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Science at the heart of medicine

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NEWS

Einstein Cancer Center



Genes, Diet and Colon Cancer

Americans have a 1 in 20 lifetime risk of developing colorectal cancer. Among cancers affecting both men and women in the United States, colorectal cancer ranks second only to lung cancer as the leading cause of cancer-related deaths. Each year more than 100,000 Americans develop the disease, and more than 50,000 die from it.

At the Albert Einstein Cancer Center (AECC), investigators with a variety of interests—in genetics, nutrition, immunology, microbiology, metabolism and stem cells—are studying the genetic and dietary factors that drive colorectal cancer and are seeking ways to detect, prevent and treat the disease.

Nineteen of these investigators are members of the cancer center’s Biology of Colon Cancer Program (BCCP). Leonard H. Augenlicht, Ph.D., has led the BCCP since its inception in 1995.

“We know quite a lot about the genetics of colorectal cancer development from studying people at high risk because of an inherited susceptibility,” says Dr. Augenlicht.

(continued on page 2)

Above, Leonard H. Augenlicht, Ph.D., a professor of medicine (oncology) and of cell biology, and Winfried Edelmann, Ph.D., a professor of cell biology and of genetics and the Joseph and Gertrud Buchler Chair in Transgenic Medicine. Their approaches to colon cancer complement each other.



I. DAVID GOLDMAN, M.D.
Director, Albert Einstein
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Genetic Accidents

For example, Lynch syndrome (formerly called hereditary nonpolyposis colorectal cancer) occurs because people inherit mutations in DNA mismatch repair genes—a family of crucially important genes responsible for repairing DNA. People with Lynch syndrome have an 80 percent risk of developing colorectal cancer during their lifetimes.

To learn how mismatch repair gene mutations contribute to Lynch syndrome, BCCP member Winfried Edelmann, Ph.D., and his team in the Spatz Family Laboratory for Cancer Research systematically knock out these repair genes in mice to see how each gene's absence affects the animals' susceptibility to cancer. Thus far, Dr. Edelmann's lab has generated knock-out mouse models for 11 members of this gene family—some of the first mouse models ever developed for colorectal cancer. This work is providing important insights that could lead to novel therapies.

For example, Dr. Edelmann has found that the drug rapamycin is able to shrink tumors in mice that lack a DNA repair gene called Msh2. When the drug is withdrawn, the cancer returns in these mice.

"I've never seen anything like it," says Dr. Edelmann, who attributes the cancer resurgence to nests of tumor-promoting stem cells that are

resistant to treatment and remain dormant during drug treatment but resume activity when the rapamycin is removed. "That's exciting, because we now have a model in which we can explore how to eliminate these nests of tumor-causing cells," says Dr. Edelmann.

Diet Derailments

While inherited genetic susceptibility is undoubtedly key in causing some cases of colorectal cancer, "for the vast majority of people who develop colorectal cancer—well over 90 percent of cases—diet plays a far greater role than genetics in determining whether someone will develop the disease," says Dr. Augenlicht. Diet's profound effect on colorectal cancer, he adds, "is absolutely clear from studies of human populations and of animals such as cancer-prone mice. That makes sense, since intestinal tissue is obviously in the path of digestion and comes in contact with many dietary components."

Dr. Augenlicht has carried out animal studies showing that in response to a Western diet that combines higher fat and lower fiber along with a number of other nutritional risk factors, intestinal cells alter their energy metabolism long before tumors form. "We think this change in energy metabolism is linked to changes in the function of intestinal stem cells and makes the cells more likely to

A National Cancer Institute–designated cancer center creates specialized facilities that support highly innovative cancer research. This newsletter describes the AECC's major research program focused on colorectal cancer. Members of this program have carried out pioneering studies on the role of genetics and diet in the genesis of this disease.

Their contributions would not have been possible without their use of the AECC's gene-targeting facility, where mice are genetically engineered to have the same defects as occur in humans at high risk for colorectal cancer. Our researchers can then assess the impact of these genetic defects over several months in diseases that occur in humans only after decades of life.

This research also requires use of the animal barrier facility. Here mice live in a germ-restricted environment to make sure that abnormalities they develop are due to their genetic defect and not to other factors such as bacterial or viral infections.

Our use of the most advanced technologies and analytical systems shouldn't obscure that something relatively simple—a healthy diet—could substantially reduce the incidence of colorectal cancer. In addition, routine colonoscopies could eliminate the overwhelming majority of small precancerous or very early cancerous colorectal lesions that do occur. So another of the AECC's important missions is to develop programs directed to our multiethnic Bronx population to educate people about the risk factors that lead to colorectal cancer and how they can prevent the disease.

CANCER Q&A

Q: Is it possible to predict who will respond to chemotherapy for colorectal cancer?

A: Patients diagnosed with colorectal cancer typically have their tumors surgically removed; then those at high risk of recurrence receive follow-up chemotherapy to eradicate cancer cells that might still remain. Half of these patients with advanced colorectal cancer soon relapse despite undergoing chemotherapy—but there's no way to predict who will do well and who won't. "What we sorely need," says Dr. Augenlicht, "is a way to identify those patients who will benefit from further treatment following surgery."

Dr. Augenlicht emphasizes that most cases of colorectal cancer could be prevented through early detection: "If everyone had colonoscopies regularly so that polyps [benign tumors] and very early cancers could be detected and removed before they became malignant, we'd dramatically reduce the incidence of this disease," he says. The American Cancer Society recommends that people at average risk for developing colorectal cancer should have a colonoscopy every 10 years beginning at age 50.

OLD DRUGS, NEW TRICKS

develop into cancer cells," he says.

