

Engineered antibodies directed against a promising therapeutic target on ovarian cancer cells

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Stealthy and stubborn, ovarian cancer is a particularly vexing malignancy, difficult to diagnose in early stages and difficult to treat once it progresses further. However, research at Fox Chase Cancer Center is now focusing on one of the most promising new approaches to dealing with the disease--using engineered antibodies to target tumor cells while leaving healthy cells intact.

Gregory Adams, Ph.D., co-leader of the Developmental Therapeutics Program at Fox Chase Cancer Center, and colleagues recently isolated a small, antibody-like molecule called GS45, which is capable of zeroing in on a sort of red flag that distinguishes [ovarian cancer](#) cells from normal cells. Tatiana Karakasheva, M.S., a graduate student in Adams laboratory, will present the findings at the 2010 annual meeting of the American Association for Cancer Research.

The GS45 molecule targets a receptor called the Müllerian Inhibiting Substance Type II Receptor (MISIIR), which is scarce in normal tissue, but more abundantly present on the surface of human ovarian cancer cells.

"A general problem with targeted therapies is that many of the targets found on cancer cells are also found on normal cells," says Karakasheva. "When you direct cell-killing drugs at those targets, you get side effects. The great thing about our target is that in healthy tissue, it's primarily

restricted to the [reproductive system](#), and its expression dramatically increases in ovarian cancer."

"But attractive as MISIIR is as a target, finding antibodies that will home in and bind to it has been a challenge," Adams says.

Using a method called combinatorial single-chain Fv phage display, in which human antibody fragments are expressed and selected on the surface of viruses that infect bacteria, Karakasheva and Adams managed to isolate a group of good candidates, including GS45.

They have just completed engineering the fragments into full-size human antibodies that will be used in experiments with a [mouse model](#) of human ovarian cancer. The first step will be to demonstrate that GS45 actually does target only ovarian cancer cells, not healthy tissue. Then, the researchers plan to attach a cell-killing drug to the antibody, to explore its potential in cancer treatment.

"Because mouse and human MISIIR are almost identical, whatever the mouse experiments reveal about targeting and toxicity is likely to apply to humans," Adams says. "This puts us in a powerful position to move this work forward through pre-clinical studies to a point where we'll know if it's worth taking to clinical trials."

Provided by Fox Chase Cancer Center

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