New method of targeting mutant RAS protein provides hope for cancer patients

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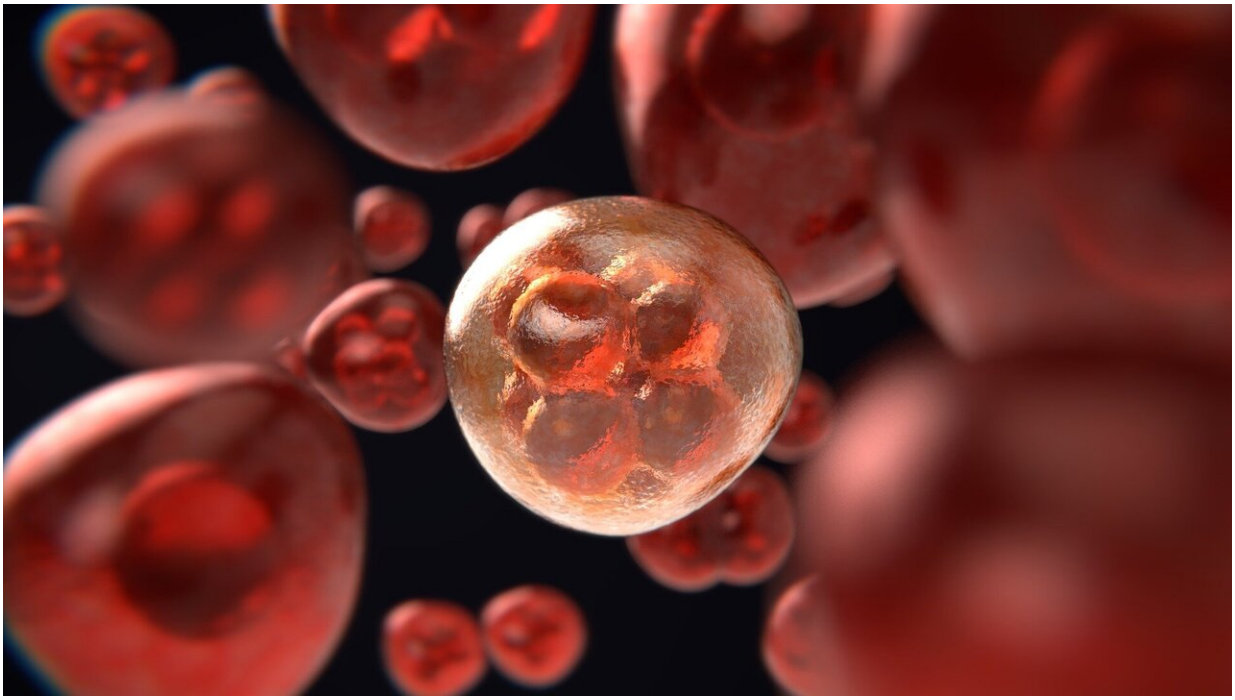

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As a 10-year journey comes to fruition, Medical University of South Carolina (MUSC) Hollings Cancer Center researcher John O'Bryan, Ph.D., and colleagues have demonstrated a new therapeutic way to block a protein that is frequently mutated in cancers. These proof-of-principle findings were published on Feb. 8 in *Cell Reports*. This work, which involves inhibiting the oncogenic protein RAS using small molecules,

lays a strong foundation for the development of clinical anti-cancer therapies.

The American Cancer Society estimates that 1.9 million new cancer cases will be diagnosed this year. Based on the urgent need for more effective therapies, researchers are always on the search for elusive treatments that can affect many cancers.

O'Bryan, who is a professor in the Department of Cell and Molecular Pharmacology and Experimental Therapeutics at the Medical University of South Carolina, said, "RAS is one of the most central and critical regulators of cell proliferation, and it is also the most mutated in cancers. Mutated RAS drives the growth of tumors. This makes it an attractive therapeutic target."

The RAS family of proteins are mutated in nearly 20% of human tumors; however, there has been little progress in drug development for this target. "Think of RAS as a slick ball that does not let anything bind to it. Until recently, it was thought that mutant RAS could not be targeted with drugs. Now there is one FDA-approved drug for mutant RAS in lung cancer, which demonstrates that it is possible to target mutant RAS in some cases," said O'Bryan.

The new drug sotorasib targets a mutant form of RAS that only occurs in less than 3% of all human cancers, so the new drug is not very useful across multiple types of cancers, O'Bryan said. His new method of therapeutically targeting mutant RAS is more promising because it has the potential to work with numerous mutant forms of RAS in multiple cancers.

"Pancreatic, lung and colorectal cancers are three of the four most deadly cancers, and their growth is driven by mutations in RAS proteins. Therefore, successfully targeting mutant RAS has big implications for

patients," said O'Bryan.

The challenge with targeting RAS is due to the way it functions. It has "on" and "off" states that are regulated by binding to other molecules called nucleotides. There is also a third state called the nucleotide-free state when it is switching between on and off modes. However, RAS proteins are in their nucleotide-free states for such short amounts of time that it was previously thought that RAS could not be targeted during this very short-lived state.

O'Bryan's collaborator Shohei Koide, Ph.D., from the Perlmutter Cancer Center at New York University, developed the monobody technology that overcomes the challenges with targeting nucleotide-free RAS. Monobodies are small synthetic binding proteins that can be designed to attach to cellular targets inside or outside of cells. Previously, targeting nucleotide-free RAS mutants was thought to be an impossible undertaking.

Targeting nucleotide-free RAS with the R15 monobody has allowed the researchers to understand RAS biochemistry more fully and discover opportunities to disrupt its cancer-promoting activity. Using a mixture of biochemistry techniques, cell culture work and animal models, they found that the R15 monobody blocks multiple forms of RAS mutants.

"We were surprised to find that many RAS mutants unlock nucleotides, and the R15 monobody can block these," said O'Bryan. "It is a good sign that more than 50% of oncogenic RAS mutants may be susceptible to inhibitors binding nucleotide-free RAS. This makes targeting nucleotide-free RAS a viable approach for inhibiting many mutant RAS-driven tumors."

There is often serendipity in a research career, O'Bryan said. "We got stuck by our early data because it did not make immediate sense.

However, it turned out to be an exciting finding. There is a skill in discerning between insignificant artifacts in the data and something novel that is real discovery."

This work provides a framework for other groups to target RAS in more effective ways. "The RAS protein, which was considered undruggable, is in fact able to be targeted by drugs," said O'Bryan.

The researchers are very hopeful that this discovery can be used more comprehensively in the future. While cancers do adapt and mutate to become resistant to therapeutics, new drugs based on this concept might serve as additional tools in the arsenal to treat cancer, he said.

The next step in the journey will be to find small molecules in MUSC's compound library that can be used to target mutant RAS in the same way as the R15 monobody. Since the R15 monobody cannot easily get into cells, O'Bryan explained that a small molecule targeting nucleotide-free mutant RAS proteins will be a more effective therapy.

"We are at a really good stage to exploit this mechanism," said O'Bryan. "MUSC and Hollings have a really great culture of collaboration, which has helped to push this project forward. MUSC's access to the massive library of small molecules helps to provide a lot of chemical diversity and intellectual property potential."

The researchers feel that this research reveals a new window of opportunity for the development of novel anti-cancer agents necessary to improve patient outcomes.

More information: Imran Khan et al, Identification of the nucleotide-free state as a therapeutic vulnerability for inhibition of selected oncogenic RAS mutants, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2022.110322

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