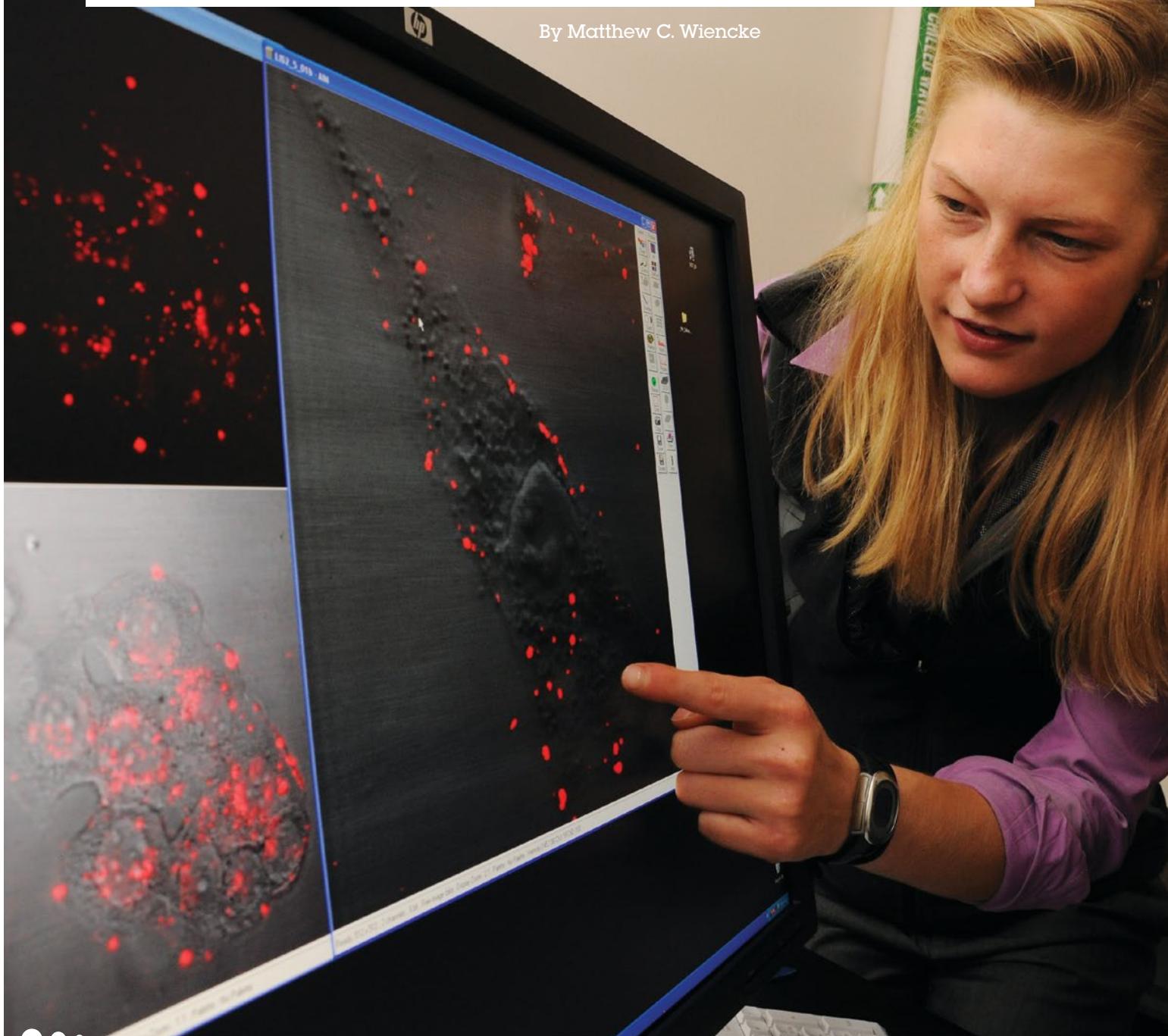


THE NEW SMOKING?

