In cases of infection, cells along the linings of blood vessels (green) separate, allowing immune cells to pass through the cracks (black) and rush to the aid of damaged tissue. MALT1 can set this process in motion.
When scientists first isolated the protein MALT1 in 1999, they discovered it was a culprit in B-cell lymphoma. Then, a decade later, other researchers found it was also a protease—a crucial kind of enzyme that busts bonds and breaks proteins down into smaller pieces. And in recent years, the plot has continued to thicken. MALT1, as it turns out, is a kind of multipurpose molecular switch in a range of cell types: certain immune cells, smooth muscle cells, and barrier cells that line blood vessels, to name a few. It performs different functions depending on its location.

MALT1 is now the focus of a wide range of studies with the potential to help treat everything from lymphoma to coronary artery disease to sepsis and acute allergic/hypersensitivity reactions, explain Linda McAllister-Lucas, an MD/PhD associate professor of pediatrics at the University of Pittsburgh and chief of the Division of Pediatric Hematology/Oncology at Children’s Hospital of Pittsburgh of UPMC, and her coprincipal investigator Peter Lucas, MD/PhD associate professor of pathology and pediatrics at Pitt.

“Pharmaceutical companies are very interested in the fact that MALT1 is a protease,” says McAllister-Lucas. “We already have drugs that target proteases. There are many examples in medicine. The most famous is probably the cocktail of protease inhibitors that treat HIV.”

Lucas adds that in 2012 a team in Germany discovered that common antipsychotics called phenothiazines inhibit MALT1. “Nobody even knew this was something these compounds did, and now we might repurpose them in new and exciting ways.”

In September, the Lucas/McAllister Lab published in Cell Reports another surprising role for MALT1.

The team found that in models of inflammation, MALT1 can set in motion a series of molecular actions that help cells along the lining of blood vessels to separate, becoming temporarily leaky. This allows immune cells to leave blood vessels and move rapidly into damaged tissue, which results in swelling, or edema. This is one way the body attempts to protect itself during trauma, as well as infection.

Too much edema, however, can be deadly. Case in point: sepsis-related acute lung injury, where infection leads to potentially fatal pulmonary edema.

The team used an animal model of inflammation, comparing controls in this setting to mice that were genetically deficient in MALT1 protease activity. They found that these deficient mice were protected from potentially dangerous vascular leak and fluid accumulation. McAllister-Lucas says this study is a proof of principle that MALT1 protease activity could be a new target in treating pulmonary edema. In new work, which has been submitted to a journal for consideration, the team has identified a protein that binds to MALT1 and inhibits it.

“We’re very excited about this,” she says. McAllister-Lucas explains that in an acute setting, MALT1 protease inhibitors might reduce acute respiratory distress syndrome (ARDS) by helping dampen endothelial leakiness.

And in a chronic setting, MALT1 inhibitors might be effective in reducing the inflammation in the lining of the blood vessel in atherosclerotic disease. You see, active inflammation is a critical feature that distinguishes unstable atherosclerotic plaque—which is susceptible to rupture—from stable plaque, so MALT1 inhibition might be able to reduce the risk of acute coronary events in advanced atherosclerosis.

Someday, McAllister-Lucas says, MALT1 research may have an even bigger impact. Though excess MALT1 activity can induce lymphoma, it is also absolutely essential for the function of both B and T immune cells, she explains. MALT1 is activated whenever a B or T cell responds to an antigen; it also is essential for the activity of natural killer cells and other types of immune cells.

“So whenever your immune system wants to fight off an infection, MALT1 is activated,” she says. “But too much [activation] causes excessive proliferation that allows cells to survive when they shouldn’t, and this can lead to cancer.”

It turns out MALT1 may be involved in more cancers besides lymphoma, where it was originally discovered. A paper along these lines is in the works, McAllister-Lucas says. “It appears that MALT1 may change the behavior of certain cancer cells and make them more capable of invading and spreading.”
At a seminar some three years ago, Edward Prochownik encountered a close acquaintance—not a colleague, but a protein. In the talk, the speaker was describing a new mouse model of hepatoblastoma, the most common type of liver cancer in children, and how his team had identified the genes with particularly cranked-up expression in the tumors. The most off-the-charts gene was Myc, which the University of Pittsburgh's Prochownik, MD/PhD professor of microbiology and molecular genetics and Paul C. Gaffney Professor of Pediatrics, had been studying for years.

Prochownik and the seminar speaker, Satdarshan (Paul) Singh Monga, a professor in experimental pathology at Pitt, decided to team up.

Myc holds an important middle-management position in the gene world; Myc is present pretty much throughout the body, and its job is to regulate the transcription of thousands of other genes. But it is also commonly overexpressed in tumors. Many tumor types carry a version of Myc that is always switched on. This persistent expression, in turn, jams several of Myc's downstream genes into their “on” positions, as well, and cancer can result. At least half of all cancers overexpress Myc in some way, Prochownik says.

Prochownik’s team at Children’s Hospital of Pittsburgh of UPMC has long explored Myc’s role in cancer, but more recently it has been studying the gene’s involvement in normal liver development, as well as liver regeneration; the liver is the only organ in the body that can regenerate itself on a grand scale, starting with as little as one-third of its original mass intact.

