

# Researchers identify a new target for treating drug-resistant melanoma

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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

A new collaborative study led by researchers at Sanford-Burnham Medical Research Institute (Sanford-Burnham), published today in *Cell Reports*, provides new insight into the molecular changes that lead to resistance to a commonly prescribed group of drugs called BRAF

inhibitors. The findings suggest that targeting newly discovered pathways could be an effective approach to improving the clinical outcome of patients with BRAF inhibitor-resistant melanoma tumors.

Melanoma is the deadliest form of skin cancer, killing more than 8,000 people in the U.S. each year. Approximately 50 percent of melanoma tumors are driven by mutations in the BRAF gene, and patients with these tumors are prescribed BRAF [inhibitors](#). Although BRAF inhibitors rapidly and effectively shrink tumors, their success is limited because most tumors become resistant to the drugs within a few months.

"Melanoma tumors can develop [resistance](#) to BRAF inhibitors by using alternate signaling pathways that promote cell growth," said Ze'ev Ronai, Ph.D., scientific director of Sanford-Burnham's La Jolla campus and senior author of the study. "Our study has identified a different pathway, JAK1, as a driver of resistance to BRAF inhibitors, and suggests that targeting JAK1 could overcome such resistance, thereby improving the durability of the response to BRAF inhibitors."

## How it works

The research team analyzed BRAF inhibitor resistance in melanoma cell lines, mice bearing human melanoma tumors, and in human [tumor](#) biopsy samples. They found higher levels of JAK1 in resistant tumors, which caused increased expression of epidermal growth factor (EGFR)—a receptor tyrosine kinase that promotes cell proliferation. The increase in JAK1 was due to low levels of the protein that regulates its expression, ubiquitin ligase RNF125.

JAK1 is part of a well-studied regulatory network of proteins that is involved in the control of cell growth, differentiation, apoptosis, inflammation, and immune response. Until now, JAK1 was not known to play a role in melanoma or its resistance to therapy.

"By helping us understand that lower levels of RNF125 confer resistance to BRAF inhibitors, we have a new strategy to stratify patients for currently approved therapy versus participation for human clinical trials to investigate whether targeting JAK1 will be more effective in patients whose tumors exhibit reduced RNF125," said Keith T. Flaherty, M.D., associate professor, Harvard Medical School, and director of Developmental Therapeutics, Cancer Center, Massachusetts General Hospital, and co-author of the study. "It will be important to determine whether JAK1 therapy alone or in combination with EGFR and BRAF inhibitors will elicit a better response."

Provided by Sanford-Burnham Medical Research Institute

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