New investigational compound shows promise against melanoma, lymphoma

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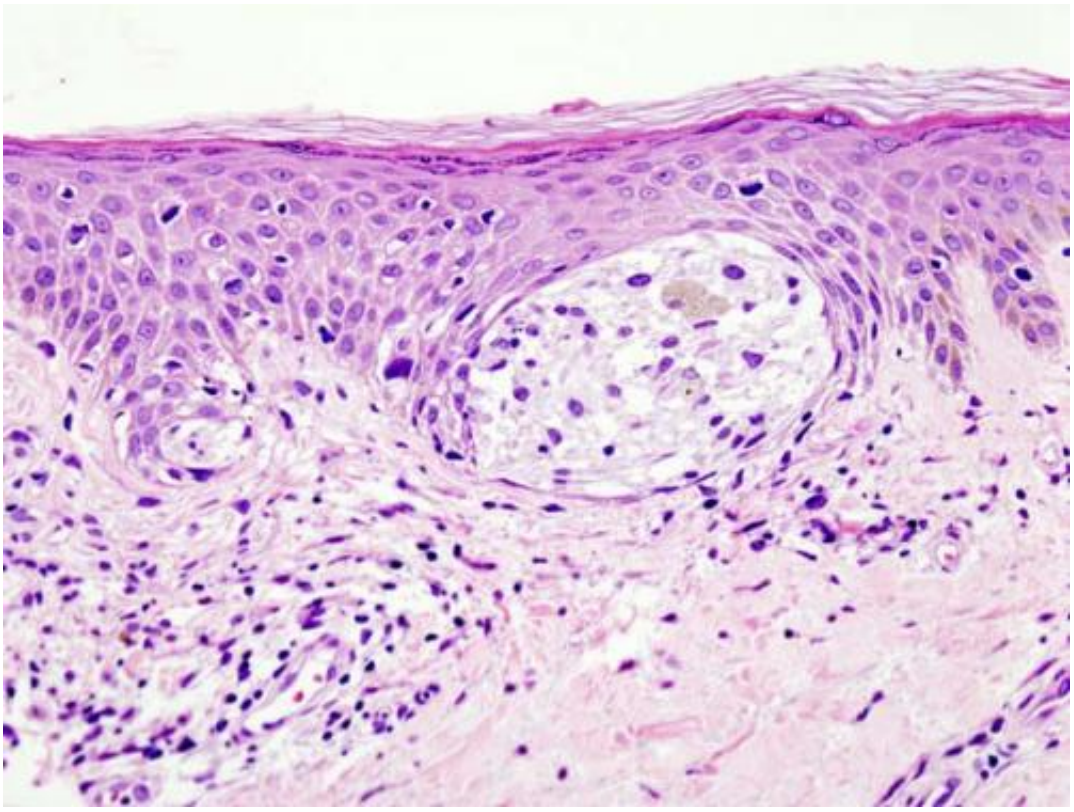

Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

In a step toward more targeted treatments for cancer patients, UNC School of Medicine and UNC Lineberger Comprehensive Cancer Center researchers have demonstrated how a genetic mutation drives the most common type of lymphoma as well as melanoma, the deadliest form of

skin cancer.

Reported in the journal *Nature Medicine*, the researchers described their new laboratory models of B-cell lymphoma and melanoma that feature a specific mutation of EZH2, a gene known to regulate cell fate. The authors also report a new investigational inhibitor currently called JQEZ5 that blocks the function of the protein made by the EZH2 gene, and show this compound is highly active in EZH2-driven cancer models.

"We have shown that the biology of tumors driven by this mutation are distinct from other types of lymphoma and melanoma, and that these tumors require persistent malfunction of EZH2 for growth," said Norman Sharpless, MD, director of UNC Lineberger and the Wellcome Distinguished Professor of Cancer Research. "And with our collaborators, we have shown that a potential new drug designed to target EZH2 mutations in such cancers is very active in our laboratory models."

The specific mutation of EZH2 studied by the Sharpless lab is a relatively common event in diverse cancers, occurring in approximately 20 percent of B-cell lymphomas, 5 percent of melanoma and at lower frequency in a variety of other cancers. This analysis suggests that this mutation affects thousands of people in the United States who develop cancer.

The researchers determined that a mutation in the EZH2 gene alone is sufficient to drive B-cell lymphoma, whereas in melanoma, the EZH2 mutation occurs in combination with mutations of the BRAF gene, which occurs in about half of melanoma patients.

These findings have important implications for both treatment and further drug development, said the study's first author George P. Souroullas, PhD, a research scientist at UNC Lineberger and in the UNC School of Medicine's department of genetics, as they indicate which

combinations of drugs could be therapeutically beneficial.

Specifically, their findings in melanoma suggest that inhibitors of the protein created by the EZH2 gene – inhibitors like JQEZ5 – might work well in combination with inhibitors of BRAF, which are already approved by the U.S. Food and Drug Administration as melanoma therapies.

The researchers treated the newly developed laboratory models of melanoma and lymphoma with the specific EZH2 mutation with a variety of therapies, including different compounds designed to inhibit EZH2. The authors found that JQEZ5, a molecule recently developed by Jun Qi, PhD, of the Dana-Farber Cancer Institute, and James E. Bradner, MD, formerly of the Dana-Farber Cancer Institute and now president of the Novartis Institutes for BioMedical Research, was highly potent in animal models of EZH2-mutant cancer. The authors showed that JQEZ5 had drug-like properties and minimal toxicity, suggesting such approaches may be of value in human patients with EZH2 mutant cancers.

The findings are important as new treatments are needed for lymphoma and metastatic melanoma, Sharpless said.

"While there has been significant progress in recent years against cancers such as lymphoma and melanoma, many patients still fail these newer therapies and need further options for therapy," Sharpless said. "Given that EZH2 malfunction is a common event in many types of cancer beyond lymphoma and melanoma, we are hopeful that well-tolerated inhibitors of this enzyme will benefit a large group of patients with cancer."

More information: George P Souroullas et al. An oncogenic Ezh2 mutation induces tumors through global redistribution of histone 3 lysine

27 trimethylation, *Nature Medicine* (2016). DOI: 10.1038/nm.4092