In animal studies, it’s long been known, removing half of the liver almost instantly causes Myc to ramp up its expression as the remaining half switches into regeneration mode. This suggested that Myc played a role in the process. But in a recent study, Prochownik’s lab deleted the gene solely from the liver—and regeneration occurred anyway, at a completely normal rate. “We showed beyond a shadow of a doubt that Myc is absolutely not required for normal liver regeneration,” he says. This finding led Prochownik to think that Myc’s role in generating tumors is not as obvious as he had originally thought.

When his and Monga’s labs tested Myc’s role in hepatoblastoma tumors, they found that without Myc, tumors do develop, but they grow at a markedly slower rate, increasing the animal’s life span five-fold. “So we realized the role of Myc in normal regeneration and in tumororigensis is very, very different,” he says. The researchers published their findings in the Journal of Biological Chemistry last fall.

If you think about it, there’s a certain parallel between normal tissue regeneration and cancer: both involve tissue growth. In the case of cancer, however, that tissue growth is on overdrive. A tumor cell divides every day, which means that every day it needs supplies—amino acids for proteins, nucleotides for DNA and RNA, lipids for membranes, and so on.

Prochownik and his colleagues speculate that Myc upregulates the metabolic processes that are needed for this uncontrolled growth. “We showed that all these processes—protein synthesis, glycolysis, the synthesis of all these different building blocks—were suppressed significantly in tumors that didn’t have any Myc,” he says. “We think that’s the role of Myc in these tissues—to really provide that extra metabolic boost that’s needed for sustaining tumor growth.”

The fact that it is not required for normal, noncancerous tissue growth means that interfering with Myc might be a way to target tumor growth. Such a therapy might not work with hepatoblastoma, where tumors do still grow even without Myc in the mix (albeit more slowly), but other cancers are much more dependent on the gene.

The researchers are now trying to better understand how exactly Myc subtly regulates metabolism. They are also fiddling with the cell’s energy-generation mechanisms in order to interfere with Myc. Such a means of metabolically “starving the tumor,” as Prochownik calls it, could be a slick new trick.
If you ask people with depression to reflect on their experiences, they tend to gloss over the good stuff. “It’s: Yeah, I went and had a great dinner with my kid . . . but then we went home and got in a fight the next week. Positive memories are ignored or discounted,” says Kymberly Young, assistant professor of psychiatry at Pitt.

As a postdoc at the Laureate Institute for Brain Research in Tulsa, Okla., Young uncovered a surprising new insight into this disorder. At the time, Young was conducting imaging studies of the amygdala, a brain region that has historically been seen as a seat of fear and other negative emotions—but as it turns out, it’s more than that. The amygdala responds to anything that’s important to you, either in your environment or in your thoughts, Young explains. “It’s actually a salience detector.”

Young observed the brain activity of patients with depression as they reflected on their memories, and she saw a pattern: The amygdala’s activity was unusually high as patients thought about negative memories, and unusually low through the good stuff. And interestingly, as these volunteers emerged from the scanner, many reported the same curious phenomenon: When they were instructed to focus on their memories, both good and bad, they got a little rush from it. Which gave Young an idea.

Young teamed up with Jerzy Bodurka, a physicist and chief technology officer at Laureate Institute who was developing a new application for brain imaging technologies, called neurofeedback. Like biofeedback, it uses real-time physiological activity data to enable conscious control over unconscious processes. The pair wondered if, just like a person can learn to control her heart rate by focusing on her own EKG strip in real time, someone with depression could use fMRI imaging to control his amygdala activity at will.

Heartened by the results of a small pilot study, the team then validated their findings in a follow-up study, the results of which came out in the American Journal of Psychiatry this April. The study showed that after just two sessions, participants’ depression scores dropped by half. And one week out, one-third of the patients no longer met the criteria for depression at all.

Here’s how neurofeedback works: The volunteer climbs into the scanner and is asked to think about three positive memories. Meanwhile, the patient looks at the thermometer on a screen—the “temperature” represents the amygdala’s level of activity. The patient aims to raise the temperature to a given target. The researchers then raise the target incrementally, as amygdala activity increases.

For people often caught in a negative-feedback loop, this experimental treatment creates a positive one. They go into the scanner with three positive memories—they come out with somewhere between seven and 12. “It leads to a cascading effect,” Young says.

When Young first started this work, she got some snide comments. “The most common was, Well, Peter Pan—he says, ‘Think happy thoughts, and then you’ll fly,’” she says. But Young has learned to embrace the metaphor. If the Darling children of Sir James Matthew Barrie’s novel were to heed that advice and step out of a window, they couldn’t fly—unless they had pixie dust onboard.

“I’m considering amygdala activity the pixie dust,” Young says. “It allows you to use the positive memories in a way that is helpful and useful,” rather than continuing to discount them. Because it’s not as simple as thinking happy thoughts, she says. Unfortunately, the more people tell depressed patients simply to “think positive,” the worse it makes them feel. “The research has shown that,” Young notes. Amygdala activity may be the magic ingredient that’s missing.

In the future, Young, who is funded by the National Institute of Mental Health and the Brain and Behavior Research Foundation, hopes to help make neurofeedback more widely available. She also plans to work with therapists to share what she’s learned. Cognitive behavioral therapy could be enhanced by these insights, she believes.

Her study volunteers immediately warm to the idea, she says. “They’re not taking a drug, they’re not talking to a stranger about their mother. [The technique] is informed by neuroscience; it’s a train-your-brain intervention—and they enjoy it.”