Targeted therapies outperform hundreds of other drugs in 'priming' lung cancer cells for destruction

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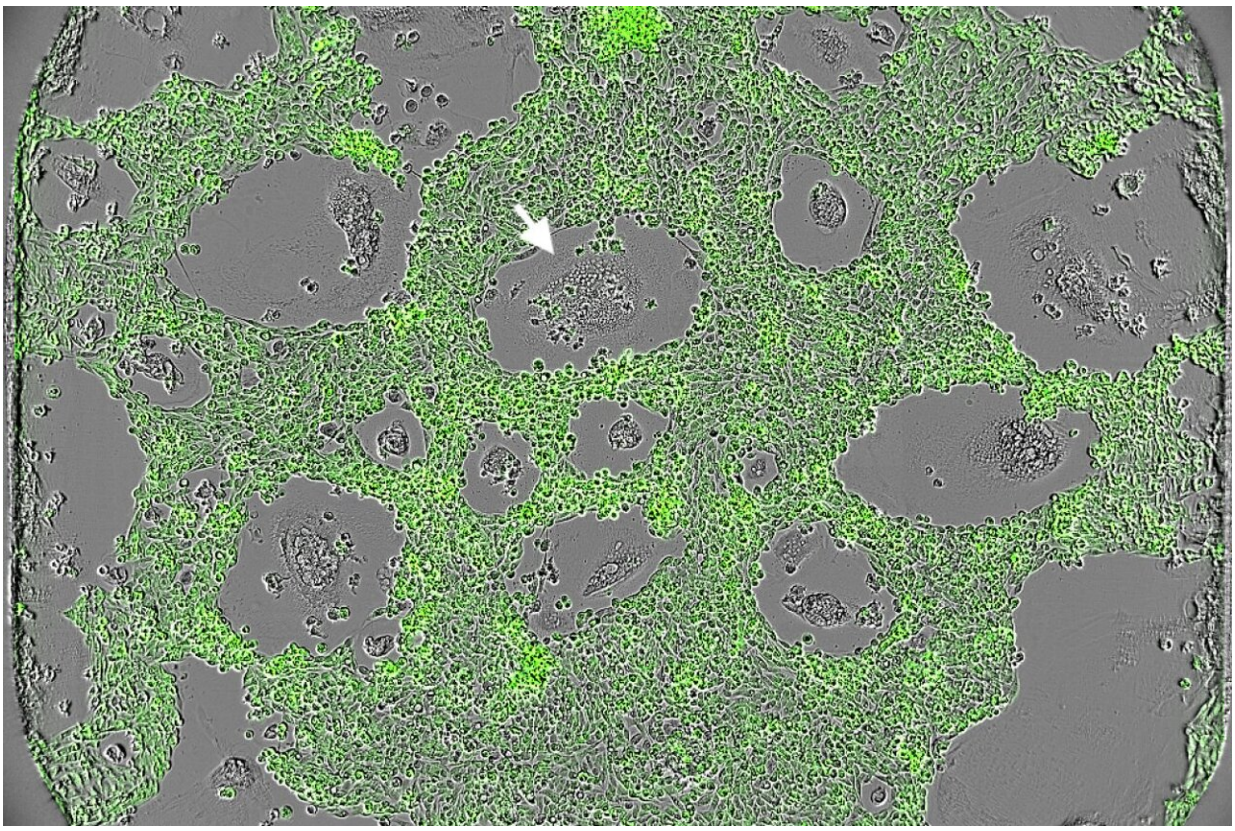


A co-culture of macrophages (unlabeled, white arrow for example) chewing away at a population of EGFR mutant lung cancer cells (green) in response to the combination therapy (EGFR inhibitor and a CD47-blocking antibody). Credit: The Weiskopf Lab/Whitehead Institute

Through millions of years of evolutionary refinement, the human body has developed a sophisticated surveillance mechanism—the immune system. This intricate network is constantly scanning the body for invaders such as bacteria, viruses, and cancer cells. Scientists have long been captivated by its prowess, and, in recent years, they've turned their attention toward leveraging its capabilities to fight cancer.

Whitehead Institute Valhalla Fellow Kipp Weiskopf's lab investigates how a group of immune cells integral to the body's innate defense system can slow down, stop, and kill cancer cells. Among them, macrophages—derived from the Greek words "large eaters"—possess a remarkable ability to engulf and digest cancer cells. Yet, too often, cancer cells manage to elude these vigilant patrollers of the immune system and proliferate unchecked.

