Ramping up research

A multipronged attack on ovarian cancer

Notorious for its ability to start furtively but advance aggressively, ovarian cancer is now the target of a coordinated research attack at Dana-Farber and its affiliated hospitals and schools, thanks to a new $11 million award from the National Cancer Institute (NCI).

The grant, known as a Specialized Program of Research Excellence (SPORE), will fund a group of studies that aim to find practical uses – new therapies, diagnostic techniques, and prevention programs – for laboratory discoveries. The money will be distributed over four-and-a-half years to researchers throughout the Dana-Farber/Harvard Cancer Center or DF/HCC (the consortium of cancer scientists at Dana-Farber and six other Harvard-affiliated institutions).

"This is a very important grant because it supports research into the leading cause of death from gynecologic cancer," says the SPORE's principal investigator, Daniel Cramer, MD, director of obstetrics and gynecology epidemiology at the Dana-Farber/Brigham and Women's Cancer Center.

Ovarian cancer is diagnosed in about 27,000 women in the United States every year and claims the lives of more than 16,000, making it the fifth leading cause of cancer death in women. Because it rarely causes pain or discomfort in its early stages, ovarian cancer usually isn't detected until it can no longer be easily treated. When symptoms do arise – such as nausea, vomiting, frequent urination, or constipation – they resemble those associated with less-serious problems. As a result, about 75 percent of cases aren't identified until the disease has reached an advanced stage, when it is most dangerous.

"Because one of the ways to improve the outcome of patients is to find an ovarian cancer when it is small and localized to the ovary, it is critical to develop ways to detect the disease early," says Ursula Matulonis, MD, of the Gillette Center for Women's Cancers at Dana-Farber. "The researchers within the SPORE will not only look for early detection means, but also try to better understand what leads an ovary to become cancerous."

With so many lives at stake, the NCI created the SPORE program to encourage the kind of research most likely to yield rapid advances. Each study covered by a SPORE grant has two principal investigators – a basic scientist and a clinician – so researchers can pounce on laboratory discoveries and harness them to the search for better treatments.

Daniel Cramer, MD, leads the new Specialized Program of Research Excellence – or SPORE – in ovarian cancer.

Alan D'Andrea, MD, with graduate student Kanchan Mirchandani, is pursuing a new lead in the effort to overcome drug resistance in ovarian cancer.

Each study also brings together researchers from different fields to take advantage of the creative ferment generated by collaborative work. The new SPORE – one of only five nationwide to focus on ovarian cancer – teams Dana-Farber and Harvard investigators with colleagues at several other research centers.

"Gynecologic cancer research is entering an exciting time where we have new opportunities to make important advances in the prevention, early detection, and treatment of ovarian cancer," says Ross Berkowitz, MD, director of Gynecologic Oncology Service at the Dana-Farber/Brigham and Women's Cancer Center.

The size and comprehensiveness of SPORE grants have made them among the most sought-after sources of funding for cancer research in the United States. "The goal is to support research that is translational in nature, linking the worlds of basic science and clinical care, so patients are quick to benefit," Dr. Cramer observes.

The DF/HCC SPORE team will focus on five projects, including:

- A study of how genes and the environment interact to raise or lower ovarian cancer risk;
- A hunt for proteins or other "biomarkers" in blood that might serve as early warning signs of the formation of ovarian tumors;
- A search for the first genetic changes in ovarian cells' transformation into tumor cells;
- A test of compounds potentially able to overcome the all-too-common problem of drug resistance in ovarian tumors;
- A clinical trial of novel ovarian cancer therapeutic vaccines.

The sensitive tumor

If there is poetry in science, it lies in the ability to make unexpected connections – to not just direct a course of research, but be directed by it. Consider the work of Dana-Farber's Alan D'Andrea, MD. For more than a decade, he and his colleagues studied the genetic roots of a rare childhood condition called Fanconi anemia. The disease, which places children at risk for bone marrow failure and cancer, arises from an error in a "pathway" of seven genes that fire in sequence, one triggering the next. Under normal conditions, the genes help repair damaged DNA. When any of them malfunctions due to a defect, or mutation, the repairs fail to be made, playing havoc with the cells' growth machinery.

By an odd twist of circumstances, the disruption of the Fanconi pathway not only causes cells to become cancerous, but also makes them vulnerable to the drug cisplatin, one of the most commonly used chemotherapy agents against ovarian cancer. About 60 percent of patients treated with the drug experience shrinking of their tumors.

But cisplatin's effectiveness rarely endures. As ovarian cancer cells continue to divide, they undergo genetic changes that make them even more tenacious than before. Dr. D'Andrea and his associates discovered that tumor cells are able to reverse the mutations that once made them susceptible to cisplatin, while retaining the mutations that turned them cancerous. The result: a mass of tumor cells resistant to a prime chemotherapy agent.

"Drug resistance is one of the main reasons why only about 10 to 30 percent of women diagnosed with

advanced ovarian cancer have long-term survival," says Dr. D'Andrea, who directs the Division of Radiation and Cancer Biology in Dana-Farber's Department of Radiation Oncology. "Now that we've shown how resistance arises in some ovarian cancers, the challenge is to find ways of overcoming it. Is there a way to resensitize these tumors to cisplatin?"

