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FDA-approved medications may have unexpected use: Stopping deadly ebola

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A class of drugs that includes treatments for breast cancer and infertility appears able to inhibit the deadly, incurable Ebola virus, new research suggests.

As part of a collaborative effort, researchers at the University of Virginia School of Medicine have shown that the drugs clomiphene, which is used to treat female infertility, and toremifene, used to treat breast cancer, can effectively block Ebola infections in mice. The drugs, and others with similar structures, appear to prevent the virus from delivering its RNA into the cytoplasm of cells. Without the ability to deliver its genetic payload, the virus degrades quickly and is removed from the body.

"These are among the first FDA-approved compounds shown to be effective against Ebola in mouse models," U.Va. researcher Judith M. White said. "With a virus this lethal, you want something to combat it."

Ebola infections carry fatality rates of up to 90 percent. It strikes both humans and other primates, and there are fears it could be used as a biological weapon. There's no cure, so it's imperative that scientists find effective treatments. The new discovery eventually could lead to the repurposing of FDA-approved drugs, already available for prescription, to combat the virus.

The findings are the result of an innovative partnership of academia, government and private industry. The drugs' potential use against Ebola

was first identified by investigators at biopharmaceutical company Zalicus and the U.S. Army Medical Research Institute of Infectious Diseases; they then turned to U.Va. for its expertise in figuring out how the drugs worked against the virus. U.Va. has developed an important assay that lets researchers analyze each step of the cellular infection process, allowing them to determine how the two drugs – and potentially other, similar drugs – undercut Ebola.

The U.Va. researchers concluded that the drugs were preventing the virus from fusing with membranes in targeted cells, essentially hemming in the viral RNA.

"Ebola virus is in a race against the clock when it gets into the cell," said Jason Shoemaker, a postdoctoral fellow who developed the assay as a graduate student in White's lab. "We want to lock the door on it."

The research could have important ramifications for understanding the Ebola infection process. "There is a lot about Ebola viruses that is very strange compared to other viruses," Shoemaker said. "Any work that helps uncover more information about the viral entry pathway is helpful."

The U.Va. research posed no health risk, as the researchers used what are known as "virus-like particles" that contain no genetic material.

In evaluating the drugs' potential for stopping Ebola, U.Va. worked closely with both Zalicus and the Army Medical Research Institute, which handled the work involving live viruses.

White noted the unconventional process that led to the discovery of the drugs' anti-Ebola properties. Instead of attempting to develop a drug starting at the molecular level, Zalicus began by looking for existing drugs that could inhibit Ebola.

"This whole approach is the reverse of how a molecular biologist might approach the problem," White said. "If we'd gone with the molecular approach, we would never have looked at this class of drugs."

The findings have been published online by the journal *Science Translational Medicine*. The U.Va. researchers plan to continue their collaborative efforts and will look for drugs that may be even better at battling Ebola than clomiphene and toremifene.

"Our findings suggest we are not talking about one specific drug," Shoemaker said. "It's a whole family. One might be better."

Provided by University of Virginia