what the brain perceives. We think of obesity as a state of excess, but biologically it's a state of deprivation, or the state of starvation. The brain sees too few calories in the bloodstream to run metabolism, so it makes us hungry. It activates hunger and craving sensors in the brain, and slows down metabolism."

This combination of rising hunger and slowing metabolism is a recipe for weight gain, he adds, and explains why only a very small proportion of people on low-calorie diets can keep weight off in the long term. A 2012 study by Ludwig and his colleagues, published in the *Journal of the American Medical Association (JAMA)*, offered some evidence. It examined 21 overweight and obese young adults after they had lost 10 to 15 percent of their body weight on diets ranging from low-fat to low-carbohydrate. Despite consuming the same number of calories, subjects on the low-carbohydrate diet burned about 325 more calories per day than those on the low-fat diet.

A related debate on whether low-fat or low-carb diets provide optimal health benefits is still fiercely contested. Ludwig argues that the type of calories you eat can affect the number of calories you burn, and that none of this is addressed in the conventional calorie-in, calorie-out model. His team observed in its studies that low-fat, high-carbohydrate diets—despite providing a surge in energy or calorie availability in the bloodstream for the first hour or so after a meal—cause problems a few hours later, "when all those calories have been taken up into storage, and can't get out as quickly as needed."

Although study after study shows that added dietary sugar leads to weight gain, Type II diabetes, and heart disease, Dean Ornish—a leading advocate of low-fat diets and lifestyle changes as ways to prevent and reverse cardiovascular disease—argues that an optimal diet is based primarily on plants: fruits, vegetables, whole grains, legumes, and soy products, with some healthy fats (omega 3 fatty acids), and predominantly plant-based proteins. Ornish advises avoiding red meat because of its saturated fat content and studies linking it to chronic inflammation and increased cancer risk. (Ludwig does not exclude red meat as a healthy option, but he also encourages alternatives such as chicken, fish, and soy products.)

Ludwig acknowledges that all low-fat diets aren't necessarily bad for body weight. But as fat intake decreases, he argues, it becomes increasingly difficult to avoid overeating grains. He notes that even whole grains can cause a spike in the level of blood sugar if heavily processed, because certain processing techniques disrupt the fiber's natural ability to lower blood-sugar concentration. (They can degrade healthy natural antioxidants as well.) He therefore recommends replacing refined carbohydrates with healthy fats (such as nuts, avocado, and olive oil) as a more practical and effective solution for most people.

In a 2015 *JAMA* article, he and Dariush Mozaffarian, now dean of the Tufts Friedman School of Nutrition Science and Policy, called for the United States to rethink its policies on dietary fat. The pair argued in a July 2015 op-ed article in *The New York Times* that limiting the total amount of dietary fat "is an outdated concept, an obstacle to sensible change that promotes harmful low-fat foods, undermines efforts to limit refined grains and added sugars, and discourages the food industry from developing products higher in healthy fats." (Ludwig's own recommendations can be found in his new book, *Always Hungry*.)

To advance the low-carb versus low-fat debate, Ludwig, founding director of the Optimal Weight for Life (OWL) program at Boston Children's Hospital and director of the New Balance Foundation Obesity Prevention Center, is working on a larger-scale study in collaboration with Framingham State University: three groups of 50 people each are being fed three different diets during the course of an academic year. The amount of protein for each group is fixed at 20 percent, but the fat and carbohydrate percentages range from a very low-fat, high-carbohydrate combination to exactly the opposite. The study design, Ludwig says, replicates the 2012 *JAMA* study but extends the diet phase to 5 months in order to study longer-term adaptation.

Ludwig is adamant that animal research, epidemiology, and clinical trials show that insulin secretion plays a major role in weight, but admits there is room for converging lines of investigation. "How do these different diets controlled for calories affect our metabolism, the number of calories being burned? How do they affect body composition? That's a key question," he says. "If you eat the same protein and the same calories, but just begin with different proportions of fat and carbohydrates, do you influence…how much fat you're storing versus how much lean tissue you have? That's never been well addressed, but it's a critical scientific question."

—LAURA LEVIS

DAVID LUDWIG WEBSITE:
www.childrenshospital.org/researchers/david-ludwig

MELANOMA MUGSHOT

A Cancer Begins

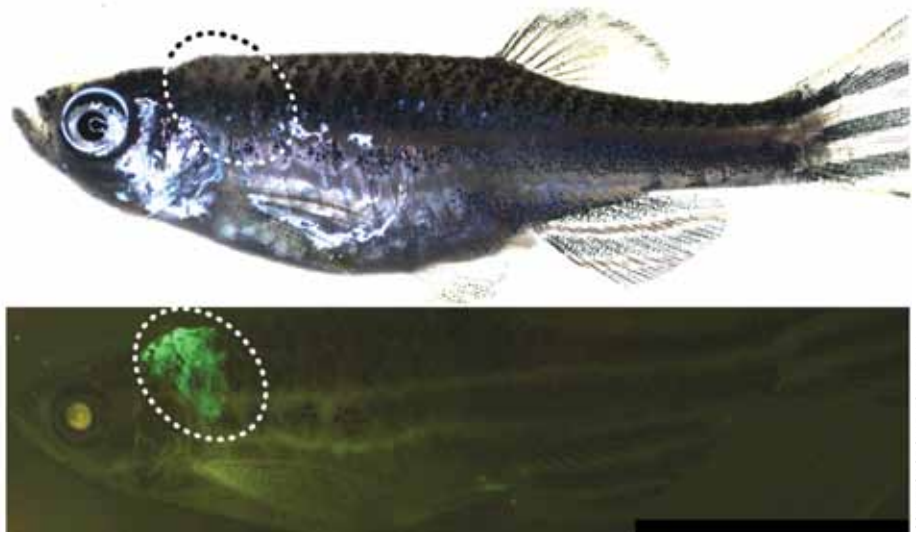
LEONARD ZON HAS CAPTURED the moment when a single cell first becomes cancerous—and he thinks that means an answer to cancer's origins may be within reach. "We're close," he says. If scientists can pin down a cancer's precise causes, they may be able to develop treatments to stop the disease even before it begins.

