# Arsenic shows promise as cancer treatment, study finds

July 12 2010

Miss Marple notwithstanding, arsenic might not be many people's favorite chemical. But the notorious poison does have some medical applications. Specifically, a form called arsenic trioxide has been used as a therapy for a particular type of leukemia for more than 10 years. Now researchers at the Stanford University School of Medicine have shown that it may be useful in treating a variety of other cancers.

Combining arsenic with other therapies may give doctors a two-pronged approach to beating back forms of the disease caused by a malfunction in a critical cellular signaling cascade called the Hedgehog pathway. The U.S. Food and Drug Administration has already approved arsenic trioxide for use in humans, which could pave the way for clinical trials of this approach.

"Many pharmaceutical companies are developing anticancer drugs to inhibit the Hedgehog pathway," said Philip Beachy, PhD, professor of developmental biology and the Ernest and Amelia Gallo Professor in the School of Medicine. In addition, Beachy recently identified an antifungal drug commonly used in humans, itraconazole, as a Hedgehog pathway inhibitor. "However, these compounds target a component of the pathway that can be mutated with patients then becoming resistant to the therapy. Arsenic blocks a different step of the cascade."

Beachy is the senior author of the new findings about arsenic, which will be published online in the Proceedings of the National Academy of Sciences July 12. Jynho Kim, DVM, PhD, a postdoctoral scholar in

Beachy's lab, is the first author of the study.

The mechanism of action described by the researchers in the current paper differs from what happens during arsenic poisoning, which occurs when higher levels of the compound choke off a cell's energy production system.

Beachy and his colleagues studied the effect of arsenic trioxide in cultured human and mouse cells and in laboratory mice with a brain tumor known as medulloblastoma. (The Hedgehog pathway is known to be overly active in this and other tumors in the skin, brain, blood and muscle.) They found that relatively low levels of the compound, equivalent to those approved for use in treating patients with acute promyelocytic leukemia, block one of the last steps of the Hedgehog pathway; it prevents the expression of a select few of the cell's genes in response to external messages. Because only the tail end of the pathway is affected, a cancer cell has fewer opportunities to mutate and sidestep arsenic's inhibitory effect.

In contrast, another Hedgehog pathway inhibitor called cyclopamine acts near the beginning of the signaling cascade. Cyclopamine, a plant-derived molecule identified as a Hedgehog pathway inhibitor by Beachy in 1998, binds to a protein on the surface of the cell called Smoothened and blocks its ability to transmit the Hedgehog signal to the cell's innards. Drugs mimicking cyclopamine's action are currently being developed for human use. However, the ability of these drugs to disrupt the Hedgehog pathway early on may be lessened by mutations in Smoothened that allow the cascade to get around this initial treatment.

Beachy and Kim became curious as to whether and how arsenic worked to interfere with the signaling cascade as a result of observations that birth defects caused by arsenic exposure resemble the physical effects of having an inactive Hedgehog pathway. They studied human cells in

culture and discovered that levels of arsenic trioxide similar to those currently used in patients with acute promyelocytic leukemia inhibit the Hedgehog pathway.

Specifically, the researchers found that arsenic trioxide blocks the ability of a protein called Gli2 to induce gene transcription in the nucleus. It works by stopping Gli2 from moving into the cell's primary cilium, a communication hub, where many of the events of Hedgehog signaling take place. Without Gli2 in the cilium, the Hedgehog message comes to an abrupt, and fruitless, dead end. This occurs even in cells known to be resistant to cyclopamine treatment.

To find out what this might mean for cancer cells, they studied mice with a type of brain tumor known to be dependent on Hedgehog signaling. Treating the mice with arsenic trioxide slowed or stopped tumor growth. They also found that combining arsenic trioxide with cyclopamine was even more effective in blocking the pathway in cultured cells.

"Arsenic might be especially effective for treating some types of cancers in combination with other drugs that act at different levels of the Hedgehog pathway, such as the cyclopamine mimics that pharmaceutical companies are developing, or itraconazole, an approved drug that we have recently shown also acts at the level of Smoothened," said Beachy, who is also a member of the Stanford Cancer Center and the Stanford Institute for Stem Cell Biology and Regenerative Medicine, as well as a Howard Hughes Medical Institute investigator.

Provided by Stanford University Medical Center