Next-gen melanoma drug, TAK-733, excels in lab tests

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Study shows TAK-733 may be be second-generation alternative for BRAF-mutant melanoma. Credit: Flickr/Rudolph Vicek

A University of Colorado Cancer Center study published online this week in the journal *Molecular Cancer Therapeutics* reports anti-cancer activity in 10 out of 11 patient tumor samples grown in mice and treated with the experimental drug TAK-733, a small molecule inhibitor of MEK1/2. While the drug is conceived as a second-generation inhibitor in patients harboring the BRAF mutation, the study shows drug activity in melanoma models regardless of BRAF mutation status. Treated tumors shrunk up to 100 percent.

"The importance of this molecule is that it's a next-generation and highly potent inhibitor of a known melanoma pathway. It was highly effective against melanoma and the method of our study - using patient-derived tumor samples grown in mice - makes us especially optimistic that we should see similar results in the human disease," says John Tentler, PhD, investigator at the CU Cancer Center, associate professor at CU School of Medicine and one of the paper's lead authors.

Between fifty and sixty percent of human melanomas have an activating mutation in the gene BRAF. According to National Cancer Institute statistics, approximately 1 million people in the United States live with melanoma at any given time. In 2011, the U.S. Food and Drug Administration approved the drug vemurafenib to treat BRAF-mutant melanoma. But while response rates to vemurafenib are in the range of 80 percent for patients with the BRAF mutation, the duration of response if frequently limited to between 2 and 18 months.

"We're learning how to use existing drugs better, for example RAF along with MEK inhibitors to block both mutations and thus a common mechanism of resistance. But there is also room for improvement in the drugs themselves and we hope that TAK-733 could improve on the results of existing, approved MEK inhibitors," Tentler says.

Tentler points to the study's use of melanoma samples contributed by

human patients and then grown in mice (called "patient-derived xenografts") as a better predictor of the drug's effectiveness in humans. A common alternative to patient-derived xenografts is to grow tumors in mice from cancer cells that have previously been cultured on plastic, sometimes having been derived from patients decades earlier. Previous work at the CU Program for the Evaluation of Targeted Therapy (PETT) lab and elsewhere shows that cultured cells adapt to their plastic environment, over time potentially losing genetic characteristics of the original cancer and also learning to grow in an environment optimized for plastic.

"When you grow cells on plastic and inject them into mice, that's not what a real tumor looks like. Instead, when you take a sample and grow it as a living tumor in a mouse model, you much more faithfully preserve the genetic and tissue landscape characteristics of the original tumor," Tentler says.

Tentler suggests that while approved BRAF inhibitors such as vemurafenib and MEK inhibitors such as trametinib have proved effective in melanoma, TAK-733 may offer substantial enough improvements to justify its continued development.

"There's always a need for better, more potent molecules," Tentler says.

More information: *Molecular Cancer Therapeutics*, www.ncbi.nlm.nih.gov/pubmed/25376610

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