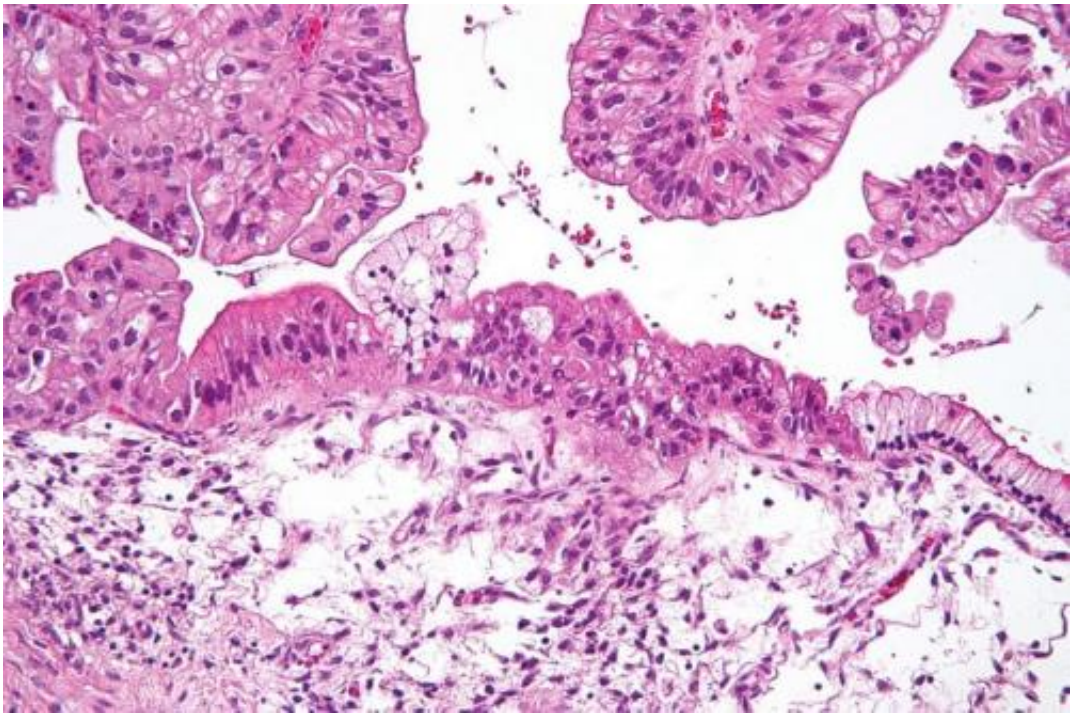
Preclinical study identifies new target for recurrent ovarian cancer

April 17 2023



Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. H&E stain. The micrograph shows: Simple mucinous epithelium (right) and mucinous epithelium that pseudo-stratifies (left - diagnostic of a LMP tumour). Epithelium in a frond-like architecture is seen at the top of image. Credit: Nephron /Wikipedia. CC BY-SA 3.0

Despite recent advances, ovarian cancer remains the fifth leading cause of cancer-related deaths among women, and there's a critical need for new treatment options, especially for advanced cancers that grow back

after standard of care treatment. Results from a preclinical study, led by researchers from the Perelman School of Medicine at the University of Pennsylvania, verified a new target for drug-resistant ovarian cancer and provided data to support a treatment approach that is already making its way into clinical trials.

Sarah Gitto, Ph.D., an instructor of Pathology and Laboratory Medicine, will present the findings (Abstract #1133) at the American Association for Cancer Research (AACR) Annual Meeting 2023.

"Unfortunately the majority of ovarian cancers recur and become resistant to standard platinum chemotherapy," said senior author Fiona Simpkins, MD, a professor of Obstetrics and Gynecology. "Platinum-resistant ovarian cancer is the most challenging type of ovarian cancer to treat, and developing new therapies in this area is an urgent priority."

PARP inhibitors (PARPi), a newer type of targeted standard of care treatment, have increased survival for ovarian cancer patients, but, similar to chemotherapy, these therapies eventually stop working for many patients, leaving them without treatment options.

To combat these challenges, this study focused on the protein B7-H4, which—as pivotal work from co-author and collaborator Daniel J. Powell Jr., Ph.D., an associate professor of Pathology and Laboratory Medicine, has shown—is a potentially high impact target that is found in the majority of breast and ovarian cancers at diagnosis. Because cancer treatment can affect which proteins are expressed on cells, the researchers set out to determine if B7-H4 was still expressed at high levels after multiple treatments in the recurrent setting, and would therefore be an appropriate target for patients who have already received chemotherapy or PARPi.

The team used matched samples from the Penn Ovarian Cancer

Research Center Tumor BioTrust Collection, to see if B7-H4 was found in tumor tissue from the same patients before, during, and after treatment—and in some cases in the setting of end-stage metastatic disease. They found that B7-H4 was overexpressed in 92 percent of high grade serous ovarian carcinoma (HGSOC) tumors analyzed at diagnosis and maintained high levels throughout the course of cancer treatment, even following chemotherapy or PARPi. Importantly, the protein was consistently found on the outside of the cells (rather than only *inside* the cells), where a drug could easily bind to it.

Antibody-drug conjugate successfully targets B7-H4

After establishing B7-H4 as a viable target, the researchers tested an antibody-drug conjugate in multiple cell lines and more than 20 patient-derived xenograft (PDX) cancer models of breast and ovarian cancer. Antibody-drug conjugates are a new class of highly targeted immunotherapy drugs that cause far less toxicity than traditional chemotherapy.

In 61 percent of PDX models that hadn't received any previous PARPi or chemotherapy treatment, the tumors decreased in size after just one dose. With continued treatment every 28 days, to better mimic clinical dosing, the drug resulted in significant tumor regression and increased survival in treatment-resistant PDX models.

"We saw excellent anti-tumor activity, sustained over a long period of time in models that are drug-resistant, which is uncommon," Gitto said. "We've been able to show that B7-H4 is a very robust and widespread target that can be used across multiple stages of patient care."

An antibody-drug conjugate targeting B7-H4 is now being tested in a multisite Phase I clinical trial (NCT05123482).

"We're excited about the potential for antibody-drug conjugates to overcome drug resistance, and this work shows they merit further development in ovarian cancer," Simpkins said. "This type of progress is possible thanks to the patients who participate in research, including biospecimen banking programs that allow scientists to learn about how their disease changes over time."

Gitto presented the findings during the Innovative Therapeutic Approaches Minisymposium on Sunday, April 16.

More information: Abstract #1133

Provided by Perelman School of Medicine at the University of Pennsylvania