Antifungal medicine shown to slow tumor growth in mice study

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(PhysOrg.com) -- A common antifungal medication can slow tumor growth in mice, according to scientists at the Stanford University School of Medicine. The drug, called itraconazole, inhibits a molecular pathway important during both fetal development and cancer progression. Because it works at dose levels already approved for use in humans, clinical trials in patients may not be far off, said the researchers.

"There is a fairly broad range of tumors in which this molecular cascade, called the 'Hedgehog' pathway, plays an important role," said developmental stem cell biologist Philip Beachy, PhD. "The virtue of screening existing drugs is that you already have all the information about dosage and toxicity, and you can move into clinical trials fairly readily."

Although itraconazole alone doesn't eliminate the tumor, the researchers hope that combining the treatment with other therapies that target the same critical pathway may be a valuable option for many patients.

Beachy is the senior author of the research, published on April 13 in *Cancer Cell*. He is the Ernest and Amelia Gallo Professor at the medical school and a member of the Stanford Cancer Center and the Stanford Institute for Stem Cell Biology and Regenerative Medicine. He is also a Howard Hughes Medical Institute investigator.

Beachy and his colleagues have spent many years understanding the Hedgehog pathway - a series of molecular events that help cells to know

where they are in the body by sensing external signals called Hedgehog proteins. These Hedgehog proteins constitute a family of signals that are important not only during fetal development, but also in many cancers.

The significance of the Hedgehog signal was first identified in fruit flies. It helps the developing fly embryo know how to order the bristles and other structures within each segment during formation of the larva. Scientists then found that mouse embryos lacking proteins involved in the Hedgehog pathway fail to properly develop their brains, skeleton, muscles and some organs, and are cyclopic (meaning they have only one eye). Researchers also showed that the pathway is involved in helping adult human stem cells know when and how to divide to maintain tissues such as the skin and other organs.

The pathway's importance has made it an attractive target for drug development companies, many of which are trying to engineer new molecules to block it. Beachy and his colleagues took a slightly different approach by choosing to screen drugs already available to see if any were able to trip up the molecular relay.

There are several opportunities to stick a metaphorical foot in the race: Activated Hedgehog protein binds to a cell-surface protein called "Patched"; this stimulates the release of "Smoothened," another protein; Smoothened then begins to accumulate in a specific cellular structure called a primary cilium, where it triggers the activity of yet another protein; and, finally, this protein regulates how the cell's genes are expressed in response to external stimuli.

The first known Hedgehog pathway inhibitor - identified by Beachy in 1998 - blocks the pathway by binding to the protein, Smoothened. Chemical derivatives of this naturally occurring molecule, called cyclopamine (because it causes cyclopia in developing embryos), are also being developed for use in humans. Beachy's lab also identified

numerous other chemical compounds that mimic cyclopamine's actions. But these compounds would have to be optimized for use in humans.

"Drug development is really an expensive and tedious exercise that is difficult to conduct in an academic setting," said Beachy. "But, given that we knew that multiple molecules are able to target Smoothened, we expected that we'd find other molecules with a similar effect by screening existing drugs."

The researchers applied about 2,400 drugs to cells specially engineered by Beachy to emit a light signal when the Hedgehog pathway is active. The drugs were either already approved by the U.S. Food and Drug Administration or had undergone human safety testing during early stages of the approval process. They then stimulated the pathway in the cells in laboratory dishes and looked to see which drugs blocked the signal.

Most of their several dozen candidates either required doses too high to be achieved in humans or would be dangerous for long-term use. But one drug, itraconazole, an orally administered antifungal medication that can be safely taken for several months, showed promise. The dose needed to block the Hedgehog pathway in the cells is similar to that used to combat the severe fungal infections that can develop in people whose immune systems are weakened by AIDS or cancer.

Further investigation showed that itraconazole, which is marketed by Johnson & Johnson under the name Sporanox, inhibited the activation and subsequent migration of Smoothened to the cilium. Its ability to inhibit the Hedgehog pathway is distinct from its antifungal action.

In mice, the researchers found that oral itraconazole treatment significantly slowed the growth of tumors implanted under the skin for up to 18 days. In contrast, the control mice's tumors had grown so large

during this time that the animals had to be euthanized. Adding cyclopamine had an even stronger effect, showing that the two drugs work on the pathway in different, yet complementary, ways.

Beachy and his colleagues are now discussing the use of itraconazole in human clinical trials in patients with skin and urologic cancers. They are also seeking other molecules that can be combined with itraconazole to block the Hedgehog pathway.

"It might be possible with two compounds to achieve a more potent block at even lower drug concentrations," said Beachy. "If so, it's possible that there is a population of patients that can be treated relatively soon."

Provided by Stanford University Medical Center