Zon, a professor of stem cell and regenerative biology in the Faculty of Arts and Sciences and Grousbeck professor of pediatrics at Harvard Medical School, runs perhaps the world's most populous aquarium.

Transparent zebrafish that develop human melanomas (bottom) facilitate the study of cancer susceptibility and carcinogenesis.

His laboratory is filled with tanks of transparent zebrafish (300,000 of them), which he uses to study skin cancer. Tagged with fluorescent proteins, some fish glow red, others green, enabling him to see what is happening inside when a melanoma starts to form. These specially bred experimental

Images courtesy Ellen van Rooijen



COURTESY OF CHARLES KAUFMAN

Researchers tagged a gene known to be active in cancer tumors so that it would fluoresce when activated, revealing the precise moment when a cancer begins.

fish have also been loaded with human-cancer-causing oncogenes. According to prevailing theory, they should *all* develop countless melanoma tumors.

But they don't. When Zon first introduced the human skin-cancer gene into the fish several years ago, they merely developed moles—dense concentrations of skin cells (melanocytes) that may become cancerous, but are harmless most of the time. He then took an additional step, turning off the tumor-suppressing genes in the fish ("silencing" the genes, in the parlance of molecular biology), thinking that would certainly lead to massive numbers of melanomas.

But after several months, each fish developed only two or three tumors. "We were shocked that there wasn't more cancer developing," says Zon. "It had to be something else that was causing the cancer to grow" in those few instances. He suspected that the culprit was *not* a mutation, because sequencing 50 tumors failed to turn up a single mutation common to all or even some of them.

So what caused those tumors to grow? "Every cell in your body has the same DNA," Zon explains. "What makes a cell in an eyeball different from a skin cell is which genes are turned on or off"—a process known as epigenetics. He quickly identified a gene that is normally active only in zebrafish embryos, but which his prior analysis of zebrafish tumors indicated was reactivated in the cancerous tumors of adult fish. He and his team tagged the gene with a green fluorescent protein so that the moment it turned on, any cell expressing it would literally light up. That made it possible to capture the cancer's moment of inception and, critically, to identify any additional genes that "turned on" at the same time.

The researchers found that a particular set of genes, when activated simultaneously, could reprogram a skin cell, shifting it back to a stem-cell-like state in which the cancer starts to grow. Scientists have long thought there might be a link between stem cells and cancer, because some cancer cells appear to possess the same capacities that characterize stem cells, which can divide indefinitely and differentiate through generations to become a variety of different kinds of cell. But they didn't know whether cancer is *caused* by stem cells.

Stem-cell researchers figured out how to turn adult cells into stem-cell-like cells in 2006 (when Shinya Yamanaka created the first induced pluripotent stem cells). But cancer, it seems, has been doing this for a long time. "The initiating event in cancer," Zon has found, is very much like the creation of those induced stem cells, involving "a reprogramming that brings the cell back to its roots by activating a set of key epigenetic regulators that work on DNA to activate and maintain" the cell in its altered, stem-cell-like state.

Zon's lab is already working to identify the environmental factors that turn these reprogramming mechanisms on and off. "We think there are signals from *outside* the cell that actually direct the process

"We were shocked that there wasn't more cancer developing. It had to be something else that was causing the cancer to grow."

to happen," he continues, "teaching the inside of the cell how to reach a different state. At that point a tumor starts to grow." The signals would need to be strong, he believes, because the strength of any signal that reaches a particular cell declines rapidly along what is known as a morphogenic gradient as it moves from one cell to the next. Furthermore, four signals need to converge on a single cell at exactly the same time to convert it to the cancerous state. That's why cancer formation, he says, is, fortunately, an extremely rare event.

He believes his findings will be generalizable to other cancers. The cells of a cigar-smoker's mouth, he points out, are bathed in carcinogens that cause mutations in DNA, predisposing the smoker to cancer in the same way that Zon's zebrafish are predisposed to cancer because they carry human oncogenes. But that isn't sufficient to cause a tumor to form. Zon speculates that the additional triggering event might be persistent inflammation or irritation, which many studies have linked to cancer. Maybe the tobacco juice, or the hot smoke drying mucous membranes, or simply the presence of a cigar hanging from the mouth, triggers inflammatory biochemical pathways in the body that in turn cause the formation of that first cancerous cell.

Now Zon is testing drugs, hoping to find one that turns on the gene tagged with the green fluorescent protein. That might provide a clue as to which signaling pathways—perhaps those involved in inflammation and stress—are most useful to study further. And if he finds a drug that turns the tagged gene *off*, it might form the basis for an anti-cancer therapy—a cream, for example, that could be rubbed on a mole to prevent cancer entirely, stopping the disease before it begins. —JONATHAN SHAW

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