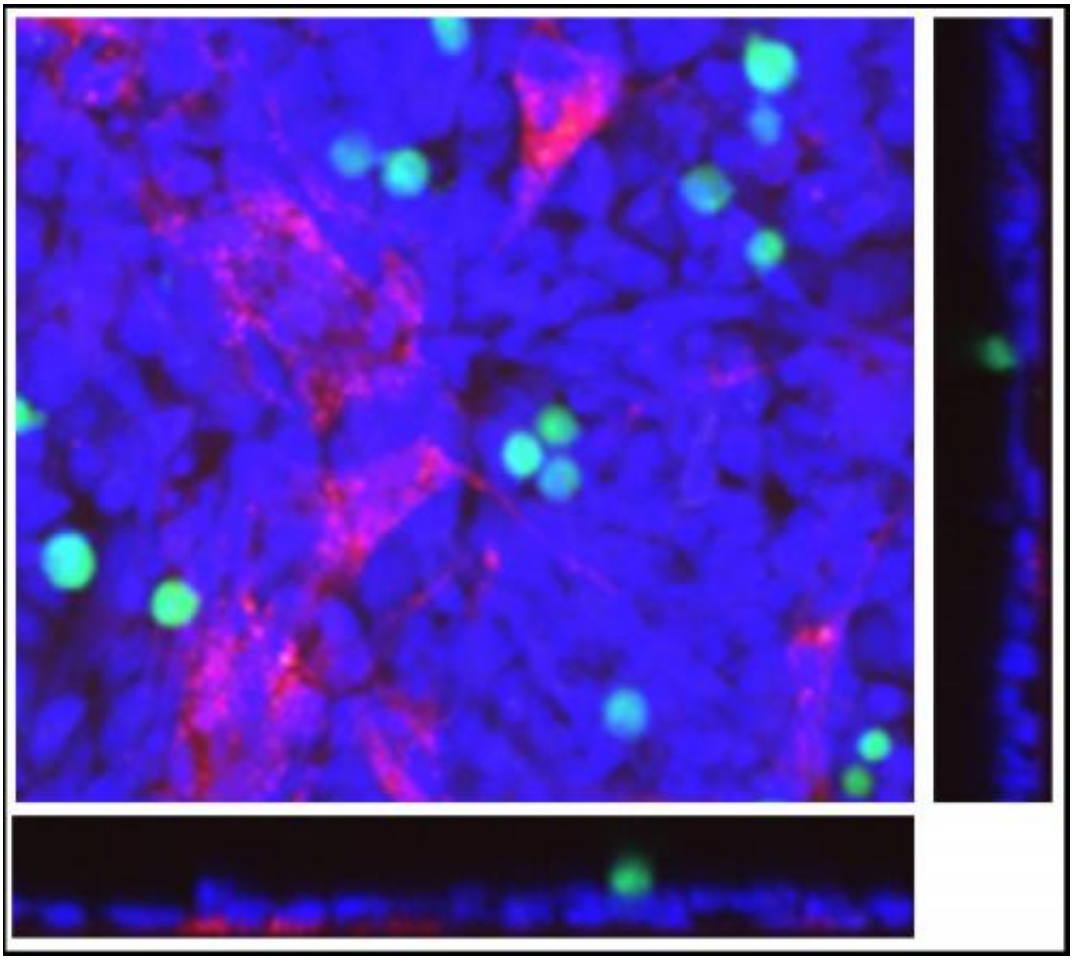
New screening tool could speed development of ovarian cancer drugs

February 10 2015



A multi-layered 3-D 'organotypic' platform for quantitative high-throughput screening to identify new therapeutics for ovarian cancer. Fibroblasts are red. Mesothelial cells are blue. Ovarian cancer cells are green. The square image is the XY-planes (up-down, right-left). The images on the sides are Z-planes (depth). Credit: Lengyel laboratory, University of Chicago

University of Chicago Medicine researchers have built a model system that uses multiple cell types from patients to rapidly test compounds that could block the early steps in ovarian cancer metastasis. Their three-dimensional cell-culture system, adapted for high-throughput screening, has enabled them to identify small molecules that can inhibit adhesion and invasion, preventing ovarian cancers from spreading to nearby tissues.