Another consequence of feeding animals a Western diet is that fewer of the cells formed by intestinal stem cells become secretory cells. These cells produce gel-like secretions that protect intestinal cells from environmental insults. As shown by Einstein's Anna Velcich, Ph.D., mice genetically altered to lack this protective barrier tend to accumulate mutations—and develop tumors.

Inflammation also plays a role in intestinal cancer. Previous research at Einstein found that mice with overactive immune cells called macrophages develop areas of inflammation in their intestines from which tumors later arise. Dr. Augenlicht has carried out studies on the role of inflammation with his colleague Pamela Stanley, Ph.D. The researchers disabled a gene that is key to normal development in mice, leading to animals that



Pamela Stanley, Ph.D.

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developed low-level chronic inflammation. The researchers observed that these mice tended to form intestinal tumors if they were also fed a Western-style diet.

All Connected

The complex web of interactions in this organ—among genes and diet, immune cells and gut microbes—“makes the intestine fascinating to study,” says Dr. Augenlicht. But successful research requires teamwork. “The collaborative spirit we have here at the AECC—coupled with our core facilities and institutes dedicated to the study of stem cells and aging, for example—makes for an ideal environment for exploring how different factors interact to generate tumors,” he says.



ON THE WEB

To learn more about the
Albert Einstein Cancer Center, please visit
www.einstein.yu.edu/cancer.

Several BCCP members are working to reduce the toxic side effects caused by certain cancer treatments.

Ionizing radiation used to treat abdominal cancers can sometimes damage the intestinal lining. Dr. Chandan Guha and his colleagues are using a growth factor that stimulates intestinal stem cells to mature; they've found that this treatment lessens the damage associated with radiation therapy.

Similarly, a drug used against colon cancer is often converted into a toxic compound by enzymes that intestinal bacteria secrete. Dr. Sridhar Mani and his collaborators have found that blocking those enzymes prevents the severe diarrhea that can otherwise occur when this drug is given.



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PHYSICIAN, HEAL THYSELF



The colon is exquisitely sensitive to its environment—especially the dietary components with which it comes in contact every day. “If we could convince people to eat a healthier diet, we could theoretically eliminate 90 percent of colorectal cancers,” says Dr. Augenlicht. His prescription? “It's no big secret. You try to eat more fruits and vegetables. You eat less fat and especially try to cut down on animal fat. You have colonoscopies. We know what to do. It's just getting people to do it.”

Even the experts don't always take their own advice. “After one cancer meeting, when the organizers and speakers went to dinner,” says Dr. Edelmann, “we headed to a steakhouse.”



our supporters

The Albert Einstein Cancer Center gratefully acknowledges the generosity of the following individuals and organizations whose support is critical to advancing its mission.

NOTABLE GIFTS AND GRANTS

Einstein Overseer Betty Feinberg has made a commitment to Albert Einstein College of Medicine of \$500,000 to support research on Lynch syndrome. M. D. Anderson Cancer Center in Houston, TX, also received a \$500,000 commitment from the Feinberg family toward this research, to be conducted in collaboration with Einstein's Winfried Edelmann, Ph.D.

Lynch syndrome is a genetic disease that predisposes individuals to colon, ovarian, uterine and possibly breast and other cancers. Dr. Edelmann, a leading expert on the disorder (see page 2 of this issue), holds the Joseph and Gertrud Buchler Chair in Transgenic Medicine at Einstein and directs the Albert Einstein Cancer Center's transgenic and gene-targeting facility.

The project's long-term goal is to discover new drugs to reduce colon and rectal cancer in patients with Lynch syndrome. The Einstein researchers plan to test the drugs in a mouse model of Lynch syndrome that Dr. Edelmann has developed, to determine the underlying molecular mechanisms and to translate

the results into treatment protocols for humans with this disorder. This research has the potential to provide new approaches to preventing all the cancers associated with Lynch syndrome.

"Einstein's excellent cancer research programs inspired me to get involved with the medical school 30 years ago," says Mrs. Feinberg. "Most people do not know about Lynch syndrome or its connection with breast cancer and other cancers that primarily affect women. My family and I are pleased to support Dr. Edelmann's important work in this area."

Einstein Overseers Marilyn and Stanley M. Katz have made an additional commitment of \$500,000 to support the Marilyn and Stanley M. Katz Comprehensive Cancer Prevention and Control Program. The program partners with community-based organizations to make the AECC's cancer prevention, screening and treatment services accessible to medically underserved Bronx residents. In addition, the program conducts research to test innovative

approaches to preventing major cancers. For example, a research team is carrying out studies to identify lifestyle and environmental factors that increase the risk of lung cancer in the Bronx population and has launched initiatives focusing on smoking cessation, exercise and healthy nutrition.

"We are very excited about the program," says Mrs. Katz. "Stan and I have wonderful memories of our childhood in the Bronx, so it's very gratifying to be able to help support the health of this community. And we hope that as Einstein's scientists make progress in their prevention and research efforts, their work may eventually benefit people not only in the Bronx, but in communities throughout the United States."

The Katzes are longtime Einstein Benefactors; Marilyn Katz is the founding chair of the Albert Einstein Cancer Center's Cancer Research Advisory Board.

EVENTS

Einstein Women's Division

The New York chapter of the Women's Division hosted its 59th Spirit of Achievement Luncheon in April at the Plaza Hotel. Among this year's honorees was Einstein faculty member Francine H. Einstein, M.D., associate professor of obstetrics & gynecology and women's health and of medicine at Einstein and a maternal fetal medicine specialist at Montefiore. Proceeds support breast and gynecologic cancer research at the AECC.

To learn more about supporting the work of the AECC, please contact:

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ALBERT EINSTEIN CANCER CENTER

Our mission: to promote and conduct research that will elucidate the origins of cancer and lead to effective new approaches for the prevention, diagnosis and treatment of malignant diseases

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