've gone through 36 combinations so far, building landscapes for each one."

"And we found some that are more effective than what's reported in this paper," Kirienko added. "But we've also found some that are antagonistic—two drugs that negate each other's effects—so it's also important to know what therapeutic cocktails should not go together."

**More information:** Svetlana B. Panina et al, A mechanism for increased sensitivity of acute myeloid leukemia to mitotoxic drugs, *Cell Death & Disease* (2019). DOI: 10.1038/s41419-019-1851-3

Provided by Rice University