New prostate cancer treatments could target metabolism

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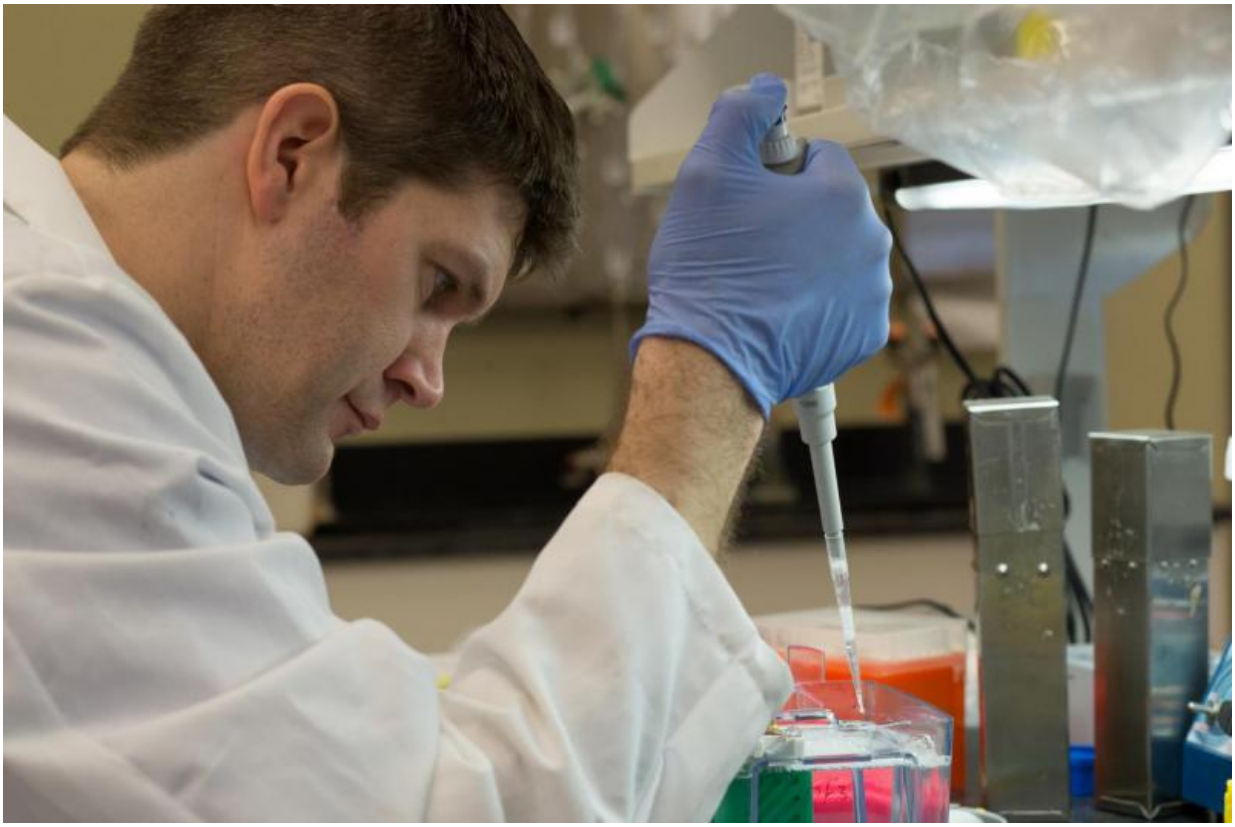

Receiving two grants within a week of each other, Dan Frigo is targeting two different mechanisms that play a role in prostate cancer. Both focus on a cascade of biochemical reactions inside cells, downstream of a protein called the androgen receptor (AR). Credit: Jessie Villarreal

Prostate cancer is the most commonly diagnosed malignancy and second

leading cause of cancer-related deaths among men in the U.S. The challenge with prostate cancer is that the standard treatment methods in the advanced stage of the disease lose effectiveness after about one to two years, leading to recurrence and, ultimately, death. A University of Houston researcher and his team are working to change that.

With the assistance of nearly $2.3 million in funding from the National Institutes of Health's National Cancer Institute, assistant professor Daniel Frigo is investigating two new avenues for detection and treatment. Receiving two grants within a week of each other, Frigo is targeting two different mechanisms that play a role in prostate cancer. Both focus on a cascade of biochemical reactions inside cells, downstream of a protein called the androgen receptor (AR).

