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'Undruggable' cancers slowed by targeting growth signals

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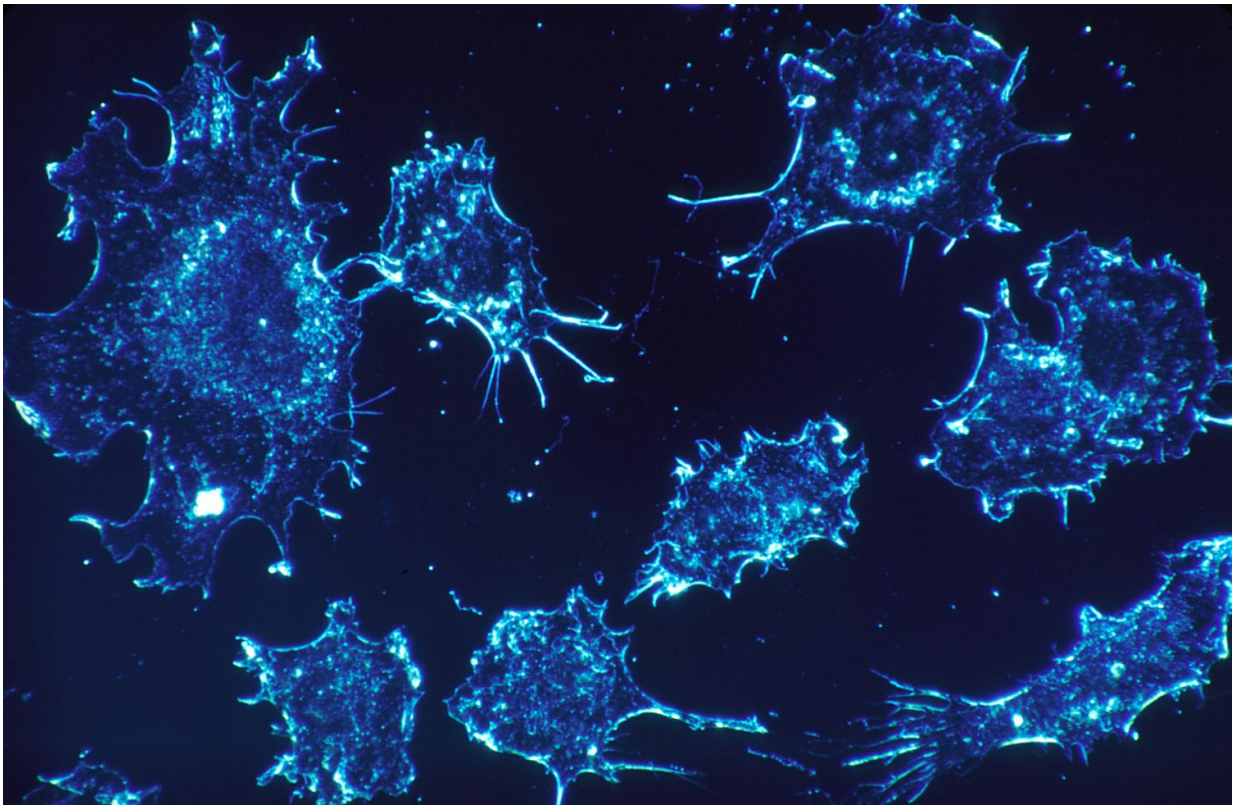

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As many as 50 percent of human cancer cases—across a wide variety of tissues—involve defects in a common cellular growth signaling pathway. These defects have so far defied most attempts to develop targeted therapies, leading some in the field to conclude that they may be

"undruggable." Now researchers at UC San Francisco and Redwood City-based Revolution Medicines, Inc, have identified a new strategy for potentially treating a subset of such intractable cancers by decoupling the entire RAS / MAP Kinase (MAPK) signaling pathway from external growth signals.

In a study published August 13, 2018, in *Nature Cell Biology*, the researchers showed that an experimental compound recently discovered by Revolution Medicines interferes with the first steps of the RAS / MAPK pathway and dramatically slowed cancer growth in lung, skin, colon and pancreatic cancer cell lines as well as human lung cancers grown in animal models. Based on these results, Revolution Medicines aims to rapidly advance this approach into clinical trials in human patients using a proprietary drug candidate called RMC-4630.

"RAS / MAPK is one of the most important cancer signaling pathways, but so far most attempts to develop targeted drugs against this pathway have ended in failure, which has led some people to start calling it a 'Holy Grail' of cancer therapy," said study senior author Trever Bivona, MD, Ph.D., a UCSF Health clinical oncologist. "Now, for the first time, we think we have a general strategy that could work against a subset of RAS / MAPK-driven cancers."

