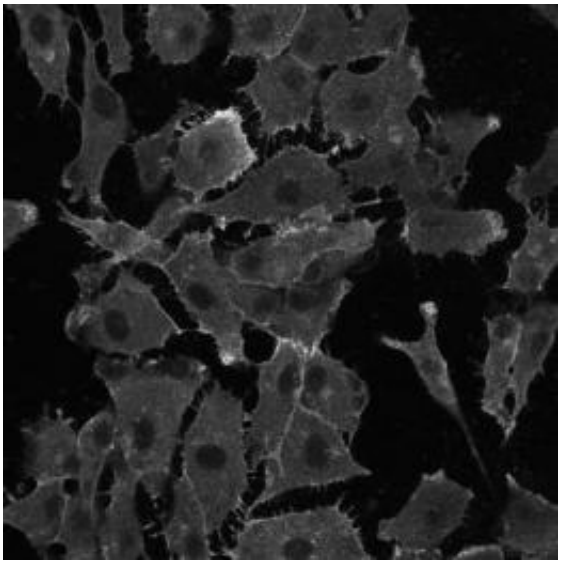
Drug may slow spread of deadly eye cancer

November 28 2011



A look at aggressive uveal melanoma cells under the microscope. These tumor calls carry the so-called "class 2 signature," meaning they are likely to be aggressive and spread outside of the eye. Credit: J William Harbour, MD

A drug commonly used to treat seizures appears to make eye tumors less likely to grow if they spread to other parts of the body, according to researchers at Washington University School of Medicine in St. Louis.

Their findings are available online in the journal Clinical Cancer Research.

Uveal melanoma, the second most common form of melanoma, can be very aggressive and spread, or metastasize, from the eye to other organs,

especially the liver.

"Melanoma in general, and uveal melanoma in particular, is notoriously difficult to treat once it has metastasized and grown in a distant organ," says principal investigator J. William Harbour, MD. "We previously identified an aggressive class 2 molecular type of uveal melanoma that, in most cases, already has metastasized by the time the eye cancer is diagnosed, even though imaging the body can't detect it yet. This microscopic amount of cancer can remain dormant in the liver and elsewhere for several years before it begins to grow and becomes lethal."

Once this happens, the prospects for survival are poor, according to Harbour, the Paul A. Cibis Distinguished Professor of Ophthalmology and Visual Sciences and professor of cell biology and of molecular oncology. He also directs the Center for Ocular Oncology at the Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine.

Harbour's new study shows that drugs known as histone deacetylase (HDAC) inhibitors alter the conformation of the DNA of the aggressive form of uveal melanoma, which changes the way key genes are expressed, rendering the tumor cells less aggressive.

"We looked at uveal melanoma cells in the laboratory and in an animal model, and we found that HDAC inhibitors can block the growth and proliferation of tumor cells," he says. "HDAC inhibitors appear to reverse the aggressive molecular signature that we had identified several years ago as a marker for metastatic death. When we look at aggressive melanoma cells under the microscope after treatment with HDAC inhibitors, they look more like normal cells and less like tumor cells."

Because HDAC inhibitors already are on the market, Harbour says he

thinks it may be possible to quickly begin testing the drugs in patients with aggressive forms of uveal melanoma.

The drugs have relatively mild side effects that are not as severe as those seen in patients undergoing chemotherapy. One HDAC inhibitor, for example, is the anti-seizure drug valproic acid. Its most common side effect is drowsiness, which is typical of all HDAC inhibitors.

Clinical trials of HDAC inhibitors could begin in the next six to 12 months, Harbour says. Already, other researchers have applied for funding to begin testing an HDAC inhibitor called SAHA (suberoylanilide hydroxic acid) in patients with metastatic uveal melanoma.

"I think this is a reasonable place to start in the challenging effort to improve survival in patients with metastatic uveal melanoma," Harbour says. "I suspect that the best role for HDAC inhibitors will be to slow or prevent the growth of tumor cells that have spread out of the eye but cannot yet be detected. This might lengthen the time between the original eye treatment and the appearance of detectable cancer in the liver and elsewhere."

Like the chicken pox virus that lives for years in nerve cells without affecting health, Harbour says treatment with HDAC inhibitors may allow patients with aggressive melanomas to live for many years without any detectable spread of their disease.

Harbour and his colleagues previously developed a screening test to predict whether the cancer would be likely to spread to the liver and other parts of the body. The test is helpful because although less than 4 percent of patients with uveal melanoma have detectable metastatic disease, up to half will eventually die of metastasis even after successful treatment of the tumor with radiation, surgery, or, in the worst cases,

removal of the eye.

Tumors that tend to remain contained within the eye are called class 1 uveal melanomas. With a needle biopsy, doctors can quickly determine whether a tumor is likely to be a class 1 cancer or whether it carries a molecular signature that identifies it as a high-risk, class 2 melanoma. Harbour's team developed a test to identify the class 2 molecular signature, and that test is now being used around the world to detect the aggressive form of uveal melanoma.

In addition, Harbour's team published a paper last year in the journal *Science* identifying a mutation in a gene called BAP-1 that helped further explain why some eye tumors develop the class 2 signature and acquire the ability to spread. Harbour explains that HDAC inhibitors appear to reverse some of the effects of BAP-1 mutations on the melanoma cell.

Provided by Washington University School of Medicine