CANCER CENTER

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Genes, Beans & Anti-Cancer Schemes

Can adding more calcium and folic acid to your diet protect you from developing colon cancer?

Studies increasingly show that many of the major cancers—colon as well as breast and prostate—are strongly linked to diet, with the connection between diet and colon cancer probably clearest of all. But just how diet determines whether colon cells will or won't become cancerous is still unknown.

In a major step towards solving that mystery, researchers at the Einstein Cancer Center have been awarded a five-year, $10-million grant from the National Cancer Institute (NCI). Using cutting-edge techniques (several developed by Einstein faculty) for studying genetic changes in both normal cells and tumors cells, they will investigate how certain nutrients in the diet influence the development of colon cancer.

"We know a lot about the genetics of colorectal cancer development from studying people at high risk because of an inherited susceptibility," says Dr. Leonard Augenlicht, the study's principal investigator. Dr. Augenlicht is professor of medicine and of cell biology at Einstein, associate director of translational research and leader of the colon cancer program at the Einstein Cancer Center and the director of Montefiore's Genome Anatomy Laboratory. "These studies of susceptible people have helped to pinpoint the genetic pathways that are likely to be extremely important in colorectal cancer," he says. "But for the vast majority of people who develop colorectal cancer—well over 90 percent of cases—diet and the environment play a far greater role than genetics in determining whether someone will develop the disease."

Diet's profound effect on colorectal cancer "is absolutely clear from studies of human populations and of animals such as cancer-prone mice," says Dr. Augenlicht. "That makes particular sense for colorectal cancer, since intestinal tissue is obviously in the path of digestion and comes in contact with many dietary components. With this new NCI grant, we'll be focused on finding out exactly how dietary factors are interacting with the different genetic pathways that lead to the formation of colorectal tumors."

Although research has revealed diet's importance in colorectal cancer, says Dr. Augenlicht, there is still much confusion over which aspects of diet are important—both for causing colon cancer and preventing it. "Conflicting reports have contributed to disagreements within the scientific community, and those disagreements will probably be resolved only when we understand how dietary components interact with underlying genetic mechanisms. Once we understand that, we won't suddenly have a magic bullet to give the population. But we will have the scientific strength to make serious recommendations that the public will be more likely to adopt, rather than dismissing them by saying, 'Well, my uncle always ate this or that and lived to be 97.'"

Scientists working in laboratories at both Einstein and Montefiore offer several "unique strengths" that were crucial to the success of this NCI grant initiative, Dr. Augenlicht says.

"First of all, our colon-cancer program has been extremely strong in developing and using mouse models for studying colon cancer and answering questions about its causation," he notes. As one example, he cites "the very important

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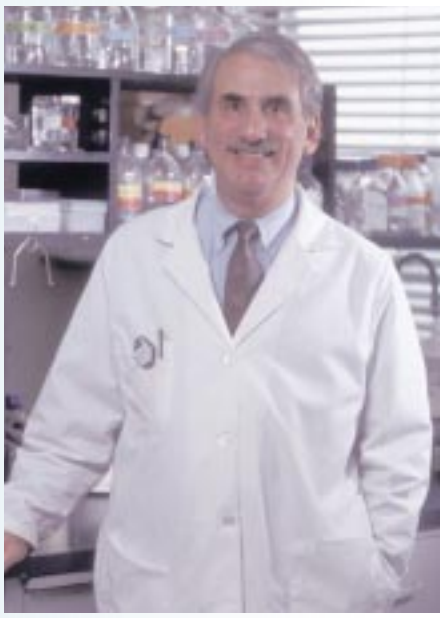

Dr. Augenlicht

mouse model, known as Muc2, that we developed here and described last year in the journal *Science*." Muc2's creator, associate professor of medicine Anna Velcich, found that disabling a particular gene caused the mouse to develop colorectal cancer throughout its entire gastrointestinal tract. In addition, says Dr. Augenlicht, the research team includes Dr. Winfried Edelmann, associate professor of cell biology, who is "internationally recognized for his expertise in developing mouse genetic models for understanding the underlying basis for colorectal cancer."

Dr. Augenlicht also notes that Einstein and Montefiore researchers at the Cancer Center have developed important molecular technologies for research on genomics (the study of the full set of genes in normal and tumor cells of humans and other species) and proteomics (the effort to catalogue all the proteins made by the body's genes and learn how they interact with each other). He cites two project participants as examples:

- Dr. Robert Singer, professor and co-chair of anatomy and structural biology and professor of cell biology, led the team of Einstein researchers that developed the "FISH and chips" technology, which they described last year in *Science*. Combining fluorescence in situ hybridization (FISH) and gene microarray "chips," the technology "has tremendous potential as a tool for cancer research," says Dr. Augenlicht. By relating gene expression patterns to what a cancer cell is doing or (in the case of pre-malignant cells) will do, the technology can help reveal where and how a cell has gone awry.

- Dr. Mark Chance, professor of physiology and biophysics and of biochemistry and director of both the Center for Synchrotron Biosciences and the Cancer Center's Structural Biology Facility, has developed a major program in structural proteomics, in which researchers infer the function of proteins by determining their molecular structure. "Mark's expertise should help us understand why a mutation leading to an altered protein is important and whether we should focus on it as we try to learn more about the genetic pathways involved in colorectal cancer," says Dr. Augenlicht.