By Matthew C. Wiencke



Leslie Lupien, a graduate student working in William Kinlaw's lab, and Jay Davis, a technician, examine images of breast cancer cells as part of their research on the relationship between fat and cancer. The red dots in the breast cancer images are fat particles inside the cells. **PHOTOGRAPHS BY JON GILBERT FOX**



William Kinlaw, a professor of medicine at Geisel, is concerned that the increase in obesity over the past few decades may contribute to an increase in some types of cancer.

Smoking has declined over the years, but a new cancer risk—obesity—may be taking its place. William Kinlaw and other Geisel researchers study how tumors obtain fat, research that supports a strong link between obesity and cancer.

RADON, SUNBATHING, AND—OF COURSE—SMOKING:

these are some of the well-known and significant risk factors for cancer. But in recent years scientists and physicians have been paying increasing attention to another source of concern for developing cancer: extra weight.

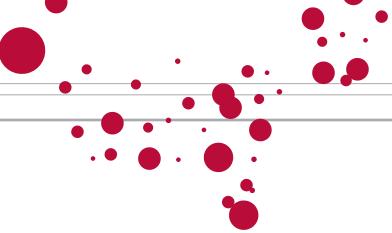
Being overweight or obese increases the risk of getting several kinds of cancer, and as the number of extra pounds increases, so does the risk. “There really is a dose-response correlation between the degree of obesity and the relative risk for several types of cancer,” said endocrinologist William Kinlaw, M.D., a professor of medicine at Geisel, speaking at a talk at DHMC.

Kinlaw worries about the implications of the rise in obesity for cancer rates. “The increase in cancer because of our obesity epidemic actually is causing a backpedaling of some of the progress that had been made largely from reduced rates of smoking,” he says.

Kinlaw’s concern is shared by the National Cancer Institute (NCI). The NCI’s 2012 annual report on cancer in the U.S. focused on the link

between cancer and obesity. The statistics are alarming. According to the report, about two-thirds of adults and one-third of children and adolescents are overweight or obese. The NCI estimates that if existing trends continue, excess weight will lead to about 500,000 additional cases of cancer in the U.S. by 2030. The report also states that about one-third of common cancers in the U.S. could be prevented through a healthy regimen of physical exercise and diet.

It’s not clear exactly why there is a link between cancer and obesity, but Kinlaw may have some answers. He has spent more than 15 years studying how tumors obtain fatty acids, which they use to fuel their growth. Scientists have long known that tumors can synthesize fatty acids from glucose, and researchers and pharmaceutical companies have worked to develop drugs to stop fatty acid synthesis. But according to Kinlaw, these efforts might not be enough. He has accumulated evidence that tumors are also able to extract fatty acids directly from fat that circulates in the bloodstream. So a fat-filled diet isn’t just a risk for weight gain; it might also promote tumor growth.



Before turning to cancer research, Kinlaw was a member of the Medical School's Department of Physiology and interested in how cells synthesize lipids. A graduate student in his lab found that a gene they had been studying in their research on the thyroid, known as *Spot 14* (or *S14*), was expressed by breast cancer cells as well and seemed to play a role in the production of fatty acids. Kinlaw began studying the relationship between fatty acid synthesis and cancer, and he soon moved his research team to the Norris Cotton Cancer Center.

Many cancer cells, including breast cancer cells, use fatty acid synthesis to create the fat essential for their growth. The cells use a protein called fatty acid synthase to turn blood sugar obtained from the cells' environment into fatty acids.

It is not entirely clear why cancer cells need fat. One theory is that the production of a large amount of fatty acids by cancer cells activates receptors in the cell membranes; these receptors then stimulate more growth. The details of this theory are still being worked out, but one point is clear, says Kinlaw. Cancer cells seem to need a steady supply of fatty acids to grow.

