

New drug shows promise in the fight against malignant melanoma

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(PhysOrg.com) -- Gavin Robertson is not a man who uses the word 'hate' lightly, but he makes no secret of his desire to slay the dragon that is malignant melanoma.

"This is the deadliest form of [skin cancer](#)," he said. "There's an approximately four percent increase per year in new cases and no effective treatment available for metastatic disease. The worst thing is getting calls from patients and their families who are desperate for a cure, for some good news. It's so hard telling them we're not there yet."

Robertson -- associate professor of pharmacology, pathology, dermatology and surgery at the Penn State College of Medicine -- has new reason to believe that hopeful treatment news is ahead.

Tests in mice suggest that the new drug he and colleagues have developed is both safer and more potent than conventional therapies in targeting melanoma tumors. Based on the anti-cancer compounds in cruciferous vegetables, the new drug called isoselenocyanate "got a 60 to 70 percent response rate in mice," said Robertson. "That's significant."

For Robertson and his research team, including professor of pharmacology Shantu Amin, the goal has been to unravel the signaling pathways involved in tumor development and identify drugs to target them.

In all life forms -- from single-celled [bacterium](#) to multi-cellular humans -- cells communicate with each other through chemicals, such as hormones and neurotransmitters. Protein molecules on the surfaces of cells, called receptors, recognize these incoming chemical messages, and, when all goes right, they react by initiating the requested change in some aspect of [cell behavior](#), from activating the immune system to fight infection to turning a fertilized egg into a fully-formed baby.

However, things don't always go right. Sometimes when complex sequences of proteins are activated, a new 'abnormally active [signaling pathway](#)' is created, and researchers believe that communication glitches in these pathways can give rise to cell changes and ultimately to cancer.

"We set out to target the proteins that trigger melanoma," Robertson said. "Ninety percent of normal skin moles contain a mutant protein called B-Raf, but don't proceed to become melanomas. We wanted to know why some do and how to turn off that mechanism."

Robertson and colleagues discovered that in about 70 percent of melanoma tumors there is another protein at work alongside B-Raf called Akt3, which is 10 times more active in malignant cells than in normal ones.

For cancer to start, the activity in the B-Raf pathway has to be in a particular narrow range, said Robertson.

"When this pathway is too active, it actually inhibits cancer and a mole develops that does not become cancerous. But when the A protein, Akt3, holds hands with the B protein, the B-Raf, and transfers information to it, it adds a phosphate to the mix and the pathway activity then drops into just the right range, and melanoma develops."

Knowing that you'd have to eat "impractical amounts" of cruciferous vegetables such as cabbage and kale to obtain a therapeutic level of their cancer-fighting nutrients, sulforaphane and selenium, Robertson and colleagues sought to develop a drug using these nutrients that could deactivate the Akt3 pathway.

"We modified the chemical structure, increased the carbon chain length to make it more soluble, then popped out the sulfur and replaced it with selenium," said Robertson. "We knew from studies that selenium deficiency is common in cancer patients, and selenium has also been shown to destabilize Akt proteins in prostate cancer."

The result?

"When we tried the sulfur version, it had no effect on the melanoma tumors in mice," Robertson said, "but when we used the selenium version of the drug, up to 70 percent of the mice showed tumor regression." The selenium-enhanced compounds "significantly reduced the production of Akt3 protein and shut down its signaling network."

Though still years away from human trials, Robertson envisions a drug that could be used intravenously by melanoma patients, as well as preventively in sunscreen by the general public (some of the research on topical applications was done by Hershey high school senior Natalie

Nguyen, an intern in Robertson's lab. Nguyen's project took third place in the 2009 Intel International Science and Engineering Fair).

"I think we're finally figuring out how to treat cancer," Robertson said. "Where today's cancer drug 'cocktails' sometimes poison nonspecifically, I think tomorrow's treatments will target several specific proteins."

"This is where I see us going, long term," he said. "The patient will come into the clinic with metastatic melanoma and we'll take a blood sample to profile what the 'bad genes' are for that particular person. Then we'll be able to choose from an arsenal of drugs to give them a personalized treatment based on their own cancer. We'll see better efficacy and lower toxicity."

"It's my belief," Robertson said, "that our new drug will be in that arsenal."

Provided by Pennsylvania State University ([news](#) : [web](#))

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