Restoring potency

Dr. D'Andrea's lab team tested dozens of ovarian tumors for genetic abnormalities and found the Fanconi pathway was shut down in about 20 percent of them. Such tumors are likely to respond to treatment with cisplatin. But what about the other 80 percent, whose restarted – but still abnormal – Fanconi pathway enables them to withstand the drug?

In the laboratory, Dr. D'Andrea and his associates surveyed tens of thousands of compounds – molecules able to reach cancers deep in the body – to see if any could block the Fanconi genes in ovarian tumors. They found six promising candidates.

"These compounds can be thought of as cisplatin helpers," Dr. D'Andrea remarks. "Used with cisplatin, they could strip away the tumors' resistance, making them once again vulnerable to the drug."

To test whether the regimen works in patients, Dr. D'Andrea and researchers at DF/HCC are launching a clinical trial of cisplatin in combination with one of the cisplatin helpers. The study will measure the effectiveness of the two compounds in patients whose ovarian cancer has relapsed after previous treatment with cisplatin.

Should the combination prove effective, it could revolutionize the treatment of advanced ovarian cancer. Women diagnosed with the disease would have their tumor cells analyzed to see if they harbor a defective Fanconi pathway. If so, they would be treated with cisplatin alone; if not, they'd receive the drug and one of its helpers.

"The field of chemotherapy enhancement is just beginning to take off," Dr. D'Andrea remarks. "It's a way of giving new life to drugs that we already know can be effective."

Calling all immune cells

While Dr. D'Andrea attempts to revive chemotherapy's cancer-killing powers, Donald Kufe, MD, is trying to do the same for the body's immune system.

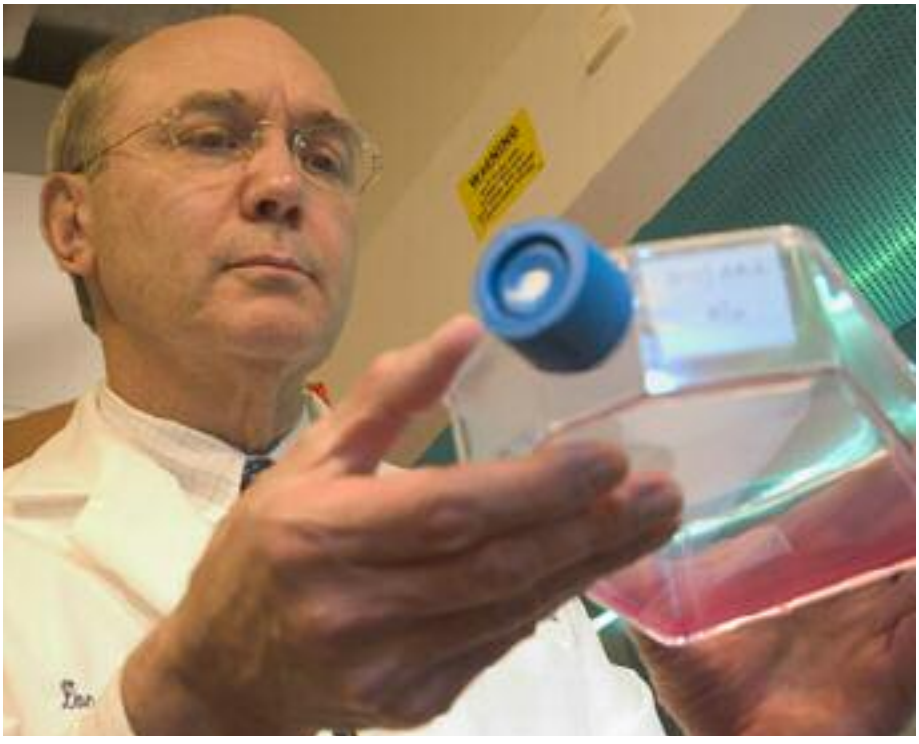
Dr. Kufe, who has led the development of a new generation of cancer vaccines, will use his portion of the SPORE grant to test two vaccines designed to rally the natural immune defenses against ovarian cancer.

The study was inspired by mucus, the substance that coats the inside of the stomach and intestines, breathing passages, and other organs, and creates a barrier against bacteria, viruses, dust, and foreign particles. Twenty years ago, when Dr. Kufe (pronounced 'Keefe') and other researchers learned that some cancer cells make more than 50 to 100 times as much mucus of the MUC1 (pronounced 'muck one') type as normal cells do, they realized they'd found an inviting target for therapy.

"Since the early 1980s, when we identified the MUC1 protein in mucus, it has become clear that overproduction of it plays an important role in tumor formation and in making tumors resistant to drugs and radiation," Dr. Kufe observes.

One way of tackling MUC1 is with a therapeutic vaccine – a preparation that prompts an immune attack on diseased cells. In Dr. Kufe's lab,

Donald Kufe, MD, holds a sample of MUC1, a substance whose overproduction in some cancer cells has suggested new approaches to vaccines against ovarian tumors.



continued on page 13