In a 2006 study, Kinlaw worked with Wendy Wells, M.B.B.S., a Geisel professor of pathology, to examine the importance of *S14* in breast cancer. They followed 88 patients for about eight years. They found that more aggressive tumors had a high expression of *S14*. About one-third of patients with such tumors experienced a recurrence of cancer during the study. But among the patients with a low expression of *S14*, there wasn't a single recurrence of cancer. The reason, they believe, is that tumors with a high expression of *S14* are better able to synthesize fatty acids.

Working with oncologists, Kinlaw and Wells are using data from this study to come up with an algorithm that would help predict a risk of recurrence and, therefore, which patients might be able to avoid additional chemotherapy and radiation treatments.

ADDRESSING THE ELEPHANT

Even as Kinlaw learned more about the mechanisms of fatty acid synthesis, he began to wonder if there was another way tumors were obtaining fatty acids. What if tumors were also able to take fat out of the bloodstream? That would mean that eating fatty foods would provide cancer cells with fuel to grow. "We realized that no one had really given this any thought," Kinlaw says. "To me, the elephant in the room is why aren't we also talking about the use of the fat by the tumor directly?"

Fat is needed by the body for various purposes. When it enters the body it is insoluble, so the body uses enzymes, such as lipoprotein lipase (LPL), to break down the insoluble fat molecules and extract fatty acids it needs. Kinlaw took a close look at several kinds of tumors and found that all of them were loaded with LPL. He found that the tumors were using LPL to obtain the fat they needed from fat in the bloodstream.

When someone eats a meal that contains fat, the fat is packaged up in the intestine and sent out into the bloodstream. LPL is secreted by muscle and fat tissue, and by tumor cells, and then sticks to the surface of capillaries near the tumor, binding to a molecule on the surface called heparan sulfate—so that LPL decorates itself all over the surface of the capillaries. From there, LPL can extract fatty acids from fat particles that travel by. The acids then diffuse out of the capillaries and into nearby tumor tissue.

This is not the only way that tumors use LPL. Leslie Lupien, a graduate student in Kinlaw's lab, made a bizarre finding. She discovered that some breast cancer cells have LPL on their surface, but it is clear they are not actually making it. (Normally LPL is produced by the cell.) Lupien and Kinlaw think that the cells are decorating themselves with heparan sulfate, which allows them to attract LPL floating around in their environment. The cells pull the LPL onto their surfaces so they can then obtain fatty acids from dietary fat. Kinlaw describes this maneuver by cancer cells as "piracy" or "hijacking."

Kinlaw has worked with Nancy Kuemmerle, D.O., Ph.D., a Geisel assistant professor of medicine and an oncologist at the White River Junction Veterans Administration hospital, to try to find ways to prevent LPL from functioning

properly. One effort led by Kuemmerle was to create an antibody to human LPL. Kuemmerle then mixed sarcoma cancer cells with LPL and the LPL antibody. The antibody binds to LPL, which helps her see where the LPL is. She then flooded the sarcoma cells with heparin (a molecule that is similar to heparan sulfate). Heparin is an anticoagulant that, the researchers knew, binds to LPL and could possibly stop LPL from functioning.

When Kuemmerle flooded the sarcoma cells with heparin, the massive amount of heparin displaced the LPL from the cell surface—LPL, she found, was binding to the excess heparin, which then removed it from the cell surface. All the LPL then floated away. This proved that the cancer cells were binding LPL to their surface, not just secreting LPL to nearby capillaries, which "was a very unexpected result," says Kinlaw. Cancer cells were making LPL and sticking it all over their surfaces, so that the LPL could then get fatty acids, from dietary fat, into the tumor. Lupien and Jay Davis, a technician in Kinlaw's lab, have confirmed this finding using imaging methods and flow cytometry.

But it doesn't stop there. Cancer cells are even wilier. Lupien and Davis have found that some cancer cells are taking insoluble fat particles and bringing them into the cells. The researchers aren't sure exactly what happens once the fat particles are inside, but they think it's possible that an enzyme other than LPL is breaking down the fat inside the cell.

