Nearly 40 percent of Americans over the age of 20 are obese, and another 32 percent are overweight. These alarming figures grow darker when combined with statistics showing that obesity is second only to smoking as a cause of preventable cancer deaths. Obesity has been linked to more than a dozen types of cancer.

Scientists know that some tumors are fiends for blood sugar—glucose, the fuel that drives their growth. Obesity, with its accompanying overabundance of glucose, makes a natural partner for these cancers. But the biological mechanisms that link the two are still under investigation. A team of scientists at Yale has identified an important key.

"We develop and apply new tools to understand the mechanistic link between obesity and cancer," said Rachel Perry, PhD, Assistant Professor in Medicine (Endocrinology) and Cellular & Molecular Physiology.

That link spotlights the hormone insulin. When we eat, food is converted into blood sugar. The rising level of glucose in the bloodstream signals the pancreas to release insulin. Eventually, insulin resistance can develop and result in a build up of glucose in the body, which leads to fat cells and an accumulation of extra pounds.

Previous studies have associated insulin with several cancers, but Dr. Perry and her colleagues mechanistically demonstrated the link. "Our study is among the first to show directly that the high insulin levels in obesity cause changes in tumor glucose metabolism and then in tumorigenesis," she said.

Her lab followed several paths to this discovery. They took three tumor cell lines associated with obesity—colon, breast, and prostate cancer—and three cell lines not associated with obesity—melanoma, B-cell lymphoma, and small cell lung cancer—and doused them with insulin. Giving extra insulin to the obesity-associated cancers was like throwing gas on a fire. The tumors not associated with obesity showed no change. They concluded that excessive circulating insulin, a condition called hyperinsulinemia, allows tumor cells to bloat themselves with glucose and burn it to fuel fast growth.

Dr. Perry and her colleagues wondered whether lowering insulin might put a kink in this link. "What's particularly exciting are the therapeutic implications," said Dr. Perry, "because there are already many drugs that reduce insulin." She theorized that putting an obese patient with cancer on an insulin-lowering drug might stall the tumor's growth.

She knew that metformin, the most commonly prescribed drug for lowering blood sugar in diabetics, had been tested against cancer in several trials, with mixed results. She decided to test two drugs that reduce blood insulin through different mechanisms. The first was dapagliflozin, an SGLT2 inhibitor, which means that it prevents the kidneys from raising blood sugar by reabsorbing glucose. Instead, the glucose is eliminated through urination. Dr. Perry found that the SGLT2 inhibitor reversed hyperinsulinemia and hence slowed the growth of obesity-associated cancer in mice. However, replacing insulin in mice treated with the SGLT2 inhibitor prevented the beneficial effects of the drug.

