# Malignant Signature May Help Identify Patients Likely to Respond to Therapy

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A molecular signature that helps account for the aggressive behavior of a variety of cancers such as pancreatic, breast and melanoma may also predict the likelihood of successful treatment with a particular anti-cancer drug. The finding, which could lead to a personalized approach to treatment for a variety of solid tumors that are currently resistant to therapies, will be published September 6 in the advance online edition of *Nature Medicine*.

Researchers at the Moores Cancer Center at the University of California, San Diego have discovered that a receptor sitting on the surface of certain aggressive tumor cells can activate a key enzyme, src-kinase, which helps tumor cells become more aggressive in the body. This enzyme is the target of the anticancer drug dasatinib, which blocks its activity and is currently approved for treating chronic myelogenous leukemia (CML). The scientists say that the presence of the receptor – a protein called integrin alpha-v beta-3 – on some of the more common solid tumors such as breast, colon, lung and pancreas could help identify individuals with many other types of cancer that are also likely to respond to the drug.

"These results could enable us to identify the subpopulation of cancer patients who are likely to respond to treatment with dasatinib," said David Cheresh, PhD, professor and vice chair of pathology at the UC San Diego School of Medicine and the Moores UCSD Cancer Center, who led the work. "Rather than treat all patients with a given tumor type the same way, by identifying a specific molecular signature consisting of the receptor and its activated enzyme, we can customize the treatment in such a way that we impact the patients most likely to be sensitive to a drug."

The researchers compared the growth properties of pancreatic and breast cancer cells that expressed the alpha-v beta-3 receptor versus those that did not, which led to the discovery of a molecular pathway that accounted for the increased malignancy.

"Once we identified the pathway, we immediately realized that the drug dasatinib, which targets this pathway, would be a logical choice to use against these cancers," Cheresh said. The group's

studies in a preclinical model of pancreatic cancer confirmed that those tumor cells with the receptor responded to the drug, while those not expressing receptors did not.

Cheresh pointed to pancreatic cancer tumors, approximately 60 percent of which carry the marker on the tumor cell surface. "We would argue that pancreatic cancer patients with alpha-v beta-3 would respond to dasatinib," he said. Tumors lacking the marker appear to be resistant to the drug.

"We discovered an unexpected pathway that accounts for increased malignancy in a population of some of the most dangerous cancers," Cheresh said, noting that the marker could be identified by a biopsy. "There are features of the findings that allow us to implicate dasatinib not just for a single tumor type, but for all tumors with the malignant signature."

The findings have led to discussions about the potential design of a clinical trial. "These observations suggest a strategy for testing the effectiveness of dasatinib in breast cancer patients who are positive for the alpha-v beta-3 receptor," said Barbara Parker, MD, medical director of oncology services at the Moores UCSD Cancer Center.

Co-authors include: Jay Desgrosellier, PhD, Leo Barnes, David Shields, PhD, Miller Huang, Steven Lau, Nicolas Prevost, David Tarin, MD, and Sanford Shattil, MD.

The UCSD Moores Cancer Center is one of the nation's 40 National Cancer Institute-designated Comprehensive Cancer Centers, combining research, clinical care and community outreach to advance the prevention, treatment and cure of cancer.

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