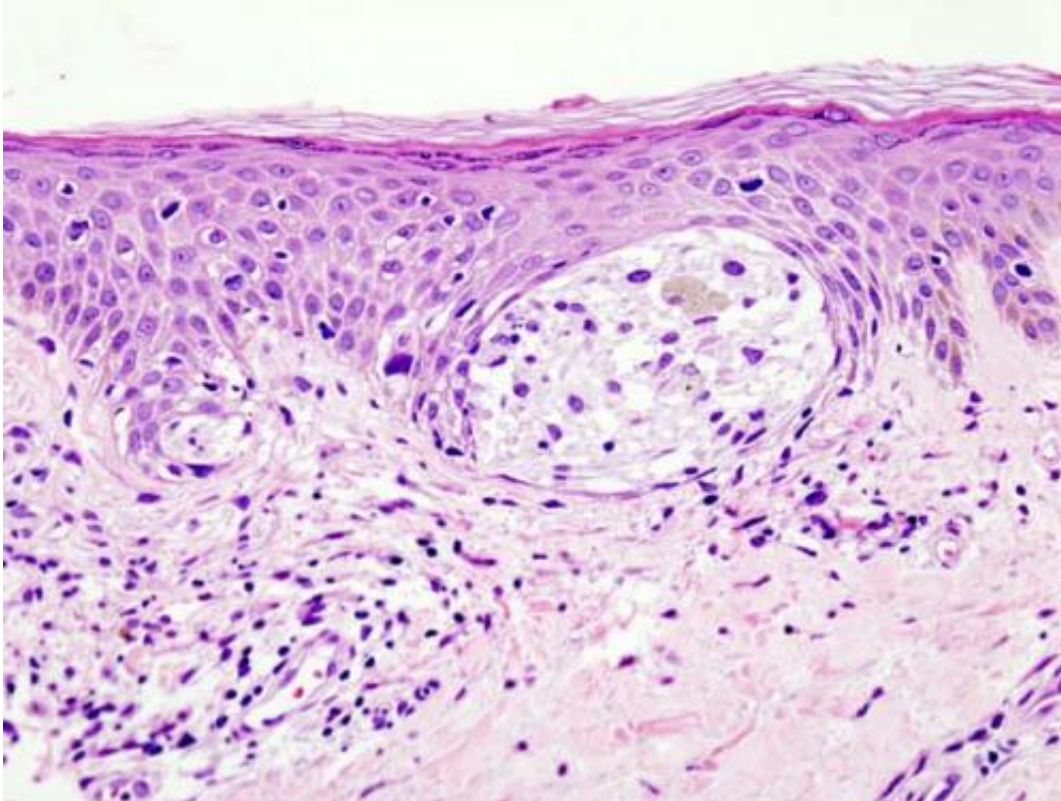


# How melanoma evades targeted therapies

November 6 2018

---



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

Melanoma is the leading cause of death from skin cancer. Many patients develop metastatic disease that spreads to other parts of the body. One commonly used targeted therapy for metastatic melanomas works by attacking melanomas with mutations in the BRAF gene that make them susceptible to RAF-inhibiting drugs. However, many cancers quickly

become resistant to the treatment. Now researchers at the NCI-designated Sidney Kimmel Cancer Center—Jefferson Health have discovered how one of the mechanisms of that resistance works, a finding that could lead to designing more effective combination therapies.

"The findings give us new clues about how we might combat resistance to this targeted [melanoma](#) therapy," said Andrew Aplin, Ph.D., Associate Director for Basic Research and the Program Leader for Cancer Cell Biology and Signaling (CCBS) at the Sidney Kimmel Cancer Center. The research was published November 6th in *Cell Reports*.

About 13-30 percent of melanomas become resistant to RAF-inhibiting drugs because of a difference in how those cells produce and process the BRAF protein. The gene these patients carry is called a BRAF V600E isoform. These RAF-resistant isoform cancers produce BRAF proteins that become active complexes with another [cancer](#)-promoting protein called MEK.

Dr. Aplin, together with first author Michael Vido, an MD/PHD student in Dr. Aplin's lab and colleagues, showed that when they blocked this complex, or dimerization, by targeting a specific site on the BRAF isoform, they could block MEK binding and restore the potency of the RAF-inhibitor.

"The work helps explain dual hypotheses for RAF-inhibitor resistance, one which focused on MEK and the other on dimerization," said Dr. Aplin. "This work weaves the two together mechanistically. The results may also help guide the design of better combination therapies for melanoma."

"This pivotal study is part of a much larger effort within the Sidney Kimmel Cancer Center at Jefferson to advance the pace of discoveries

leading to clinical translation," said Karen Knudsen, Ph.D., Enterprise Director of the Sidney Kimmel Cancer Center. "Dr. Aplin's findings bring critical insight into the molecular underpinnings of therapeutic resistance, and nominate new possibilities for treating advanced disease."

**More information:** Michael J. Vido, Kaitlyn Le, Edward J. Hartsough, and Andrew E. Aplin, "BRAF splice variant resistance to RAF inhibitor requires enhanced MEK association," *Cell Reports*, [www.cell.com/cell-reports/full ... 2211-1247\(18\)31638-3](http://www.cell.com/cell-reports/full...2211-1247(18)31638-3) DOI: [10.1016/j.celrep.2018.10.049](https://doi.org/10.1016/j.celrep.2018.10.049), 2018.

Provided by Thomas Jefferson University

Citation: How melanoma evades targeted therapies (2018, November 6) retrieved 8 May 2024 from <https://medicalxpress.com/news/2018-11-melanoma-evades-therapies.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.