In addition to using heparin to displace LPL, Kinlaw has been working on a second possible method of stopping LPL from delivering fatty acids to tumor cells. By chance, he heard a presentation by Nicole Smits, Ph.D., a postdoctoral researcher at Geisel who happens to be an expert on heparan sulfate, the molecule that binds to LPL. She has developed an antibody to heparan sulfate that she is studying as a treatment for sepsis. Smits and Kinlaw have found that the antibody can release LPL from the surface of cancer cells, just as heparin can.

Smits is doing experiments to convert the antibody into a larger molecule that will increase its life span and make it more effective as a therapeutic agent to battle sepsis. Kinlaw plans to use this larger molecule Smits is developing in experiments to suppress LPL in tumors.



Nicole Smits, an expert on the molecule heparan sulfate and its use in treating sepsis, happened to give a presentation heard by William Kinlaw, who was interested in the implications of the same molecule for his research on cancer.

"TUMORS HAVE ADAPTED TO THIS HORRIBLE DIET THAT WE EAT.... THESE THINGS ARE JUST PIGGING OUT ON FAT."



THE NEXT SMOKING

Recently, Kinlaw has been exploring a possible method of targeting both fatty acid synthesis and the uptake of dietary fat by tumors. He has been working with conjugated linoleic acid (CLA), which he describes as a "very weird fatty acid" that is made by a bacterium that lives in the rumen of cows, goats, and sheep. CLA is already available to consumers and is marketed as a weight-loss supplement. Scientists have found that in animals, CLA travels into cells and suppresses fat synthesis and dietary fat intake. Kinlaw discovered in lab work that CLA can kill breast cancer cells in tissue culture, and he has been working with Margit McGowan, D.O., an assistant professor of medicine, on a clinical trial in breast cancer patients.

The trial involved 24 women with stage I to stage III breast cancer. All the women took CLA for an average of 10 days—between the time they had a biopsy and surgery. The purpose of the trial was to examine whether taking CLA can suppress fatty acid synthesis and fat uptake and to see if it slows down tumor growth. The study has been "promising," Kinlaw says, and the final results should be published soon.

There is still more that Kinlaw would like to know about the relationship between cancer and dietary fat. He wants to find out what tumors are doing with fat particles inside their cells. He also wants to see what effect a high-fat diet has on mice that lack LPL. As he digs deeper into the mysteries of tumors and LPL, he is sure of one thing: the epidemic of obesity does not bode well for rates of cancer. Obesity, he says, "could be the next cigarette smoking."

Kinlaw emphasizes that he does not think dietary fat itself is the initial cause of cancer, but he does think that an abundance of available fat can increase the chances that a cell that has gone awry will turn into a full-fledged tumor. A cell absorbing dietary fat is "not a transforming genetic event," as he puts it, but it is a "permissive feature of the interaction of that transformed cell with its host environment." In other words, it is an enabler that increases the efficiency of cells, allowing them to obtain fat without having to synthesize it. "Tumors have adapted to this horrible diet that we eat," says Kinlaw. "These things are just pigging out on fat."

CANCER TYPE	RELATIVE RISK FOR OVERWEIGHT	RELATIVE RISK FOR OBESITY
Adenocarcinoma of esophagus	1.55	2.10
Colorectal	1.18	1.36
Endometrial	1.60	2.20
Kidney	1.31	1.62
Pancreatic	1.14	1.28
Postmenopausal breast	1.13	1.25

Being overweight or obese raises the risk of getting several types of cancer. For example, for people who are overweight the risk of getting cancer of the esophagus is 1.55 times higher than it would be if they were normal weight. For people who are obese, their risk of getting the same cancer is 2.1 times higher.

SOURCE: Annual Report to the Nation on the Status of Cancer, 1975–2008, Featuring Cancers Associated With Excess Weight and Lack of Sufficient Physical Activity. National Cancer Institute, et al., 2012.