ILLUSTR. BEING REVISED. FIT IT IN SOMEWHERE HERE

ABOVE: **A vaping robot (the real thing is shown right) gives researchers the opportunity to study what vaping introduces into the lungs without the time and cost needed to run clinical trials.** RIGHT: **The system uses a vacuum pump to draw in vapor from an e-cigarette; other components dilute the vapor, mimic breathing and control temperature and humidity.**

PUFF PIECE

A ROBOT IS HELPING TO EXPOSE VAPING'S HEALTH RISKS

BY ANDREW DOERFLER

In September 2019, the Centers for Disease Control and Prevention reported an outbreak of severe lung disease among patients with something in common: They all vaped regularly. Today, more than 2,500 cases of vaping-associated lung illness have occurred in the United States, along with dozens of deaths.

But scientists have yet to fully determine how e-cigarettes and other vaping devices threaten health. With hundreds of different products with an array of different ingredients on the market, any number of culprits could play a role.

Researchers now have a new partner helping them get to the bottom of the mystery: A vaping robot, devised by Pitt's Kambez Hajipouran Benam, a DPhil associate professor of medicine.

Benam

The tabletop system mimics inhalation while simulating the conditions inside the human body to measure what people are drawing in when they take a puff from an e-cigarette. Benam's team can program the robot to match the breathing patterns of people of different ages or those with asthma and other lung conditions.

"We are concerned that vaping is seen as a completely safe thing to do, especially among young people," Benam says. For adults looking to quit smoking cigarettes, it may present a less harmful alternative. "But when someone in middle school or high school thinks, 'Oh, it's safe, so I can try it,' that is where the problem emerges."

The robot, which the journal Nature featured in a roundup of research highlights in 2021, offers the chance to study what vaping introduces into the lungs without the time and cost needed to run clinical trials. It can also help researchers keep up as new products, flavors and ingredients hit shelves, some attempting to evade new FDA regulations.

"We want to use the robot to generate the data much more quickly than any other platform," Benam says. "We will be able to test tens or even hundreds of e-liquids, so people will have a better understanding of the potential for toxicity."

When the CDC announced the rash of vaping-associated lung illness, the agency linked hospitalizations to an additive called vitamin E acetate. The compound, commonly found in hand lotions and many foods, is used in some vaping liquids, especially those containing THC or other cannabinoids. But it's not certain how exactly its presence leads to lung damage.

Benam suspects part of the answer lies in the size and quantity of particles drawn into the lungs when vaping. Even a small amount of vitamin E acetate in e-liquid, the robot has shown, dramatically increases the total number of particles, especially very small ones, that end up in the lungs.

Further: "The very small particles can make it deeper into the lungs, and they're more likely to coat the inner surface of your respiratory tree," Benam says. "They're more likely to even penetrate into your bloodstream."

The robotic system—called the Human Vaping Mimetic Real-time Particle Analyzer—uses a finely regulated vacuum pump to draw in vapor from an e-cigarette, while a diluting component adds filtered air (since vape users aren't breathing in a vapor puff alone). Two air-tight syringes, programmed to simulate the flow rate of breathing, inhale and exhale. An exposure chamber senses and controls the robot's "body" temperature, humidity and gas levels. With all these factors taken into account, a laser sensor measures the size and number of particles breathed in.

"Basically whatever breathing profile you want, whether it's restrictive or obstructive or normal breathing, you can customize it to that," says Rachel Bogdanoff, a research technician in the lab.

In a related, FDA-funded project, Benam's
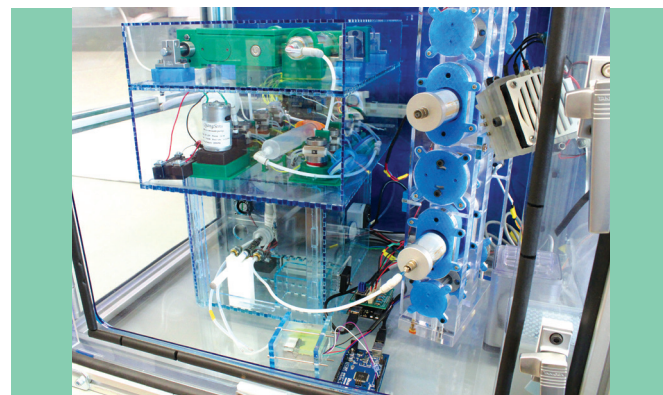
team is engineering a "next-generation organo-mimetic human lung system" that, combined with the vaping robot, could show the effects of these products on living cells. In the meantime, the team is looking to confirm their findings through clinical validation and retrospective analysis.

