

Ovarian Cancer: Discovery Could Yield Early Test

By MICHAEL WALDMOLZ

AS MICHEL SCHUMMER recalls it, he was looking for the proverbial needle in a haystack when he came across two rare substances that someday may help prevent thousands of women a year from dying of ovarian cancer.

Dr. Schummer, a molecular biologist at the University of Washington, Seattle, was working in the late 1990s on a lab technique for detecting activity of genes inside cells, scanning the genetic behavior of ovarian tumors, when he found his needle: chemical proteins produced in large amounts only by ovarian cells that have turned cancerous.

Why tumor cells churn out the proteins is a mystery, although it is likely they promote tumor growth somehow. But what captivated Dr. Schummer back then, and is exciting cancer researchers now, is that the proteins dribble into the bloodstream. "It meant to me that I'd found biomarkers that could be the basis of a new cancer-detection test," Dr. Schummer says. "It's what I was looking for."

Much work remains before the discovery results in a blood test to spot ovarian tumors before they turn lethal and spread. But a prototype of the test already has passed some crucial hurdles. In preliminary studies published last summer, researchers detected the proteins in blood taken from women known to have cancer, but found no evidence of the proteins in blood of women without the disease. Encouraged, Fujirebio Diagnostics, a Malvern, Pa., unit of Japan's Fujirebio Inc., last year licensed the technology, hoping to develop a commercial screening test.

"An early diagnostic marker for ovarian cancer has been one of the most difficult targets to get," says Paul Touhey, president of the U.S. unit. "We want to be very careful not to raise hopes at this time. But the research is promising."

Currently, there is a blood test for ovarian cancer that detects another protein, called CA-125. But its use is limited. Doctors use the CA-125 test to monitor treatment in ovarian cancer patients, to check whether treated cancer has returned and to gauge how aggressively to treat the disease, says Beth Karlan, director of gynecologic cancers at Cedars-Sinai Medical Center, Los Angeles.

But the CA-125 test isn't sensitive enough to detect ovarian cancer cells as they are forming. "It misses women who may have early-stage can-

Please Turn to Page B3, Column 5



Michel Schummer

A Step to Earlier Cancer Test

Continued From Page B1

cer, and it can suggest the presence of tumors when none exist," Dr. Karlan says. "A much better test is needed if we want to screen the population."

An estimated 25,580 new cases of ovarian cancer are expected to arise this year, and an estimated 16,090 women are expected to die from the disease. Ovarian cancer accounts for only 4% of all cancer among women, but it is one of the deadliest forms, because it typically isn't diagnosed until it has spread.

When the cancer is detected while still localized to the ovaries, the American Cancer Society says, 95% of women can expect to survive five years or more, the benchmark for successful cancer treatment. But when the cancer is identified after it has spread, the five-year survival rate drops to 31%.

A number of commercial and academic teams are searching intensely for easily identifiable biomarkers of ovarian cancer that can be detected with a relatively simple and inexpensive blood test.

Breast cancer, for example, often is caught early because developing tumors can be felt when they are still small lumps, or they can be visualized early in periodic mammograms. Breast cells can be readily removed, via surgical biopsy, and viewed under a microscope to determine if they are cancerous.

But because of the ovaries' location deep within the reproductive tract, screening biopsies for ovarian cancer aren't possible. Doctors say they want conclusive evidence that cells are potentially cancerous before performing such an invasive exam. At present, the evidence usually arises when women experience lower abdominal pain or other symptoms that typically occur when ovarian tumors have already grown large or, more dangerously, have spread.

"A reliably predictable, early detection test would revolutionize treatment of the disease," says Martin McIntosh, a researcher at the Fred Hutchinson Cancer Research Center in Seattle.

A separate test is being developed by Correlogic Systems Inc., Bethesda, Md. It uses a mass spectrometer to look for a protein pattern found in the blood of women with cancer but not in healthy women.

Critics say the test is expensive and more likely to produce both false positives and false negatives, because it is measuring patterns of largely unknown proteins. "Many of us are more comfortable with a test that is measuring something known to be produced by the tumor," Dr. McIntosh says. Peter Levine, Correlogic's chief executive, says he expects his test to "fill an unmet medical

need."

After Dr. Schummer found the two proteins—called HE4 and mesothelin—in 1999, he contacted Ingegerd and Karl Erik Hellstrom, a wife-and-husband research team at Seattle's Pacific Northwest Research Institute and pioneers of monoclonal-antibody technology. The scientists exploit the natural power of the immune system by creating synthetic antibodies that latch on to specific target proteins secreted by cancer cells into the bloodstream.

A team led by the Hellstroms reported in July in the *Journal of Cancer Research* that it had performed antibody tests for both HE4 and mesothelin, as well as the existing CA-125 test, on

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"blinded" blood samples, in which researchers didn't know if samples came from women with or without cancer. All three tests were accurate about 85% of the time in identifying the samples from women with cancer. Both antibody tests were slightly more sensitive than CA-125, yielding fewer false positives.

In a study to be published soon, a test combining all three techniques was more accurate than any one of them alone. "The unpublished results suggest that, when combined together, we may be able to pick up very early cancers," Ingegerd Hellstrom says. "But that won't be known for certain until Fujirebio carries out much larger trials."

One near-term outcome may be more-sensitive testing for diagnosed patients, measuring both CA-125 and the new proteins. But the big hope for the future remains a screening test for seemingly healthy women. A monoclonal antibody-based test kit would cost perhaps only about \$10 a test and could be performed by commercial labs that do other monoclonal antibody-based diagnostic testing.

For now, both uses remain uncertain. Meanwhile, scientists continue the hunt for other biomarkers. A research team at Mount Sinai Hospital in Toronto has recently reported the discovery of a separate family of proteins, which could lead to development of a test by **Ibex Technologies Inc.**, a small Montreal biotech firm. Says Eleftherios Diamandis, who heads the Toronto discovery team, "None of us believes a single marker by itself is going to be the answer."