Targeted viral therapy destroys breast cancer stem cells in preclinical experiments

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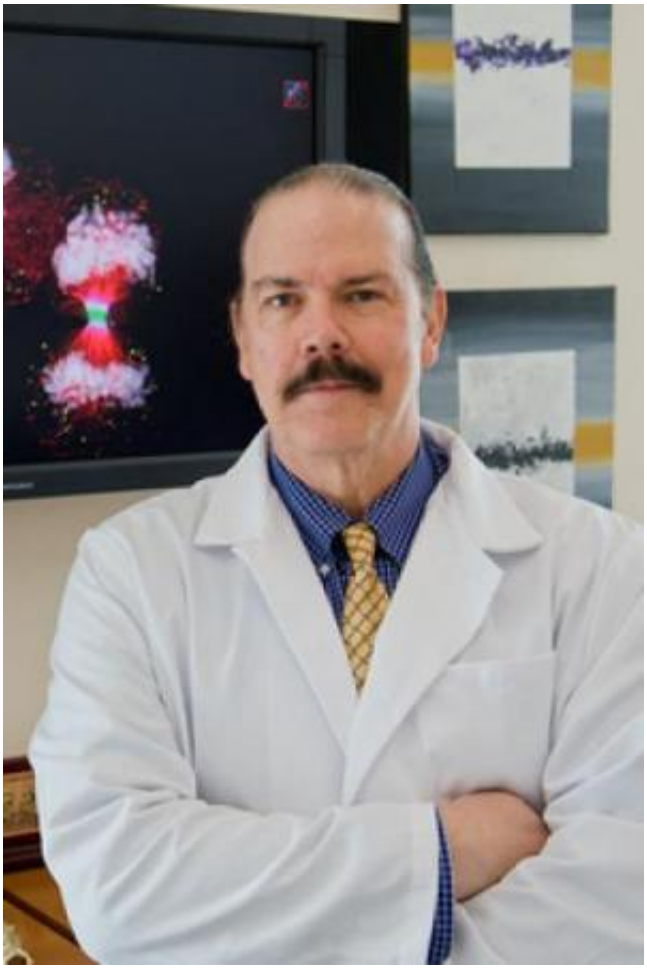

This image shows Paul B. Fisher, Ph.D., Thelma Newmeyer Corman Endowed Chair in Cancer Research and co-leader of the Cancer Molecular Genetics program at VCU Massey, chairman of VCU School of Medicine's Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine. Credit: Virginia Commonwealth University

A promising new treatment for breast cancer being developed at Virginia Commonwealth University Massey Cancer Center and the VCU Institute of Molecular Medicine (VIMM) has been shown in cell culture and in animal models to selectively kill cancer stem cells at the original tumor site and in distant metastases with no toxic effects on healthy cells, including normal stem cells. Cancer stem cells are critical to a cancer's ability to recur following conventional chemotherapies and radiation therapy because they can quickly multiply and establish new tumors that are often therapy resistant.

The study, published in the *International Journal of Cancer*, focuses on a gene originally cloned in the laboratory of primary investigator Paul B. Fisher, M.Ph., Ph.D. The gene, melanoma differentiation associated gene-7 (mda-7), also known as interleukin (IL)-24, has been shown to directly impact two forms of cell suicide known as apoptosis and toxic autophagy, regulate the development of new blood vessels and also play a role in promoting cancer cell destruction by the immune system. In the present study, the researchers used a recombinant adenovirus vector, an engineered virus with modified genetic material, known as Ad.mda-7 to deliver the mda-7/IL-24 gene with its encoded protein directly to the tumor.

"Therapy with the mda-7/IL-24 gene has been shown to be safe in a phase I clinical trial involving patients with advanced cancers, and prior studies in my laboratory and with collaborators have shown that the gene could also be effective against breast, prostate, lung, colorectal, ovarian, pancreatic and brain cancers," says Fisher, Thelma Newmeyer Corman Endowed Chair in Cancer Research and co-leader of the Cancer Molecular Genetics program at VCU Massey, chairman of VCU School of Medicine's Department of Human and Molecular Genetics and director of the VCU Institute of Molecular Medicine. "Our study demonstrates that this therapy may someday be an effective way to eradicate both early and advanced stage breast cancer, and could even be

used to reduce the risk of cancer recurrence."

The researchers found that infection of human breast cancer cells with the adenovirus decreased the proliferation of breast cancer stem cells without affecting normal breast stem cells. It was also shown to induce a stress response in the cells that led to apoptosis by disrupting Wnt/B-catenin signaling, a process cells rely upon to transmit signals that initiate biological functions critical to survival. In mouse models, the therapy profoundly inhibited the growth of tumors generated from breast cancer stem cells and also killed cancer cells in distant, uninjected tumors.

Since discovering the mda-7/IL-24 gene, Fisher and his team have worked to develop better ways to deliver it to cancer cells, including two cancer "terminator" viruses known as Ad.5-CTV and Ad.5/3-CTV. Cancer terminator viruses are unique because they are designed to replicate only within cancer cells while delivering immune-modulating and toxic genes such as MDA-7/IL-24. Coupled with a novel stealth delivery technique known as ultrasound-targeted microbubble destruction (UTMD), researchers can now systemically deliver viruses and therapeutic genes and proteins directly to tumors and their surrounding tissue (microenvironment) at both primary and metastatic tumor sites. UTMD uses microscopic, gas-filled bubbles that can be paired with viral therapies, therapeutic genes and proteins, and imaging agents and can then be released in a site and target-specific manner via ultrasound. Fisher and his colleagues are pioneering this approach and have already reported success in experiments utilizing UTMD technology and mda-7/IL-24 gene therapy in prostate and colorectal cancer models.

"We are hopeful that this targeted gene therapy could be safely combined with conventional chemotherapies to significantly improve outcomes for patients with breast cancer and potentially a variety of other cancers," says Fisher. "When paired with promising new delivery

techniques such as UTMD, physicians may one day be able to better target site-specific cancers and also monitor the effectiveness of these types of therapies in real time."

More information: onlinelibrary.wiley.com/doi/10 … 2/ijc.28289/abstract

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