Compound shows promise in treating melanoma

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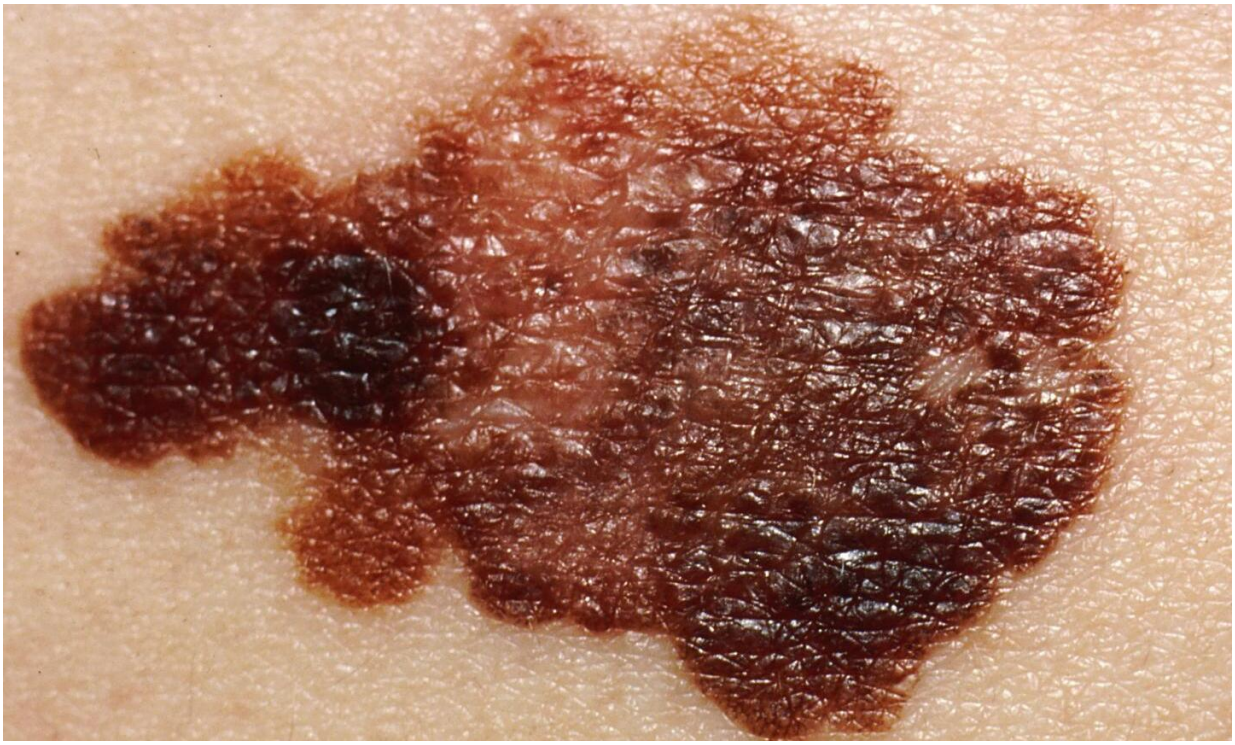

Melanoma. Credit: Wikimedia Commons/National Cancer Institute

While past attempts to treat melanoma failed to meet expectations, an international team of researchers are hopeful that a compound they tested on both mice and on human cells in a petri dish takes a positive step toward creating a drug that can kill melanoma cancer cells without harming nearby healthy cells.

In a series of studies led by Dr. Arun Sharma, associate professor of pharmacology and Dr. Shantu Amin, professor of pharmacology, both of Penn State College of Medicine, researchers designed and synthesized a compound called napthalamide-isoselenocyanate—NISC-6—to inhibit both the Akt1 pathway and human topoisomerase IIα—topo IIα—activity, which contribute to melanoma tumor growth. Melanoma, which is caused primarily by exposure to the sun's ultraviolet rays, accounts for less than 5 percent of skin cancer cases, but causes more than 75 percent of skin cancer deaths.

In the study, the compound caused human melanoma cells to die and inhibited tumor growth by about 69 percent in a mouse model.

According to the researchers, who report their findings in a recent issue of the *European Journal of Medicinal Chemistry*, recent attempts to use drugs to treat melanoma are not completely effective. Current treatments for melanoma patients include dacarbazine and temozolomide, which have an unsatisfactory response rate. Another drug, vemurafenib—PLX-4032—works well initially, but the tumors develop resistance within 6 to 7 months.

The researchers combined a few different approaches from their earlier work to develop the new compound.

"It was more of a fragment-based drug design," said Sharma. "We took isoselenocyanate moiety (fragments) from an earlier drug design we had worked on and then combined it with napthalamide moiety of mitonafide, a topo IIα inhibitor." Mitonafide showed antitumor activity both preclinically and in phase I and phase II clinical trials but failed due to systemic toxicity issues.

The isoselenocynate moiety was designed based on naturally occurring isothiocyanates, which can be found in vegetables, such as broccoli and

cauliflower, and are known for their cancer prevention properties.

"There are a lot of recommendations that, for example, broccoli can reduce your chances of getting cancer," said Sharma. "Those are OK recommendations for prevention, but the compounds in the vegetables alone may not be potent enough to be used in a therapeutic environment."

To improve the effectiveness, the researchers modified the drug by replacing the sulfur in a compound they studied earlier with selenium, as well as varying the length of the alkyl chain to create isoselenocynate. Several variations were screened before the researchers arrived at a compound that they thought could kill the cancer cells without increasing toxicity levels.

The researchers added that the new compound was designed to reduce toxicity and to improve drug resistance by treating melanoma cells containing wild type BRAF as well as mutated BRAF. For example, vemurafenib is more effective in melanoma containing BRAFV600E mutation, than melanoma cells with wild type BRAF protein.

"We designed it for easy elimination from the body, so, consequently, toxicity should be reduced," said Sharma. "We also think, with this compound and this type of approach, if it goes further, we should be able to delay, or overcome resistance because it not only targets BRAF mutant melanoma cells, but also BRAF wild type melanoma cells."

While the researchers are still in the process of studying the actual mechanism behind how the drug works, the compound appears to target a process that guides cell division and growth, according to Deepkamal Karelia, a post-doctoral scholar in pharmacology, Penn State, who worked with Sharma.

"When a cell divides and grows, the DNA inside will become tangled much like the way a rope will if you take it and keep turning it in circles, it will get tangled. To untangle the rope you can either cut and join the rope or spend long time turning it in opposite direction to untangle it," said Karelia. "The DNA has the same issue in our cells. To solve the problem, our bodies have a protein called topoisomerase, which cuts the DNA and joins it back to release the stress. What we show in this paper is this compound may be able to inhibit that activity of topo IIα protein—the DNA is unable to unwind itself."

Sharma said NISC-6 may also work on other forms of cancer, which will likely be included in future research.

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