Benam notes that the project brings together engineering, lung pathobiology, breathing mechanics and inhalation toxicology. "The beauty of bringing multiple disciplines together is that you come up with creative solutions for a growing or emerging problem." ◾

The New Power of Positive Thinking
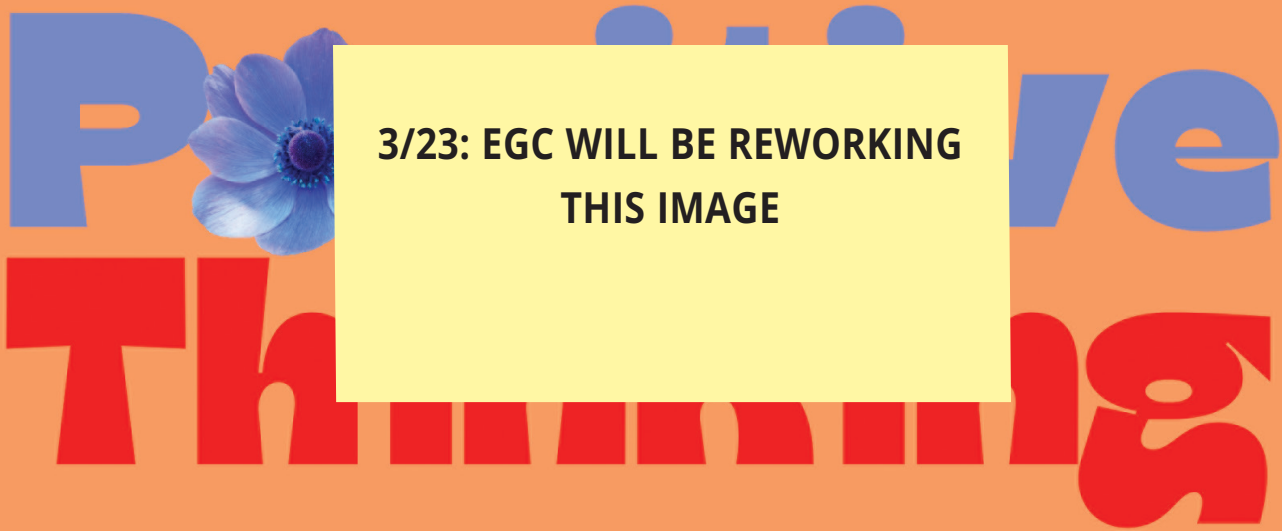
3/23: EGC WILL BE REWORKING THIS IMAGE

COGNITIVE TRAINING ENHANCES KETAMINE THERAPY FOR PEOPLE WITH SEVERE DEPRESSION

BY ELVIRA DIPAOLO-HOFF

Price

Imagine if your brain could reroute itself away from depressive thoughts just as easily as your car's GPS reroutes itself when you make a wrong turn.

Rebecca Price, a PhD associate professor of psychiatry in Pitt's School of Medicine, thinks a similar concept could help the roughly 30% of depression patients whose illness doesn't respond to traditional treatments. Using an approach that incorporates computer-based neurocognitive training, Price is prolonging the antidepressant effects of ketamine therapy.

In a study published in The American Journal of Psychiatry, Price found that showing positive words and images to people with treatment-resistant depression after a single ketamine infusion can help them quickly learn new ways of processing information that lead to happier thoughts.

Ketamine has been used worldwide as an anesthetic in medical settings for more than half a century. Around 2000, researchers began noticing and testing its quick-acting efficacy against depression. Soon, there was enough evidence to prompt clinicians to start prescribing it off-label for treatment-resistant depression, and clinics began opening across the country to administer intravenous ketamine therapy.

Price became interested in ketamine's potential while a graduate student in clinical psychology at Rutgers University. Her mentor connected her with investigators at the Icahn School of Medicine at Mount Sinari who were conducting some of the earliest studies on ketamine use for depression treatment. As a clinician interviewer for those studies, Price was floored by the nearly immediate ability of ketamine to transform a patient's thinking.

"I would speak to a patient one day and they would be describing decades of chronic depression that had not ever really remitted to any approach they tried," says Price, who is also an associate professor of psychology at Pitt. "Then I would come back the following day and it was like speaking to almost a totally different person."

However, the benefits tend to be short-lived, with symptoms of depression returning in a matter of a weeks after an infusion. Price is working to change that.

A "psychoplastogenic" drug, ketamine quickly increases the brain's plasticity, or ability to adapt in response to stimuli. In a study involving 154 adults, Price was able to capitalize on the brain's malleable period following a single dose of ketamine by adding an automated self-association training twice daily over four consecutive days.

The training paired words like "I" with cues like positive traits and images of smiling actors. In the group of 53 participants who received both the single dose of ketamine and the self-association training, the "package deal" was shown to prolong depression relief for a full three months.

