

# Protein GRP78 identified as possible universal therapeutic target for multiple viral and bacterial infections

December 29 2014

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A protein called GRP78 could be a universal therapeutic target for treating human diseases like brain cancer, Ebola, Influenza, Hepatitis and superbug bacteria such as MRSE and MRSA, according to a Virginia Commonwealth University-led pre-clinical study published this month in the *Journal of Cellular Physiology*.

By using a [drug combination](#) of the clinically tested OSU-03012 (AR-12) and FDA approved Phosphodiesterase 5 Inhibitors (Viagra, Cialis) to target GRP78 and related proteins, researchers prevented the replication of a variety of major viruses in infected cells, made antibiotic-resistant bacteria vulnerable to common antibiotics and found evidence that [brain cancer](#) stem cells were killed. Data were obtained in multiple brain cancer stem cell types, and using Influenza, Mumps, Measles, Rubella, RSV, CMV, Adenovirus, Cocksakie virus, Chikungunya, Ebola, Hepatitis, *E. coli*, MRSA, MRSE and *N. gonorrhoeae*, among others.

"Basically, we've got a concept that by attacking GRP78 and related proteins: (a) we hurt [cancer cells](#); (b) we inhibit the ability of viruses to infect and to reproduce; and (c) we are able to kill superbug [antibiotic-resistant bacteria](#)," said the study's lead investigator, Paul Dent, Ph.D., Professor in the Department of Biochemistry and Molecular Biology at VCU School of Medicine, and Universal Chair for Signal Transduction.

GRP78 is part of a family of proteins called chaperones. The job of a

chaperone is to help shape chains of amino acids into proteins and then to keep those proteins active in the correct 3D shape. The OSU/Viagra drug combination attacks GRP78 and other chaperones, thereby killing cancer cells. After learning of the drug combination's effect on GRP78 in cancer cells, Dent and his team began to target GRP78 for infectious diseases such as viruses and bacteria.

The chaperone proteins are very important in cancer cells or virus infected cells because these cells make extra protein compared to normal / uninfected cells. The team found that the OSU/Viagra drug combination reduced infectivity via reduced viral receptor expression on the surface of target cells and the prevention of virus replication in [infected cells](#). The drug combination was able to reduce expression of viral receptors for Ebola, Marburg, Hepatitis A, B and C, and Lassa fever viruses. In cancer cells the drug combination reduced the expression of oncogene receptors, too.

In bacteria, the drug combination reduced expression of the equivalent GRP78 protein, in bacteria called Dna K, and induced cell death in pan-antibiotic resistant forms of *E. coli*, MRSE, MRSA and *N. gonorrhoeae*.

"The findings open an avenue of being able to treat viral infections, infections that certainly most people would say we'll never be able to treat; they prove that GRP78 is a "drugable" target to stop viruses from reproducing and spreading," Dent said. "And in the case of bacteria, we have a new antibiotic target, Dna K, that if we're careful and only use the OSU drug in hospitals, we've got something that can help to treat the superbugs."

Dent said that the next steps have already been taken and are leading to new discoveries: "we know in mice that the OSU/Viagra treatment can kill tumor cells but doesn't harm normal tissues like the liver and the heart. Of even more importance we've just discovered that the

OSU/Viagra combination can reduce the levels of proteins called "pumps" in the mouse brain. Pumps are responsible for making [tumor cells](#) resistant to chemotherapy and for stopping life-saving brain cancer chemotherapy from entering into the brain and killing cancer."

VCU researchers previously have found Viagra drug combinations to be beneficial in many ways. In 2010, for example, Rakesh Kukreja, Ph.D., scientific director of the VCU Pauley Heart Center and the Eric Lipman professor in cardiology in the VCU School of Medicine, in collaboration with Dent, found that Viagra improved the effectiveness of the breast cancer treatment Doxorubicin while protecting the heart from harm caused by the chemotherapy. In 2013 and 2014 Dr. Dent obtained similar data with Viagra and conventional chemotherapy in bladder, pancreatic and pediatric brain cancer [cells](#). Based on work from Dent's group, in the spring of 2015 a new phase I clinical trial will open at VCU Massey Cancer Center combining the colon cancer drug regorafenib with Viagra for all solid tumor patients.

**More information:** The full article is available online at [onlinelibrary.wiley.com/doi/10 ... 2/jcp.24919/abstract](https://onlinelibrary.wiley.com/doi/10.1002/jcp.24919/abstract)

Provided by Virginia Commonwealth University

Citation: Protein GRP78 identified as possible universal therapeutic target for multiple viral and bacterial infections (2014, December 29) retrieved 26 April 2024 from <https://medicalxpress.com/news/2014-12-protein-grp78-universal-therapeutic-multiple.html>

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