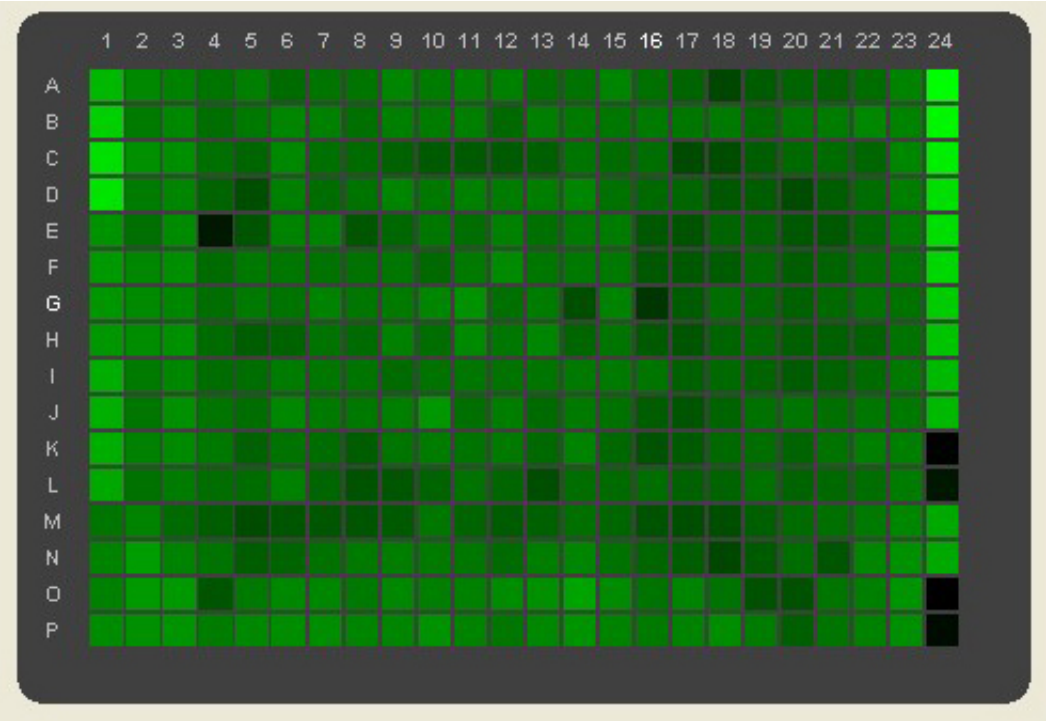
The study, published online February 5, 2015, in the journal *Nature Communications*, is the first to describe a high-throughput screening drug-discovery platform for ovarian cancer that mimics the structural organization and function of human tissue. The model reconstructs the surfaces of the omentum and the peritoneum, membranes that line the abdominal cavity, which are the most frequent sites of ovarian cancer metastasis.

"Visualizing how cancer cells interact with a tumor microenvironment that accurately reflects the complex biology of ovarian cancer should help us understand the mechanisms underlying metastatic progression as well as identify new therapeutics that can inhibit this process," said clinical gynecologic oncologist Ernst Lengyel, MD, PhD, senior author of the study and a professor of obstetrics and gynecology at the University of Chicago.

This is a long overdue step forward for ovarian cancer therapy. The current treatment for metastatic ovarian cancer is surgery and chemotherapy, which has a low five-year survival rate. Although recently approved therapies can increase progression-free survival by a few months, "we think this novel screening system has the potential to uncover new, more effective medications that could be targeted more specifically at a patient's cancer," Lengyel said.

Each year about 21,290 women in the United States will be diagnosed

with ovarian cancer and about 14,180 women will die from the disease. Ovarian cancer is aggressive and is rarely detected at an early stage. Tumors that form in the ovary or fallopian tube typically travel through the peritoneal fluid to the surfaces of other abdominal organs. Metastatic tumors are usually confined to the abdominal cavity and initially cause few symptoms.