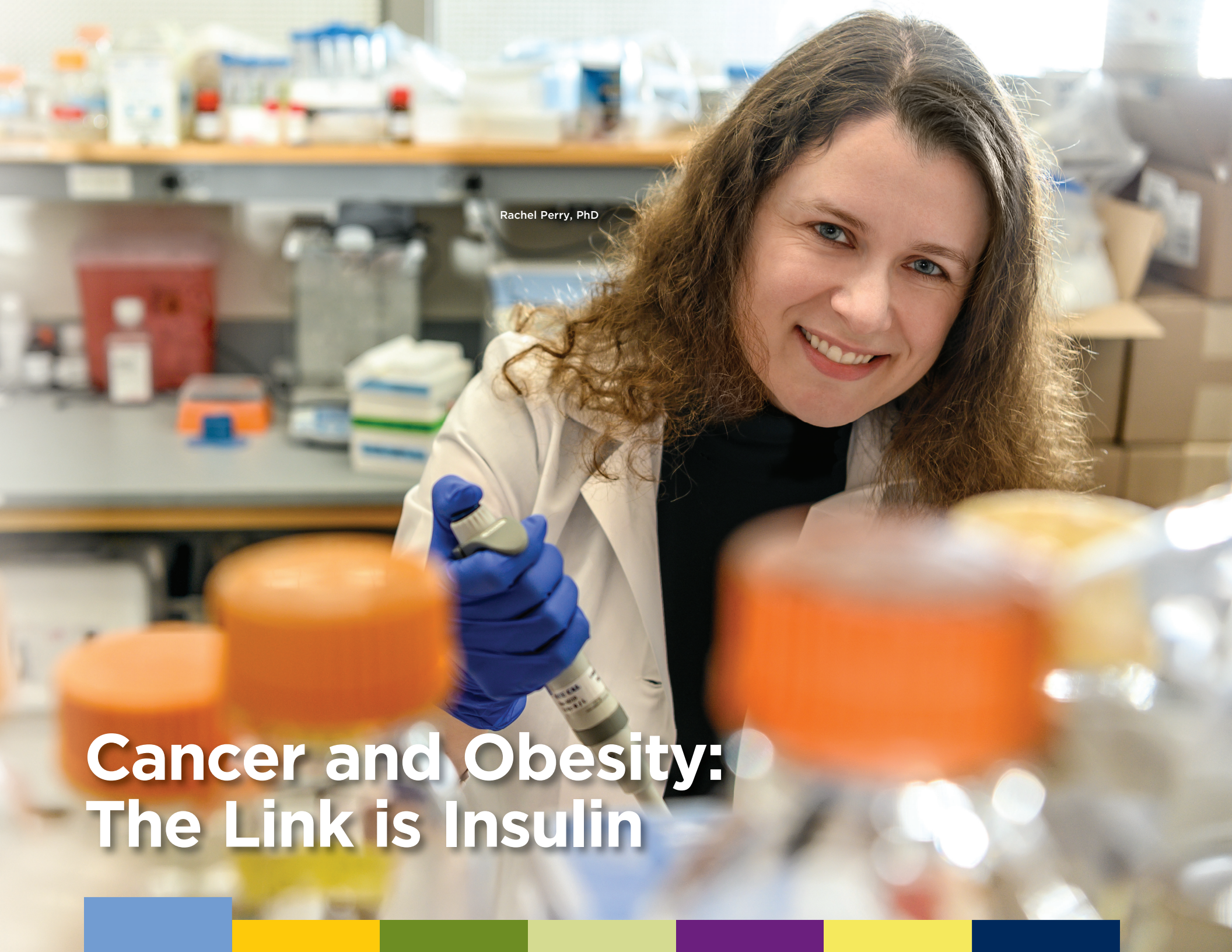
The second drug was a controlled-release mitochondrial protonophore (CRMP) designed by Dr. Perry and her post-doctorate mentor, Gerald Shulman, MD, PhD, the George R. Cowgill Professor of Medicine (Endocrinology) and Cellular & Molecular Physiology. CRMP is an insulin sensitizer, meaning that it lowers blood sugar by reversing insulin resistance. Specifically, it promotes the burning of fat in the liver. Dr. Perry found that CRMP also reverses hyperinsulinemia and slows the growth of tumors associated with obesity.

These findings further confirmed the link between insulin and obesity-related cancers. Significantly, both drugs lowered insulin concentrations whether the mice were fasting or had just eaten a high-glucose meal.

"Conventional wisdom has said that tumors take up a lot of glucose, but it's not hormonally regulated," said Dr. Perry, "so there would likely be no differences in tumor glucose uptake over the course of a day. But we're saying no, it is likely hormonally regulated, a dynamic regulation of insulin signaling and tumor glucose uptake. That suggests that an intervention that lowered both fasting and postprandial glucose and insulin levels would be therapeutically beneficial."

Dr. Perry is working with other scientists at Yale Cancer Center to explore the possibility of clinical trials with a SGLT2 inhibitor as an adjuvant to standard care for colon and breast cancers. She is also running experiments to see whether insulin-sensitizing drugs can enhance the effects of chemotherapy and of immunotherapy.

"My hope," she said, "is that we can apply insulin-lowering therapies to alter tumor glucose metabolism and slow the obesity-associated increase in tumor cell division, and thereby buy more time for curative therapies to work."



Rachel Perry, PhD

Cancer and Obesity: The Link is Insulin