Androgens, such as testosterone, are a class of hormones that control the development and maintenance of male characteristics. These hormones bind to AR molecules, which regulate a variety of different processes and parts of a cell. While it is needed for basic male development, like puberty, it can become overactive and cause prostate cancer by altering different genes. So, too much of it can be a bad thing.

"The standard of care for advanced prostate cancer is to block the AR molecule. One of the major ways to treat it is through androgen ablation therapy," Frigo said. "You can either chemically castrate the patient to prevent him from making androgens, or you can administer a drug that blocks where androgens bind to the AR. But the AR is a sneaky molecule that can become reactivated in a number of different ways to get around these drugs."

Invariably, the disease goes through two stages. One is called the hormone-sensitive stage where you can successfully block the prostate cancer, but the patient always relapses to a stage called castration-resistant prostate cancer, which is when the same treatments no longer

work.

"While it is well understood that aberrant AR signaling starts a chain of events that is crucial in driving prostate cancer, little is understood what happens after this initial event," Frigo said. "Since the AR becomes a very difficult-to-target molecule and the drugs currently being used don't remain effective, we're taking a new approach that bypasses the problem, which is to look downstream of AR."

In the first study, funded by a $1.9 million R01 grant, Frigo and his team are looking at a potential new androgen-regulated signaling pathway that appears to drive the development and progression of prostate cancer by shifting the metabolism of the cancer cell. This pathway is made up of a cascade of proteins that include two called CaMKKbeta and AMPK that allow the cancer cell to use a more diverse range of nutrients, such as sugars, fatty acids and proteins, to then metabolize and use for making more energy and provide building blocks to feed tumors.

Cancer cells are greedy and always looking for more ways to divide and grow. AR proteins, Frigo explains, can increase the expression of the CaMKKbeta gene. This enables cancer cells to become really aggressive, giving them the power to soak up a number of different nutrients from the outside. That gene, in turn, activates AMPK, which is a master regulator of metabolism and further strengthens metabolic processes leading to prostate cancer.

"We've been interested in this pathway because we think that the way it gets activated could be a potential new therapeutic target," Frigo said. "It seems like it's very restricted to prostate cancer and controls several different aspects of it. By controlling metabolism, it can then also regulate the proliferation and survival of cancer cells, as well as controlling their migration, which is needed for metastasis. Our goal with this grant is to figure out how it does this and how to stop it."

The good news, Frigo says, is that it appears to be a druggable pathway, so something can be done about it. While many cancer signaling pathways look like they could be driving cancer, there's nothing you can do about it. His team is currently performing validation studies to show that the CaMKKbeta-AMPK cascade is indeed a viable therapeutic target. If they are successful, it will provide the rational for developing new ways to target this pathway and, ultimately, move into clinical trials to test new cancer drugs for suppressing it.

"In fact, we know that some of the pathways downstream don't drive cancer and some might even suppress cancer," Frigo said. "So, if we can identify those that are causing cancer progression, we think those might be good new targets, as well."

In the second study, funded by a $400,000 R21 grant, Frigo and his colleagues are focusing on an oncogene called Myc that becomes activated to drive cancer cells and regulates how they use glutamine, an amino acid that can be used in a variety of ways by the cell. For example, different aspects of glutamine can indirectly control dangerous reactive tumor-causing, or oncogenic, species that can attack different parts of the cell.

Data suggests that AR signaling, Myc and glutamine metabolism may coordinate to drive prostate cancer progression. The research team hypothesizes that AR signaling promotes prostate cancer cell growth through Myc-mediated glutamine metabolism. Understanding their relationship could lead to glutamine-directed therapeutics to treat prostate cancer.

"Like AR, Myc is a big driver of prostate cancer and also historically difficult to target, so we're looking downstream of both of them and think their two pathways converge on the process of glutamine metabolism," Frigo said. "We think there are elements of glutamine

metabolism needed for cancer to progress, and we're trying to identify one area that is common to both AR and Myc. Our aim is to find out what and where that is and, ultimately, target it. Our long-term goal is to develop new metabolic-based therapeutic approaches for the detection and treatment of prostate cancer."

While the bulk of work is being done at the Center for Nuclear Receptors and Cell Signaling in UH's College of Natural Sciences and Mathematics, both projects are being done in collaboration with researchers at Baylor College of Medicine.

Provided by University of Houston

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