Extending the effects of a single ketamine treatment could dramatically increase access for patients. Most health insurance plans don't cover ketamine treatments, so patients incur high out-of-pocket expenses. Patients get started with anywhere from four to eight infusions administered in the first few weeks and return for booster doses as necessary, often creating long waiting lists at clinics.

"I've been flooded with requests from ketamine providers, patients and their families," Price says. The work has also piqued the interest of colleagues who wonder if the same type of therapy could be adapted to treat phobias, eating disorders or similar conditions. Pitt's Innovation Institute has filed a provisional patent for the combined treatment protocol as Price continues to refine her research.

She is currently testing her protocol in hospitalized patients who have just attempted suicide. Price is also seeking next-step funding to study either making the combination treatment powerful enough that it lasts longer than three months—or determining what form of intervention at that juncture could help boost its effects. Although there is more to do, the work already offers a great deal of practical new hope for what's often a devastating condition. ■

Telomeres (those caps on the ends of chromosomes) typically shorten as people age, but not in the case of cancer cells.

THE LONG GAME

DISCOVERY REVEALS A KEY TO MELANOMA'S IMMORTALITY

BY HAYLEY REIN AND ANDREW DOERFLER

When Pattra Chun-on first reached out to Jonathan Alder hoping to join his lab at the School of Medicine, Alder was hesitant.

Chun-on, an internist with a background in cancer biology, had come to the University of Pittsburgh for a PhD and wanted to study the extra-long telomeres found in cancer. Telomeres are the caps at the end of chromosomes that protect DNA from degrading. In healthy cells, they become shorter with each cycle of replication until the cell can no longer divide. Cancer cells, meanwhile, have telomeres that maintain their length, allowing the cancer to continue replicating and keeping them effectively immortal.

Though she was an excellent candidate, Alder told the physician that his lab focused on short telomeres, associated with premature death and aging, not the long ones she was interested in. But Chun-on insisted. "This went on until I realized that Pattra would never take 'no' for an answer," says Alder, a PhD assistant professor of medicine.

Her persistence paid off. Chun-on, Alder and their collaborators found a combination of mutations that promote extra-long telomere growth in melanoma, a discovery that could change the way oncologists understand and treat it.

Published in the journal Science in November, their findings identified two genetic alterations that work together to stimulate telomerase, the enzyme that keeps telomeres from shortening. Until now, no one had ever seen them work together to help make melanoma immortal.

"We did something that was, in essence, obvious based on previous basic research and connected back to something that is happening in patients," Alder says.

For years, scientists have seen strikingly long telomeres in melanoma tumors, especially compared to other cancers. About 75% of melanoma tumors contain mutations in the TERT gene that activate telomerase and allow cells to continue growing. Yet, when scientists mutated TERT in cells in culture, they couldn't produce extra-long telomeres. It turns out that TERT promoter mutations were just half of the story.

The road to discovering the other half began when Chun-on heard a talk from Patty Opresko, a PhD professor of environmental and occupational health in Pitt's School of Public Health who studies DNA damage and repair at telomeres.

"She gave a talk that was so impressive to me," Chun-on says, "and I just decided, 'Oh, I will focus on the telomere angle with cancer.'"

As it turned out, Alder had tried studying long telomeres before. Years earlier at Johns Hopkins University, where Alder earned his PhD, he had bandied about an ambitious idea with Carol W. Greider, the Nobel-winner who discovered telomerase: What if they could classify all cancers by how they maintain their telomeres? The idea fizzled out in 2015; four years later, Chun-on was taking it up again.

Alder's team had previously discovered a region in a telomere binding protein called TPP1 that was often mutated in melanoma tumors. Chun-on found that mutations in TPP1 were strikingly similar to those of TERT. "Biochemists more than a decade before us showed that TPP1 increases the activity of telomerase in a test tube, but we never knew that this actually happened clinically," Alder says.

Chun-on

When Chun-on—a PhD candidate in Environmental and Occupational Health in the School of Public Health—added mutated TERT and TPP1 back to cells, the two proteins together created the distinctively long telomeres seen in melanoma tumors. TPP1 was the missing factor scientists had been searching for, and it was hiding in plain sight.

Alder

By identifying a telomere maintenance system that is unique to cancer, scientists now have another target for the development of new chemotherapeutics.

Alder's team collaborated on the National Institutes of Health–funded study with researchers at the UPMC Hillman Cancer Center. John Kirkwood, the Sandra and Thomas Usher Professor and Distinguished Service Professor of Medicine, Dermatology and Translational Science at Pitt and coleader of the UPMC Melanoma Program, provided many of the cell lines the team used.

"We were in the right place, and many things lined up," Alder says. "But so much of this was driven by Pattra's absolutely unbreakable determination." ∎