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Targeting a Deadly Type of Uterine Cancer

Endometrial cancer, which originates in the lining of the uterus and is the most common type of gynecological cancer, often has a good prognosis. Patients with the more frequently diagnosed type I are often cured. Type II, however, is responsible for most of the recurrences and deaths that occur in endometrial cancer. Uterine Serous Carcinoma (USC), the most aggressive kind of type II endometrial cancer, accounts for just 10 percent of endometrial tumors and is particularly deadly: in its earliest stages the survival rate can be as low as 50 percent, and for those with more advanced disease, there is no cure.

"A striking majority of these patients die too early and very quickly," said Alessandro Santin, MD, Professor of Obstetrics, Gynecology & Reproductive Sciences at Yale School of Medicine and Clinical Research Program Leader of the Gynecologic Oncology Program at Smilow Cancer Hospital. Dr. Santin has spent a decade unraveling the biology of USC in an effort to develop targeted treatments that will have an impact on this devastating disease.

Dr. Santin's interest in USC was born of frustration. Before he came to Yale in 2008, he worked at the University of Arkansas for Medical Sciences, where his practice included a significant number of African American women, who have a threefold higher incidence of USC. "I was stunned by the high number of this relatively rare tumor that I was seeing every day and I wanted to understand what was responsible for its biological aggressiveness," he said. USC is resistant to chemotherapy and quickly spreads to other parts of the body. Dr. Santin wanted to find out why this was the case with the ultimate goal of developing new targets for therapy.

He began by using gene expression profiling to identify the genes that were expressed in USC tumor cells. He found that the HER2/neu receptor, which is sometimes linked to breast and ovarian cancer, was overexpressed in USC, but not in less aggressive types of endometrial cancer. He also found that patients with tumors that expressed HER2/neu had the poorest prognosis.

The drug trastuzumab (herceptin) is used to treat breast cancers that overexpress HER2/neu and was also approved last year to treat gastric cancer. Dr. Santin and his colleagues at Yale and more than a dozen institutions across the country are now using it in combination with two other chemotherapeutic agents in the first ever clinical trial to test whether it may be an effective therapy against USC.

A few years ago, Dr. Santin began to look even more deeply at the molecular pathways of USC. In collaboration with Gilead Sciences, Inc., he worked with Richard Lifton, MD, PhD, Sterling Professor of Genetics and Professor of Medicine, Joseph Schlessinger, PhD, MSc, William H. Prusoff Professor of Pharmacology and Director of the Cancer Biology Institute, and other colleagues to sequence the whole exome – the 21,000 genes that encode for proteins – of tumors from 57 women with USC. Published in the *Proceedings of the National Academy of Sciences* (PNAS) in February, their landmark study was the first to report on a large scale the genetic landscape of USC. Besides confirming Dr. Santin's earlier discovery that HER2/neu was highly expressed in USC cells, which further supports the clinical trial currently underway, it also uncovered several pathways that represent potential new drug targets.

In one pathway, the study found that the oncogene cyclin E, which helps cells proliferate, was highly active in USC due to a mutation in a gene called FBXW7. Another large group of tumors did not have the FBXW7 mutation but had the cyclin E gene amplified, illustrating that USC cells may be addicted to cyclin E in order to grow. Dr. Santin is about to begin clinical studies using a drug to target this pathway. The study also showed that about two-thirds of USC tumors either harbored a mutation in the PIK3CA gene or had amplification of this gene. This points the way to using drugs that target this pathway in other cancers to treat USC.

Other pathways related to PIK3CA that are active in tumor cells and for which there are drugs in development were also identified in USC cells, offering additional targets that Dr. Santin is testing in clinical studies.

Dr. Santin's work revealing pathways that are potentially targetable with existing drugs is allowing him to test different agents in the lab and in animals before moving to clinical trials. "It's a unique opportunity for our USC patients because we will soon be able to translate our discoveries into novel therapeutics that will improve patient outcomes," he said. "In addition to providing superior quality of care surgically, we will also be able to follow up with personalized therapies targeting key signaling pathways highly active in this lethal type of endometrial cancer."

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