Now, Weiskopf, alongside research technician Kyle Vaccaro and former lab member Juliet Allen, has developed a novel drug screen in collaboration with the Hata Lab at Massachusetts General Hospital (MGH). This screening method aims to identify existing cancer therapies capable of rendering lung cancer cells more vulnerable to attack by macrophages.

The researchers' detailed findings, published in the *Journal of Clinical Investigation* on March 14, reveal that therapies blocking the activity of cancer-driving genes outperform hundreds of FDA-approved drugs in priming lung cancer cells for destruction by macrophages.

"Cancer cells have certain molecules on their surface that protect them from macrophages and targeted therapies help remove some of those barriers, making these cells more vulnerable," Weiskopf says. "It's almost like these drugs stress cancer cells in a way that butters them up to make them more palatable for macrophages."

Redirecting cancer down a rocky trail

Despite being the second most common cancer in the U.S., an estimated 53% of lung cancer cases are diagnosed after they have metastasized. This means there's often limited treatment options and clinicians end up relying on conventional routes like chemotherapy and radiation to kill off rapidly dividing cells. But some tumors respond by growing back faster and more aggressively.

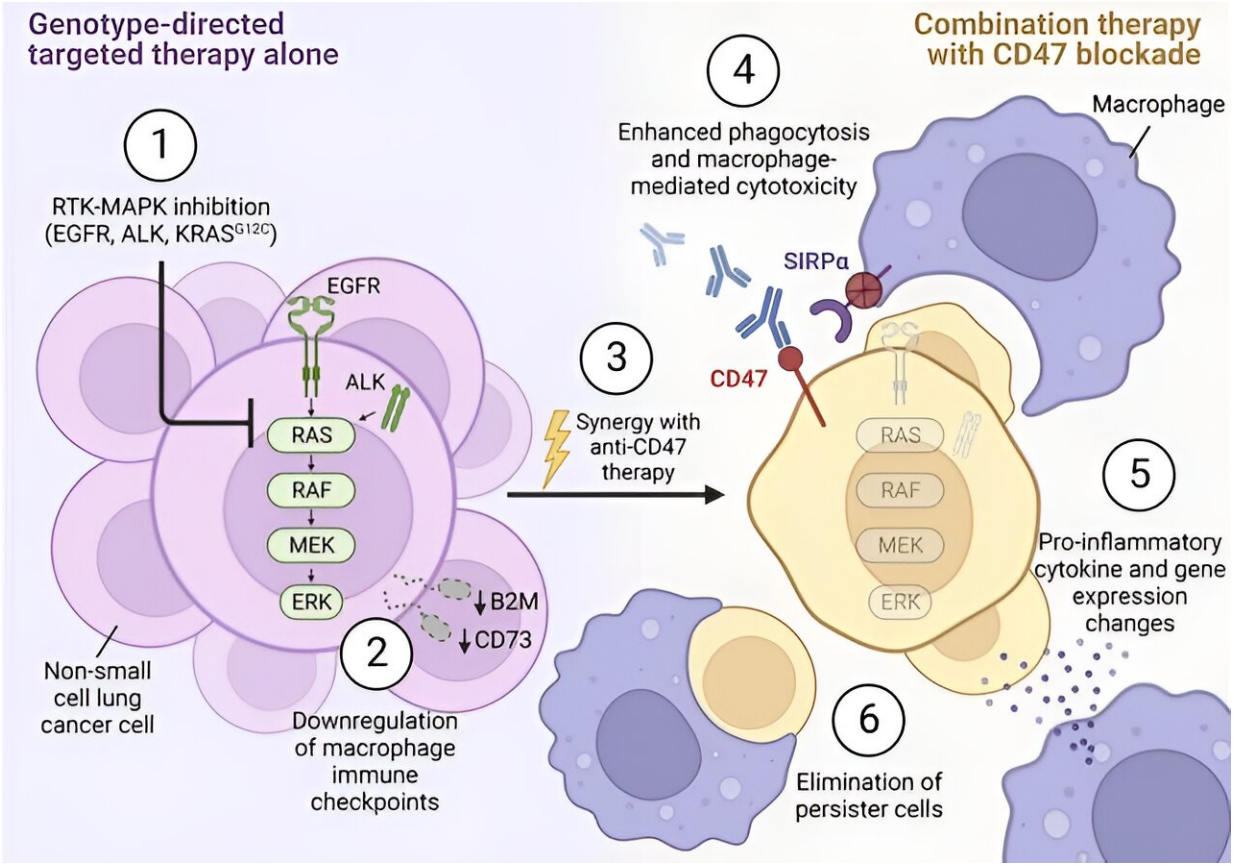
Cancer cells often cloak themselves with a signaling protein called CD47. When macrophages encounter cells adorned with this protein, the interaction triggers a "don't eat me" signal via receptors on the macrophages' surface. Radiation and chemotherapy can influence the production and signaling of CD47, at times even enhancing cancer cells' ability to evade immune system surveillance.

