

## **Yale team identifies successful combination drug therapies for melanoma mutations**

Yale UniversityYale University

Yale Cancer Center researchers have identified several effective combinations of therapies that inhibit melanomas driven by two of the most formidable cancer genes. Some combinations include cholesterol-lowering statin drugs. The study appears in the journal *Cancer Discovery*.

The Yale scientists were seeking to overcome the problems of resistance and partial response to single-drug cancer therapy in patients with melanoma. Until now there has been no effective method reported to target mutated *RAS* melanoma oncogenes through combination drug therapy. *RAS* genes drive many types of cancer that are notoriously difficult to treat. The *BRAF* gene is a second key driver of melanoma and can be targeted by new therapies. However, even when single-drug therapy is initially successful, recurrence nearly always occurs and is associated with poor patient prognosis.

[Read about the science behind the discovery \[1\]](#)

Using novel high-throughput screening techniques, the Yale researchers mixed and matched among 150 small molecule compounds, searching for pairs that could inhibit melanoma cell growth. They used cell lines derived directly from human metastasized melanomas. The compounds were all genotype-selective for *RAS* or *BRAF* mutations.

The team identified several unique combinations, including some that inhibited cells with resistance to vemurafenib, the *BRAF* inhibitor drug used in the treatment of late-stage melanoma. Further, they discovered that combining statins with drugs that inhibited cyclin-dependent protein kinase enzymes, which regulate and promote the cellular growth of cancer, produced a similar response with both *RAS*- and *BRAF*-mutated oncogenes.

This study is believed to be the first to show extensive positive results of combination drug therapy, including combinations that include statins, in fighting late-stage melanoma, and could set the stage for clinical trials in patients. "Many melanoma patients have been greatly helped by identification of gene mutations that drive subsets of the disease. But even when they respond to initial single-drug treatment, most eventually become resistant to the drug, and their cancers return," said co-senior author David F. Stern, professor of pathology at Yale School of Medicine. "Our hope, when we begin human clinical trials, is that we will see a much better, longer-lasting response."

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Published on Electronic Component News (<http://www.ecnmag.com>)

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Perhaps the most interesting observation, the authors say, is that including statins in the drug combinations killed RAS-driven melanoma. "These results confirm earlier research showing that RAS activity is inhibited by statins," said co-senior author Marcus Bosenberg, M.D., associate professor of dermatology and pathology at Yale School of Medicine. A recent study, he adds, showed that patients using statins at the time of diagnosis were less likely to die from their cancer.

Other authors are Matthew Held, Casey Langdon, James Platt, Tisheeka Graham-Steed, Zongzhi Liu, Ashok Chakraborty, Antonella Bacchiocchi, Andrew Koo and Jonathan Haskins of Yale School of Medicine.

The study was supported by grants from an anonymous foundation, the Harry J. Lloyd Charitable Trust, the U.S. Public Health Service, and the Yale SPORE in Skin Cancer, funded by the National Cancer Institute.

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