As for the consortium's other strengths, Dr. Augenlicht cites "our collective expertise in diverse areas that will come together as we engage in this project, including nutritional sciences, cell biology, molecular biology, mouse genetics, molecular genetics as well as genomics and proteomics." He also notes that many of the project's participants have worked together successfully in the past—an important consideration when competing for a grant of this size.

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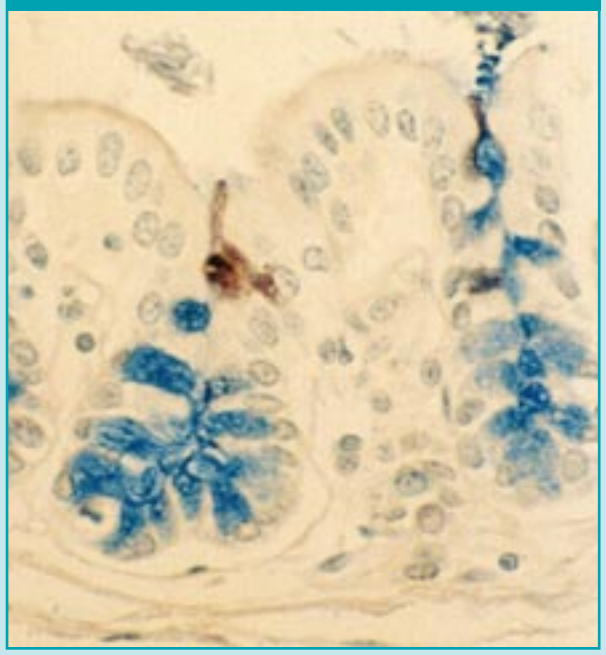
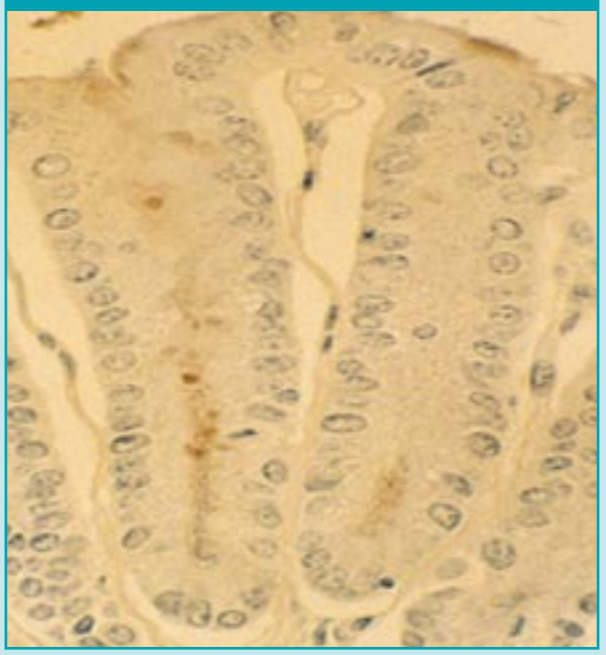


The intestinal mucosa, or lining, of a normal mouse that possesses two healthy copies of the Muc2 gene. The lining's tiny indentations, or crypts, are filled with mucin (stained in blue), the liquid that is secreted into the intestine to lubricate and protect the mucosa.



The intestinal lining of a mouse that has undergone a targeted inactivation ("knockout") of both copies of its Muc2 gene. Note the lack of mucin within the crypts. These Muc2 knockout mice, developed by Dr. Anna Velcich, go on to develop tumors throughout their intestines.

The research will involve three projects:

In one project, mouse genetic models of colon cancer (including the Muc2 mouse described above) will be fed Western-style diets that are either high- or low-risk for colon cancer (i.e., high-risk diets are rich in fat and phosphorous and low in calcium, vitamin D3, choline, methionine, folic acid and fiber). "The high and low levels of these dietary components are within the normal range that people actually consume—we're not talking about extreme differences in intake," says Dr. Augenlicht. For one mouse model, the study will be extended so groups of mice will receive diets that differ by just a single nutrient. Researchers will be studying not only how these diets affect cell maturation and tumor formation but also how they alter the activity of genes in these tissues.

"If our study can show how dietary factors affect colorectal-cancer risk, then hopefully we can help reduce this cancer's deadly toll."

The second project will focus on the beta-catenin-Tcf signaling pathway that is implicated in almost all cases of colon cancer, in animals as well as humans. Dr. Augenlicht notes that this project "follows up on important work" done by Dr. John Mariadason, assistant professor of medicine at Einstein. Using mouse tissue from project 1, researchers will determine how genetic and dietary factors, alone and in combination, affect this signaling pathway.

Finally, a third project extends the scope of research to the study of human volunteers, who will be sequestered for several weeks at a clinical facility. Participants in this study will eat defined diets analogous to those fed to the mice and will undergo colon biopsies during the study and at its conclusion. The aim is to find how specific dietary components—calcium and vitamin D3, for example—affect both the maturation of intestinal cells and their gene expression, and to see whether these findings validate results from the mouse feeding studies.

More than 150,000 Americans are diagnosed with colorectal cancer each year, making it the third most common cancer in both men and women—and the cause of about 10 percent of all cancer deaths. "If our study can show how dietary factors affect colorectal-cancer risk, then hopefully we can help reduce this cancer's deadly toll," says Dr. Augenlicht.

Researchers from Rockefeller University, the University of Nebraska School of Medicine and North Shore University Hospital are also participating in the study. ■