To beat cancer cells at this game of hide-and-seek, scientists have made strides in the past decade in developing antibodies that bind to the CD47 protein, blocking its interaction with macrophage receptors. However, there's a growing recognition in the field that relying solely on CD47 blockers may not be sufficient for triggering an onslaught by the immune system.

While working as a Hematology and Oncology Fellow at the Dana-Farber Cancer Institute in Boston, Weiskopf examined one of his first patients—an individual who had recently received a diagnosis of lung cancer. In caring for this patient, he came to appreciate that about 50% of individuals with a new diagnosis of lung cancer have a specific genetic alteration—also called a driver mutation—that prompts cells to divide uncontrollably.

Could pairing targeted therapies for these genetic alterations with CD47-blocking agents serve as a gateway for enhanced macrophage

attack?



Credit: *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI169315

Crafting an anti-cancer recipe

To explore this intriguing possibility, researchers in the Weiskopf lab began by investigating macrophage function in response to a common genetic alteration found in lung cancer called the EGFR (epidermal growth factor receptor) gene mutation. This type of alteration leads to the EGFR protein—which is typically involved in cell growth and division—becoming hyperactive.

They cultured human macrophages alongside EGFR-mutant lung cancer cells. These cancer cells were modified to produce a green fluorescent protein, enabling the scientists to easily monitor their behavior and interaction with macrophages. Then, they introduced FDA-approved cancer drugs to the mixture in order to assess their effectiveness in eliminating cancer cells, in the presence of CD47-blocking antibodies.

Out of the 800 drugs tested, two targeting the EGFR-mutant protein—erlotinib and gefitinib —stood out: macrophages in these mixtures were markedly better at identifying and killing cancer cells that had been exposed to these drugs.

"Combining targeted therapies with CD47-blocking antibodies could help activate macrophage antitumor functions even in resistant cell lines," says Allen. "In the clinic, this would mean that patients with tumors that have become resistant to targeted therapies because of previous treatment could have hope of being treated again with new immunotherapies."

To confirm if these findings would be consistent over a longer stretch of time, the Weiskopf lab developed an assay that allowed them to observe macrophage efficacy in killing the cancer cells in different drug combinations for up to two weeks. When the researchers used only one type of drug, the cancer cells often survived, forming small clusters. But when they paired drugs that target the EGFR-mutant protein with antibodies that block CD47 protein, the cancer cells dramatically reduced. These effects were consistent at different drug concentrations.

Researchers say these findings aren't limited to EGFR-mutant lung cancer alone—they've demonstrated in the study that other types of driver mutations can benefit from the same approach. This is particularly exciting, according to Weiskopf, since pancreatic and gastrointestinal cancers often involve mutations in a gene called KRAS, which fuels the

growth and spread of cancer cells.

The Weiskopf lab is currently investigating whether combining therapies that target the KRAS-mutant protein with CD47 blockers might be effective for combating these aggressive forms of cancer. They're also working with clinicians at MGH and Dana-Farber to design clinical trials that will take the lab's research on lung cancer from the bench to patients.

"This collaboration between our group and the Hata lab has been exceptional," Weiskopf says. "We've benefitted tremendously from their clinical expertise and foundational knowledge of targeted therapies for lung cancer, and we're thrilled to continue building on this synergy to help patients."

More information: Kyle Vaccaro et al, Targeted therapies prime oncogene-driven lung cancers for macrophage-mediated destruction, *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI169315

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