A signal in a 384-well HTS assay. Green indicates more cancer cells bound to tissue. Black means fewer cancer cells bound, showing that the compound tested in that well inhibited adhesion/invasion. Credit: Lengyel Laboratory, University of Chicago

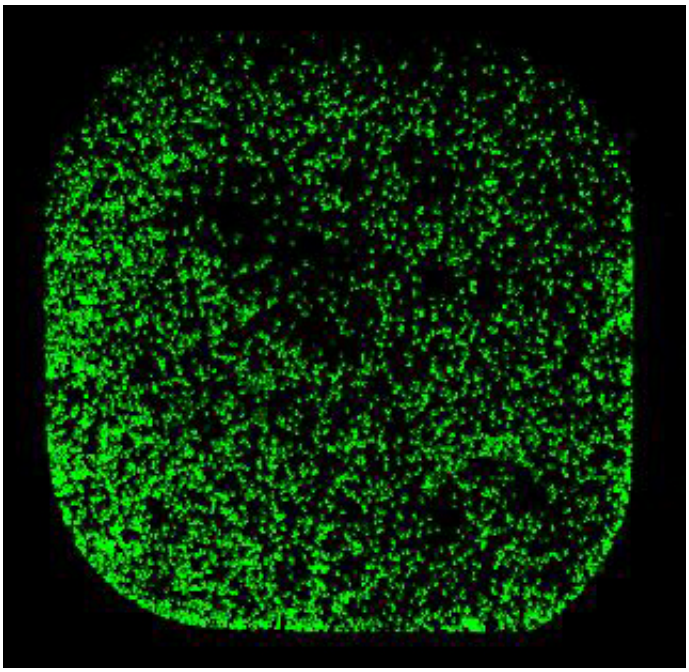
To assemble their model, the researchers collected non-cancerous omental tissue from patients undergoing abdominal surgery. In the laboratory, they isolated and cultured mesothelial cells and fibroblasts, two of the predominant cell types found in omental tissue. Then they

combined these cells with extracellular matrix proteins to generate a multi-layered cell-culture model.

The authors were able to miniaturize their model for use in high-throughput screening (HTS), a drug discovery process that can quickly determine the biological or biochemical activity of thousands of compounds. Because HTS has traditionally been performed on an unrealistic platform—monolayers of cancer cells cultured on plastic surfaces—many drugs that seemed promising in initial screens proved ineffective in clinical testing.

So the researchers developed a new system that better reflects human biology and is specific to ovarian cancer. Instead of growing cancer cells on plastic, they inserted a multi-layered omental tissue culture model into each well of a 384-well or 1536-well HTS platform.

Next, ovarian cancer cells, expressing a fluorescent marker to distinguish them from the other cells, were added. Then the wells were exposed to a library of small-molecule compounds. The numbers of ovarian cancer cells that adhered to and invaded the HTS model were counted, and the inhibitory potential of each compound evaluated.



Green indicates cancer cells bound to tissue in a single well. Credit: The Lengyel Laboratory, University of Chicago

In a primary screen, the researchers identified 17 compounds that inhibited cancer cell adhesion and invasion by at least 75 percent. Six of these compounds were active in a dose-response relationship in three distinct ovarian cancer cell lines. Four compounds significantly inhibited key ovarian cancer cell functions in the early steps of metastasis at low doses.

The research team confirmed those results by testing the four compounds at a low dose in mice injected with ovarian cancer cells. Remarkably, all four compounds inhibited metastasis. Two compounds more than doubled survival. In a follow-up study, one of the compounds—beta-escin, isolated from the seed of the Chinese horse chestnut—inhibited tumor growth and metastasis by 97 percent.

"This study was based on our initial tests of 2,420 compounds," said first author Hilary Kenny, PhD, a research associate (assistant professor) in obstetrics and gynecology at the University of Chicago. "Our model has since been used to test more than 68,000 compounds. This could exceed 100,000 by the end of this year. We are learning to identify compounds with similar structures and functions that may be important for inhibiting key steps in metastasis."

This project emerged as a result of the patient-oriented approach taken by the researchers and clinicians. It is "an important step towards personalized medicine, as described in the new precision medicine initiative proposed by President Obama," Kenny said. "In the future, organotypic models that reflect the unique biology of individual patients could be used in screening. Therefore, personalized high-throughput screening platforms could enable the identification of effective therapeutics for each patient. This is exactly how personalized medicine is supposed to work."

Provided by University of Chicago Medical Center

Citation: New screening tool could speed development of ovarian cancer drugs (2015, February 10) retrieved 26 April 2024 from https://medicalxpress.com/news/2015-02-screening-tool-ovarian-cancer-drugs.html