New molecular targets identified in some hard-to-treat melanomas provide potential treatment option

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Stand Up To Cancer (SU2C), the charitable initiative supporting ground-breaking research aimed at getting new cancer treatments to patients in an accelerated timeframe, announces that Jeffrey A. Sosman, M.D., a Stand Up To Cancer Melanoma Dream Team investigator, William Pao, M.D., Ph.D., a 2009 Stand Up To Cancer Innovative Research Grant recipient and colleagues identified two novel BRAF fusions in melanomas previously considered to be negative for molecular targets, and that melanomas with these fusions were found to be potentially sensitive to anticancer drugs called MEK inhibitors, according to a study recently published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

According to Dr. Sosman, professor of medicine at Vanderbilt-Ingram Cancer Center in Nashville, Tenn., "About 35 percent of melanomas are, as of today, considered 'pan-negative,' which means they are devoid of any previously known driver mutations in the genes BRAF, NRAS, KIT, GNAQ, and GNA11." Dr. Sosman explained that at Vanderbilt, researchers have been interested in looking at patients whose tumors have none of these driver mutations, to see what their tumors do have that can be targeted therapeutically. In some cancers, two or more genes fuse erroneously to produce abnormal proteins, which can function as the "drivers" of those cancers. –

"Performing a sophisticated analysis called targeted next-generation sequencing, it appears that about 8 percent of pan-negative melanomas have BRAF fusions," said Sosman. "Our results are important because they obviously suggest that there probably are other, as yet unidentified, molecular changes that make these melanomas susceptible to drugs that are available right now."

"It is very exciting to see work of Stand Up To Cancer funded researchers yield important results which advance our understanding of cancers and accelerate the science towards treatments that can make a difference for patients," stated Sherry Lansing, co-founder & member of the SU2C Council of Founders and Advisors. This research is a direct outcome from the Stand Up To Cancer Melanoma Dream Team Grant and involved the work of a Stand Up To Cancer Innovative Research Grant recipient, representing work made possible by both funding models created by SU2C to focus on groundbreaking translational research aimed at getting new therapies to patients quickly. To date, SU2C has funded $139.5 million for 11 Dream Teams and $19.4 million for 26 IRG research grants for brightest young researchers across disciplines to think out of the box and attempt to make major breakthroughs in their field with bold research projects.

In a pan-negative melanoma sample from one of their patients, Drs. Sosman and Pao and their colleagues identified a fusion between two genes, PAPSS1 and BRAF, which they called PAPSS1-BRAF. They then evaluated melanomas from an additional 51 patients, 24 of which were pan-negative. In one of these 24 pan-negative samples, they identified a second novel BRAF fusion, called TRIM24-BRAF.

The investigators conducted further studies in the laboratory and found that both BRAF fusions activated a pathway in the cancer cells called the MAPK signaling pathway. They then treated these fusion-bearing cells either with the BRAF inhibitor vemurafenib or with trametinib, a drug that inhibits a protein in the MAPK signaling pathway called MEK. They found that signaling induced by the BRAF fusions was not responsive to vemurafenib but could be inhibited by trametinib, which led them

to suggest that the novel fusions they identified could make melanoma cells harboring them sensitive to MEK inhibitors.

"One of the primary objectives of Stand Up To Cancer is to accelerate the development of effective treatments to help patients. This research from Drs. Sosman and Pao advances that objective because identifying novel genetic mutations helps identify targets that might be sensitive to existing or future drug therapies," explained William G. Nelson, M.D., Ph.D., a member of the SU2C Scientific Advisory Committee and director of the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University in Baltimore, MD.

Provided by Stand Up To Cancer