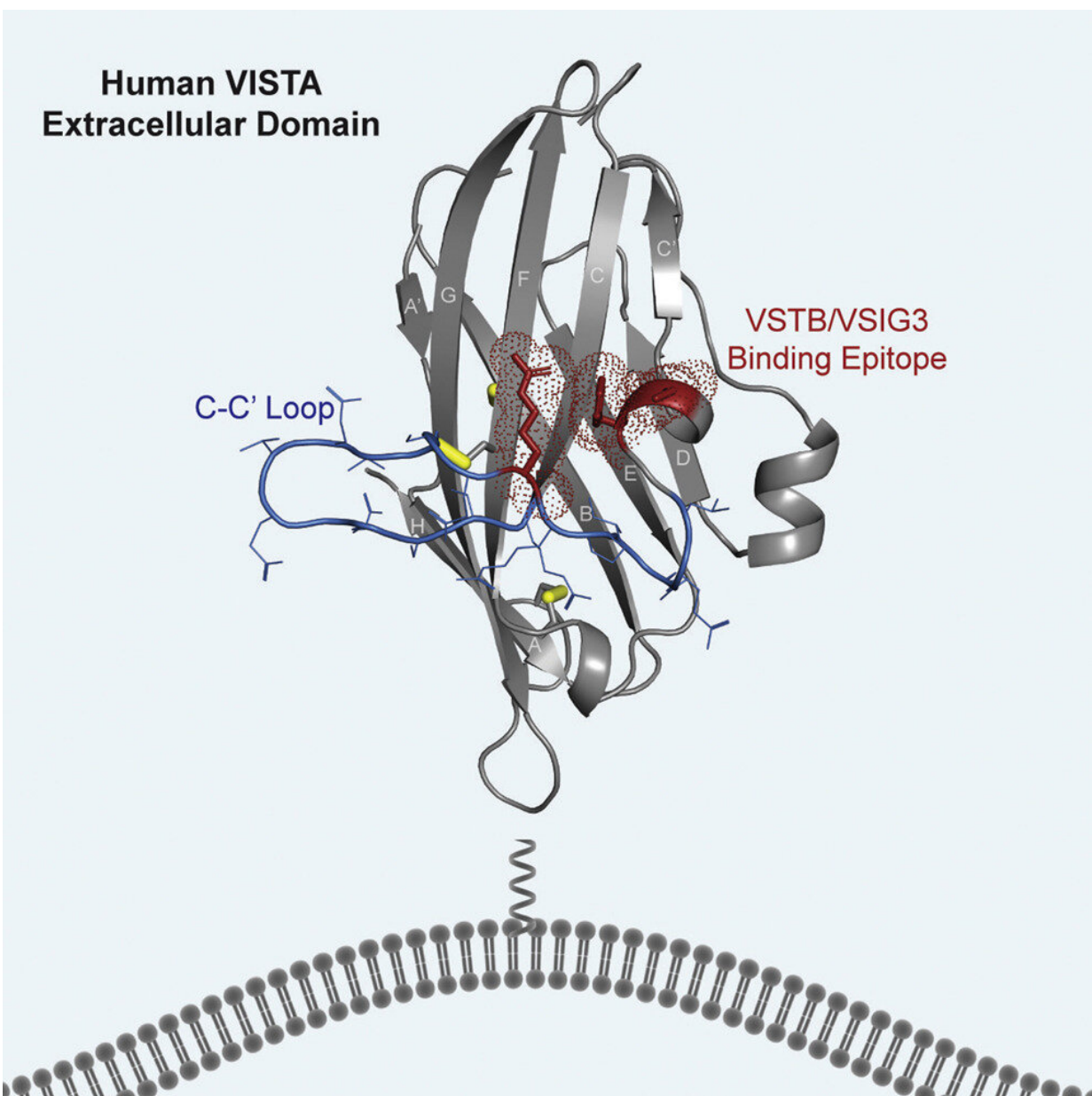


New insight into a cancer-shielding protein could guide a new generation of cancer treatments

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Using a combination of computation and experiment, researchers were able to map the shape of VISTA, a ‘checkpoint’ protein that defends cancer cells from immune system attacks, as well as the part of the protein molecule that the immune system can recognize and target. Credit: SLAC National Accelerator Laboratory

In a paper published in *Cell Reports*, a team of researchers from the Department of Energy's SLAC National Accelerator Laboratory and Stanford University discovered unique characteristics of a protein called VISTA that protects cancer cells against immune system strikes. A better understanding of how this protein works could guide the design of treatments that target these proteins, infiltrating cancer's first line of defense.

Picking the weeds

The [human body](#) is made up of trillions of cells that are constantly created, destroyed and replaced with new ones, like blades of grass on a lawn. But when cells start to grow and divide uncontrollably, like pesky weeds, they can form a solid mass called a [tumor](#). If cancerous, this tumor can deepen its roots and spread to other parts of the body.

The solution seems straightforward enough. Just as one might weed a garden, the [immune system](#) can attack these diseased cells and nip the cancer in the bud. But the tumors have a secret weapon: The ability to cloak themselves, using special "checkpoint" proteins such as VISTA, and masquerade as normal, healthy grass.

"When [tumor cells](#) arise, they are recognized as foreign and are cleared

by the immune system via specialized cells known as T cells," says Jennifer Cochran, a professor of bioengineering at Stanford University. "But surface markers on the cells surrounding the tumor known as 'immune checkpoints' have been shown to act as an invisibility cloak of sorts to shield a tumor from immune system recognition and destruction."

Stripping the invisibility cloak

FDA-approved antibodies that strip this cloak of invisibility and unleash immune system attacks on tumors have demonstrated remarkable power in treating a variety of cancers because they allow the immune system to find and destroy cancer [cells](#) without the toxic effects of chemotherapy. But due to a lack of information about how checkpoint proteins work, these drugs are only effective for about a quarter of patients.

In a first, the team, led by Cochran, Possu Huang, a professor of bioengineering at Stanford, and Nishant Mehta, a Stanford Ph.D. candidate, in collaboration with Irimpan Mathews, a researcher at Stanford Synchrotron Radiation Lightsource (SSRL), was able to map the structure of VISTA at high resolution, which required a combination of computational and experimental techniques.

To better understand its structure, the researchers crystallized VISTA molecules, then measured how the crystals diffracted X-rays at one of SSRL's specialized beamlines. When researchers analyzed the data using computational tools, the patterns formed when the X-rays irradiated the crystals allowed them to map the shape and detailed atomic structure of the protein as well as its epitope, the part of the molecule that the immune system can recognize and target.

"This research was only possible because of the collaboration between experts in molecular engineering, computational protein design and

structural biology," says Mathews.

Breaking down defenses

To follow up on this research, Mehta hopes to use what they learned about the structure and binding region of VISTA to develop drugs that work against it and other checkpoint proteins.

"These proteins keep our immune systems from finding and destroying the [cancer cells](#)," Mehta says. "Until now, researchers didn't have a detailed picture of what VISTA looks like on a molecular level. What we learned in this study is extremely useful in designing new drugs because it tells us which areas to target to block the checkpoint [protein](#)'s function."

More information: Nishant Mehta et al. Structure and Functional Binding Epitope of V-domain Ig Suppressor of T Cell Activation, *Cell Reports* (2019). [DOI: 10.1016/j.celrep.2019.07.073](https://doi.org/10.1016/j.celrep.2019.07.073)

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