The RAS / MAPK pathway (also known as the MAPK / ERK pathway), which plays a central role in telling normal cells when to grow and divide, works via a Rube Goldberg-like cascade of protein interactions. It begins with an "upstream" growth signal from outside the cell binding to a receptor protein on the cell surface, which activates the protein RAS inside the cell, which in turn triggers a sequence of steps (RAS recruits RAF, RAF activates MEK, MEK stimulates MAPK) that ultimately direct a wide variety of "downstream" growth-promoting genetic programs in the cell nucleus. At the same time, regulatory proteins such as the tumor suppressor NF1 keep the volume of growth signaling

through the RAS / MAPK pathway within a healthy range.

Mutations in one or a combination of proteins involved in this cascade can send cellular growth into overdrive, leading to tumor formation. However, most attempts to develop drugs targeting individual defects in the RAS / MAPK pathway or to block its downstream effects have failed—either because the pharmacology of affected proteins makes them too difficult to drug, or because patients' cancers were able to quickly develop resistance to treatment through alternative arms of the RAS / MAPK pathway.

But recent studies have suggested a new opening for potential therapies, Bivona says. Scientists have long thought that cancer-associated RAS / MAPK defects always involve one of the pathway's proteins getting jammed in its pro-growth position so that cells no longer respond to normal growth signals and become locked in a mode of constant growth. In contrast, recent research has shown that some of cancer-linked mutations merely make the associated protein hypersensitive to normal growth signals—essentially turning up the volume of the RAS /MAPK signaling pathway as a whole. In cancers driven by such mutations, Bivona and others reasoned, blocking upstream growth signaling at the source could halt cancers' growth.

Bivona and colleagues have now tested this hypothesis—demonstrating that the growth of multiple cancers can be slowed by supressing RAS / MAPK signaling using a novel experimental compound that targets an enzyme and scaffolding molecule called SHP2.

The research was a collaboration with Revolution Medicines, a biotech company co-founded by UCSF's Kevan Shokat, Ph.D., which has identified a small molecule called RMC-4550 that potently inhibits SHP2 signaling. Researchers at Revolution Medicines, including Robert Nichols, Ph.D. and Jacqueline (Jan) Smith, Ph.D., brought this

compound and initial findings in cancer cell lines to Bivona, where Nichols and Bivona lab post-doctoral researcher Franziska Haderk, Ph.D., led a team that further explored the compound's mechanism of action and tested it against a variety of additional human cancers.

The team found that SHP2 plays a key role in allowing receptor proteins on the cell surface to activate RAS, and that RMC-4550 effectively decouples the entire RAS / MAPK pathway from normal external growth signals. They then tested the compound on several dozen cancer cell lines with mutations thought to be dependent on upstream growth signals, including so-called class 3 BRAF mutations, a subset of KRAS mutations, and mutations that cause a loss of the tumor suppressor gene NF1. They found that RMC-4550 inhibited cancer growth in multiple subtypes of lung, melanoma, colorectal, and pancreatic cancer cells with the above mutations, and in some cases directly killed the cancer cells.

The researchers also tested the compound against human tumor samples grown in mice, a state-of-the-art preclinical technique called patient-derived xenografts (PDX). In PDX models of five different non-small-cell lung cancers—each containing one of the three classes of SHP2-sensitive mutations listed above—the researchers found that RMC-4550 blocked tumor growth or caused tumors to shrink while causing minimal side effects in the animals.

"We were able to demonstrate that this compound successfully suppressed the RAS pathway in the rodent tumor models and that this not only slowed tumor growth but even led to tumor regression in some cases, with minimal side effects in the animals," Bivona said. "This was very exciting to me because it meant that the compound was not just arresting cell growth but actually killing cancer cells."

As with any preclinical study, the results now wait on human safety and efficacy trials, which Revolution Medicine plans to launch later this year

using a distinct small molecule inhibitor of SHP2 called RMC-4630, which is designed to have a good profile for use in patients.

"The implications of being able to block SHP2 are broad and may extend to more types of cancer than seen in the present study," Bivona added. "Almost every major oncogene I can think of coopts this pathway in one way or another, and many of these cancers currently have no effective targeted therapies or eventually develop resistance to available targeted therapies."

"It's exciting to anticipate such important work moving quickly from the laboratory to the clinic," Bivona added. "UCSF is a uniquely rewarding place to conduct this type of dual scientific research that links biological and translational science in collaboration with industry partners like Revolution Medicines."

More information: RAS nucleotide cycling underlies the SHP2 phosphatase dependence of mutant BRAF-, NF1- and RAS-driven cancers, *Nature Cell Biology* (2018). DOI: 10.1038/s41556-018-0169-1 , www.nature.com/articles/s41556-018-0169-1

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