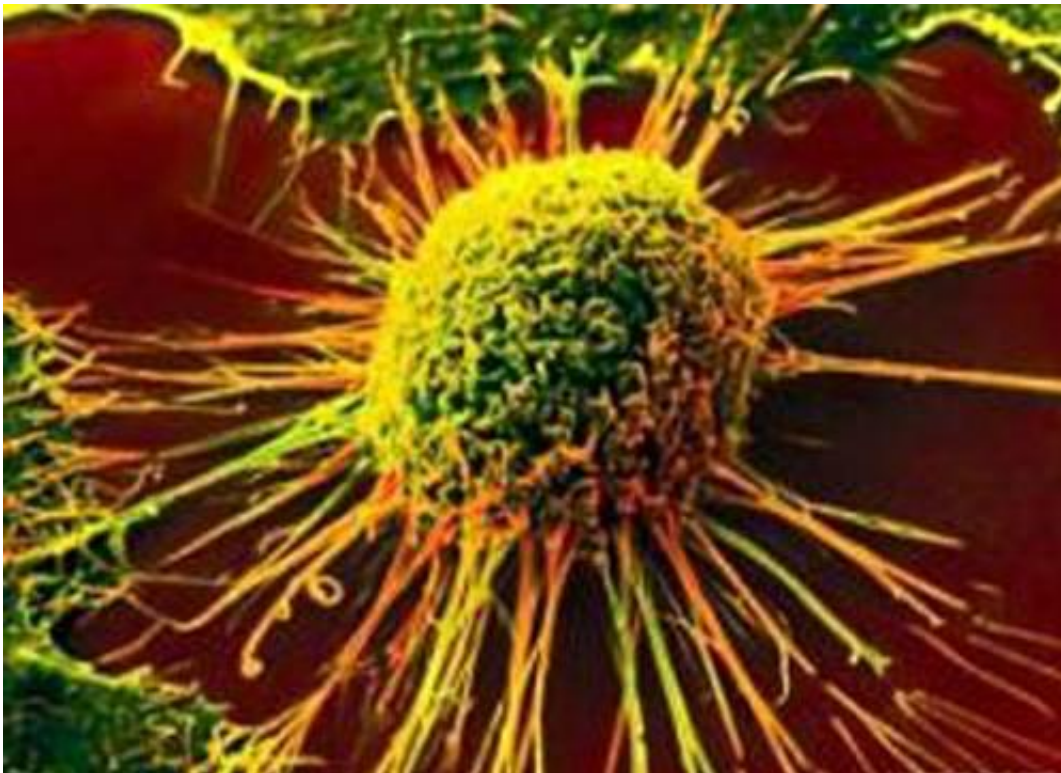


Scientists describe novel drug mechanism that fights brain cancer

March 4 2015, by Dorsey Griffith



Researchers at UC Davis have developed and characterized a molecule that interferes with the internal regulation of cancer cells, causing them to self-destruct. This novel mechanism was found to be effective against glioma cells—responsible for a usually fatal type of brain cancer—and could be applicable to other highly aggressive cancers.

The article, to be published in the April 2015 issue of *Molecular Pharmacology*, is [available online](#).

"We have elucidated the mode of action of a drug that destroys glioma cells in a manner that has not previously been described," said Nagarekha Pasupuleti, lead author of the study and project scientist in the Department of Neurology. "We anticipate that it will lead to new treatments to fight cancers that are resistant to standard therapies."

The investigators performed a series of studies utilizing high-content analysis, which quantifies changes in living cells in response to a drug treatment. The lab focused on the effects of a patented small molecule previously developed at UC Davis, known as UCD38B, on four different human glioma cell lines.

Gliomas arise from glia cells in the brain, which provide structural support and protection to neurons. Treatment of glioma typically involves a combination of surgery, radiation therapy and chemotherapy. Although apparently eradicated from the body after treatment, the cancer has a high rate of recurrence.

According to Pasupuleti, the problem with conventional therapy is that a subpopulation of non-dividing [cancer cells](#) tends to remain unaffected by treatment. These cells, which have many properties in common with normal stem cells, remain quiescent for a time, later replicate and regenerate the tumor. This population of glioma-initiating cancer cells resides in tumor regions having negligible or no blood supply and minimal oxygen, making them very difficult to destroy.

The research team's study showed that UCD38B is effective against such non-dividing glioma cells, as well as dividing cells destroyed by conventional therapy. They found that UCD38B acts by targeting a cellular regulatory system called the urokinase plasminogen activator

system. This system is normally important when tissue needs to be re-organized, such as during wound healing, a process that requires new cells to be made and others destroyed. Components of the urokinase plasminogen activator system have been found to be highly active in many aggressive cancers, including gliomas, as well as metastatic breast, lung and pancreatic cancers. The system is believed to play an important role in the ability of cancer cells to grow uncontrollably and metastasize to other parts of the body.

UCD38B disrupts the intracellular components of the urokinase plasminogen activator system. After entering glioma cells, UCD38B causes "mis-trafficking" of urokinase plasminogen activator system components to the wrong region of the cancer cell, ultimately triggering the cells to signal their own destruction rather than proliferate. UCD38B does this by disrupting the cell's endosomal transport system, which normally functions to direct cellular components to areas where they may be needed, or if not needed, destroyed. Within a few hours of administration, UCD38B causes plasminogen activator system components to be sent to mitochondria near the cell nucleus instead of the cell surface, causing factors to be released that destroy the cell.

Preliminary studies in rodents implanted with human glioma cells have found that a new small molecule based upon UCD38B is very effective in destroying this population of hypoxic glioma [cells](#) within the tumor without evidence of adverse effects. The research team will continue these studies and, in collaboration with the UC Davis School of Veterinary Medicine, hopes to try the drug in dogs with high- grade glial brain cancers, for which there are no other treatment options.

"Understanding the drug mechanism of action of UCD38B and its more potent derivatives is the culmination of many years of work of characterizing the processes causing cancer recurrence and developing molecules that target therapeutically resistant cancer cell types," said

Fredric Gorin, principal investigator, chair of the UC Davis Department of Neurology School of Medicine and professor of molecular biosciences in the UC Davis School of Veterinary Medicine. "We are hopeful that this new class of drug will one day become an important adjunct to conventional therapies in fighting these especially difficult-to-treat cancers."

The article is titled "Mis-trafficking of endosomal urokinase proteins triggers drug-induced glioma non-apoptotic cell death."

In addition to Gorin and Pasupuleti, Ana Cristina Grodzki of the Department of Molecular Biosciences in the UC Davis School of Veterinary Medicine, was a co-author and played an important role in quantifying the endosomal trafficking caused by UCD38B.

More information: "Mis-Trafficking of Endosomal Urokinase Proteins Triggers Drug-Induced Glioma Nonapoptotic Cell Death" *Mol Pharmacol* April 2015 87:683-696; published ahead of print January 29, 2015, [DOI: 10.1124/mol.114.096602](https://doi.org/10.1124/mol.114.096602)

Provided by UC Davis

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