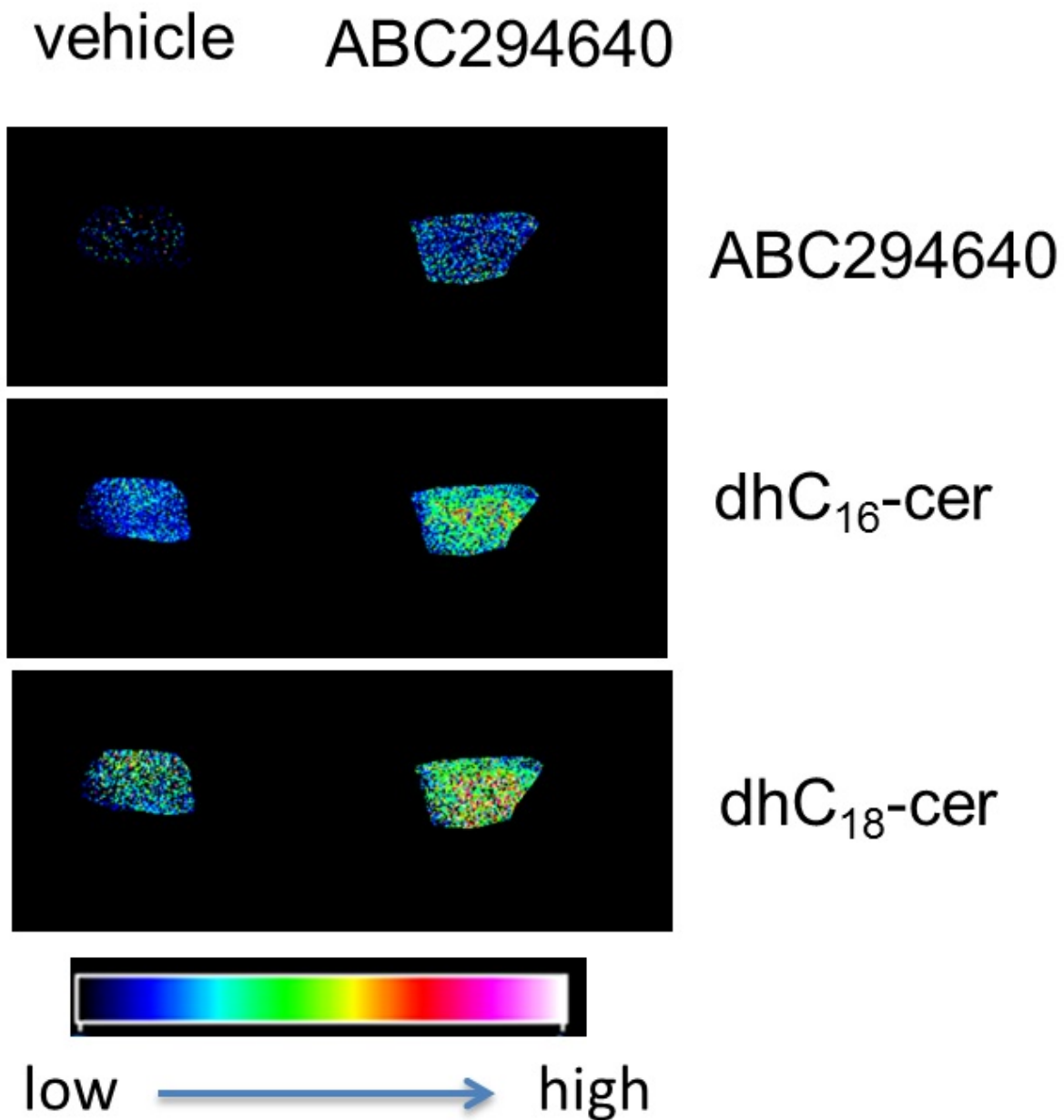


# A new class of drug slows growth of castration-resistant prostate cancer cells

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The signal for ABC294640 is detected only when the drug but not the vehicle was administered (upper panel). The intensity for two different dihydroceramides is shown in the middle panel (dhC16-cer) and lower panel (dhC18-cer). A color bar indicates the signal intensity Credit: Adapted with permission from the American Association for Cancer Research : Venant H, *et al.* The Sphingosine kinase 2 inhibitor ABC294640 reduces the growth of prostate cancer cells and results in accumulation of dihydroceramides In vitro and In vivo. *Molecular Cancer Therapeutics*; 2015 Dec; 14(12):2744-52. doi: 10.1158/1535-7163.MCT-15-0279

A first-in-class sphingosine kinase 2 inhibitor slowed the growth of castration-resistant prostate cancer cells, in part by inhibiting the enzyme dihydroceramide desaturase (DEGS), but did not kill them, according to the results of preclinical in vitro and in vivo studies published in the December 2015 issue of *Molecular Cancer Therapeutics* by researchers at the Medical University of South Carolina (MUSC) and others.

Christina Voelkel-Johnson, Ph.D., Associate Professor of Microbiology and Immunology at MUSC, led the study, which was funded by a pilot grant from MUSC Hollings Cancer Center. Co-authors include Charles D. Smith, Ph.D., who developed the compound and led an earlier phase 1 trial at MUSC Hollings Cancer Center; MUSC Health oncologist Michael Lilly, M.D., a prostate cancer specialist; and Richard Drake, Ph.D., director of the Proteomics Core at MUSC, who has developed techniques to use MALDI imaging mass spectrometry to measure sphingolipid levels.

Sphingosine kinase inhibitors are a new category of drugs that reduce the generation of sphingosine-1-phosphate. This lipid signaling molecule promotes cancer cell growth and survival, thereby supporting the

development of resistance to chemotherapy and radiation by cancer cells.

