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Researchers identify potential targeted therapy for lung cancer using fly model

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A drug approved by the Food and Drug Administration (FDA) for melanoma in combination with a common cholesterol-lowering drug may show promise in controlling cancer growth in patients with non-small cell lung cancer (NSCLC), according to new research from the Icahn School of Medicine at Mount Sinai. Study findings will appear in the February 16 print issue of the journal *Cell Reports*.

Lung cancer remains the No. 1 cancer killer in both men and women, and causes more deaths than breast, prostate, colon, and pancreatic cancers combined. It is often discovered too late to be treated successfully, and current therapies are highly toxic. Researchers have attempted to identify targeted therapies that are effective and do not harm unaffected tissues.

A team of researchers, led by Ross Cagan, PhD, developed a multi-gene lung cancer model in the fruit fly *Drosophila* to better understand the mechanisms that promote tumors in NSCLC. Previous studies have highlighted the similarities among key genes in fruit flies and people. Using both fruit fly and human lung cancer cell lines, researchers targeted two of the most common genetic mutations associated with NSCLC— Ras and PTEN (P13K).

"We developed *Drosophila* lung cancer models by targeting Ras alone and in combination with PTEN knockdown in the tracheal system of the fruit fly," says Cagan, PhD, Professor in the Department of Developmental & Regenerative Biology, Senior Associate Dean of the

Graduate School of Biomedical Sciences, and Director of the Center for Personalized Cancer Therapeutics at Icahn School of Medicine at Mount Sinai. "This led to formation of tumor-like growths."

Using a robotics-based screening approach, researchers screened a library of 1,192 FDA-approved drugs for any that suppressed tumors in the fly and identified several that improved overall survival. They further explored combining two drugs, the FDA-approved melanoma drug trametinib and fluvastatin, a common cholesterol-lowering drug. Oral administration of these drugs inhibited Ras and PI3K pathway activity, respectively, and combining both drugs led to suppression of tumor formation.

"Our study results suggest a new drug cocktail that is effective in both human lung cancer cell lines and fly models," says Cagan. "Next steps are to further explore this possibility in human trials in order to assess if it will help patients, but these two drugs make sense from a variety of studies and we find that they act together through multiple mechanisms to control cancer growth in the laboratory."

Fruit flies can provide an important animal tool in the fight against cancer, says Cagan, providing new molecular and genetic understanding of disease biology and leading to treatments that more specifically kill cancer cells. Use of this knowledge to screen several different drugs, or combinations of drugs, is emerging as an important approach to cancer treatment.

"These simple model systems can be useful for identifying new drug combinations that act in the context of the whole body. Our goal is to leverage them as tools to help identify cocktails that are more effective and less toxic than current standard of care," added Cagan.

Provided by The Mount Sinai Hospital