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Embargoed Until:
SEPTEMBER 9, 2025 at 10:00 A.M. EST

Contact:
Darien Sutton
(215) 898-3988
dsutton@wistar.org

Wistar Scientists Identify Novel Therapeutic Target for Ovarian Cancer

PHILADELPHIA — (SEPT. 9, 2025) — New research by Wistar Institute scientists shows how targeting a cleft in the retinoblastoma protein can kill tumor-protecting macrophages in ovarian cancer. The discovery provides a novel therapeutic target that could potentially make ovarian and other cancers more sensitive to immunotherapies. Their findings are published in *Cancer Immunology Research*, a journal of the American Association for Cancer Research.

It's a surprising finding, since retinoblastoma protein is more often understood to suppress cancer cells; in theory, blocking it should speed up cancer growth. However, researchers found that by targeting only part of the protein, they could turn off its ability to protect tumor-supporting macrophages, without affecting its cancer-suppressing abilities.

"This is a first-in-kind target against a solid tumor, in this case ovarian cancer," said senior author Dr. Luis Montaner, D.V.M., D.Phil., executive vice president of The Wistar Institute, and director of the HIV Cure and Viral Diseases Center. "It's exciting, because it opens up a novel therapeutic target that has never been described before."

Macrophages are immune cells that have different functions in the body. While some macrophages help the immune system target and fight diseases, others support wound healing by calming the immune response to protect tissues undergoing repair. Tumors like ovarian cancer use these second kind of macrophages to create a protective environment that shields them from immune attack. Previous studies have shown that these macrophages could be targeted with drugs. However, scientists found they could not target tumor-supporting macrophages without also wiping out beneficial macrophages that fight disease.

While the new discovery has important implications for cancer treatment, it actually grew out of HIV studies, noted Montaner, a prominent HIV researcher. He said scientists had been investigating the role of macrophages in HIV infection when they discovered that retinoblastoma protein plays a key role in helping macrophages survive HIV infection. Researchers then wondered if the protein played a similar role in the survival of tumor-supporting macrophages in cancer.

In subsequent lab studies they found that blocking a specific cleft in the protein turned off this survival mechanism without disabling the protein itself. This depleted the population of tumor-protecting macrophages, leaving the tumor cells vulnerable to immune attack.

NCI Cancer Center
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Researchers then tested this approach in animals and found that their tumors shrank.
Montaner noted that the discovery was a years-long process because the findings were so unexpected and went against established thinking about the role of retinoblastoma protein in cancer. With each new experiment, researchers expected to be proven wrong.

"As time progressed the data kept piling up, until we ended up with a large body of evidence behind one straightforward conclusion," he said.

Altogether it took more than 10 years from the time his team first linked retinoblastoma with macrophage survival to the publication of their collective findings supporting this new approach to treat cancer.

Montaner said the study pointed to the importance of interdisciplinary research, and how discoveries in one area of medicine, like HIV, can lead to breakthrough in other fields like cancer.

"Our bodies were designed to survive in a hostile environment where you cannot predict what kind of threat you will encounter," he said. "So whether it's autoimmunity, cancer, or an infection, a lot of the same processes are engaged. When you learn how to manipulate or control a certain response, it is very likely it is reflected in other aspects of your engagement with disease, which is exactly what happened here."

Next, the team is working on follow-up research, including studying how regulating retinoblastoma protein affects macrophages in acute myeloid leukemia and pancreatic cancer. They will also test the approach in combination with immunotherapy.

"We've learned a lot about how to manipulate this target," he said. "We also know its therapeutic potential may not be restricted to ovarian cancer, and that there may be an opportunity to join it with other therapies that would then be more impactful."

Co-authors: Evgenii N. Tcyganov, Taekyoung Kwak, Xue Yang, Adi Narayana Reddy Poli, Colin Hart, Avishek Bhuniya, Joel Cassel, Andrew Kossenkov, Noam Auslander, Lily Lu, Paridhima Sharma, Maria De Grecia Cauti Mendoza, Dmitry Zhigarev, Gwendolyn Cramer, David Weiner, Laxminarasimha Donthireddy, Joseph M. Salvino from The Wistar Institute; Mark Gregory Cadungog, Stephanie Jean, Sudeshna Chatterjee-Paer, Bryan Bristow from Helen F. Graham Center, Christiana Health Care System; Vladimir A. Tyurin, Yulia Y. Tyurina,Valerian E. Kagan from University of Pittsburgh; Hülya Bayir from Columbia University Irving Medical Center; Rugang Zhang from University of Texas MD Anderson Cancer Center.

Work supported by: NIH grant R01CA1665065 (to L.J.M.); Department of Defense grant W81XWH-19-1-0092 (to L.J.M.); PA Department of Health CURE funds; the Robert I. Jacobs Fund of The Philadelphia Foundation; Ovarian Cancer Research Alliance [596552] (to R.Z.); and NIH Cancer Center Support Grant CA010815 for Wistar Institute core facility support.

Publication information: "Targeting LxCxE cleft pocket of retinoblastoma protein in M2-like immunosuppressive macrophages inhibits ovarian cancer progression," *Cancer Immunotherapy Research*, 2025. Online publication.

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