The study reported in *Molecular Cancer Therapeutics* showed that the compound YELIVA (ABC294640; RedHill Biopharma Ltd.; Tel Aviv, Israel) slowed prostate cancer cell proliferation by inhibiting sphingosine kinase 2, but also that it did something unexpected. "By inhibiting a second sphingolipid enzyme (DEGS), the compound increases levels of another class of lipids—dihydroceramides—which may contribute to the growth suppressive effects of the drug," says Voelkel-Johnson.

This study is the first to show activity for this compound against DEGS and to potentially link inhibition of DEGS to slowing the growth of castration-resistant prostate [cancer cells](#). Treatment with YELIVA (ABC294640) increased dihydroceramide levels even in the absence of sphingosine kinase 2.

The MUSC team conducted both in vitro and in vivo studies with YELIVA (ABC294640) in castration-resistant prostate cancer, relying on the MUSC Lipidomics Shared Resource for measurement of sphingolipid levels and the MUSC Proteomics Center for MALDI imaging mass spectrometry.

In vitro studies conducted with castration-resistant mouse [prostate cancer cells](#) (TRAMP-C2) showed that treatment with YELIVA (ABC294640) reduced expression of the androgen receptor and the oncogene c-Myc, both important therapeutic targets for prostate cancer. Although many existing prostate cancer therapies target the androgen receptor, none directly target c-Myc.

To test in vivo response, one million TRAMP-C2 cells were injected under the skin of mice with an intact immune system, which were then treated with YELIVA (ABC294640) three days later. MALDI imaging

mass spectrometry showed the presence of YELIVA (ABC294640) within murine tumors and confirmed in vitro findings of increased dihydroceramide levels.

"The significance of these findings is that this compound might be a novel therapeutic for advanced [prostate cancer](#)," says Voelkel-Johnson, who believes that combination regimens of YELIVA (ABC294640) and focal radiation in this difficult-to-treat patient population deserve further study.

**More information:** *Molecular Cancer Therapeutics*,  
[dx.doi.org/10.1158/1535-7163](https://doi.org/10.1158/1535-7163)

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