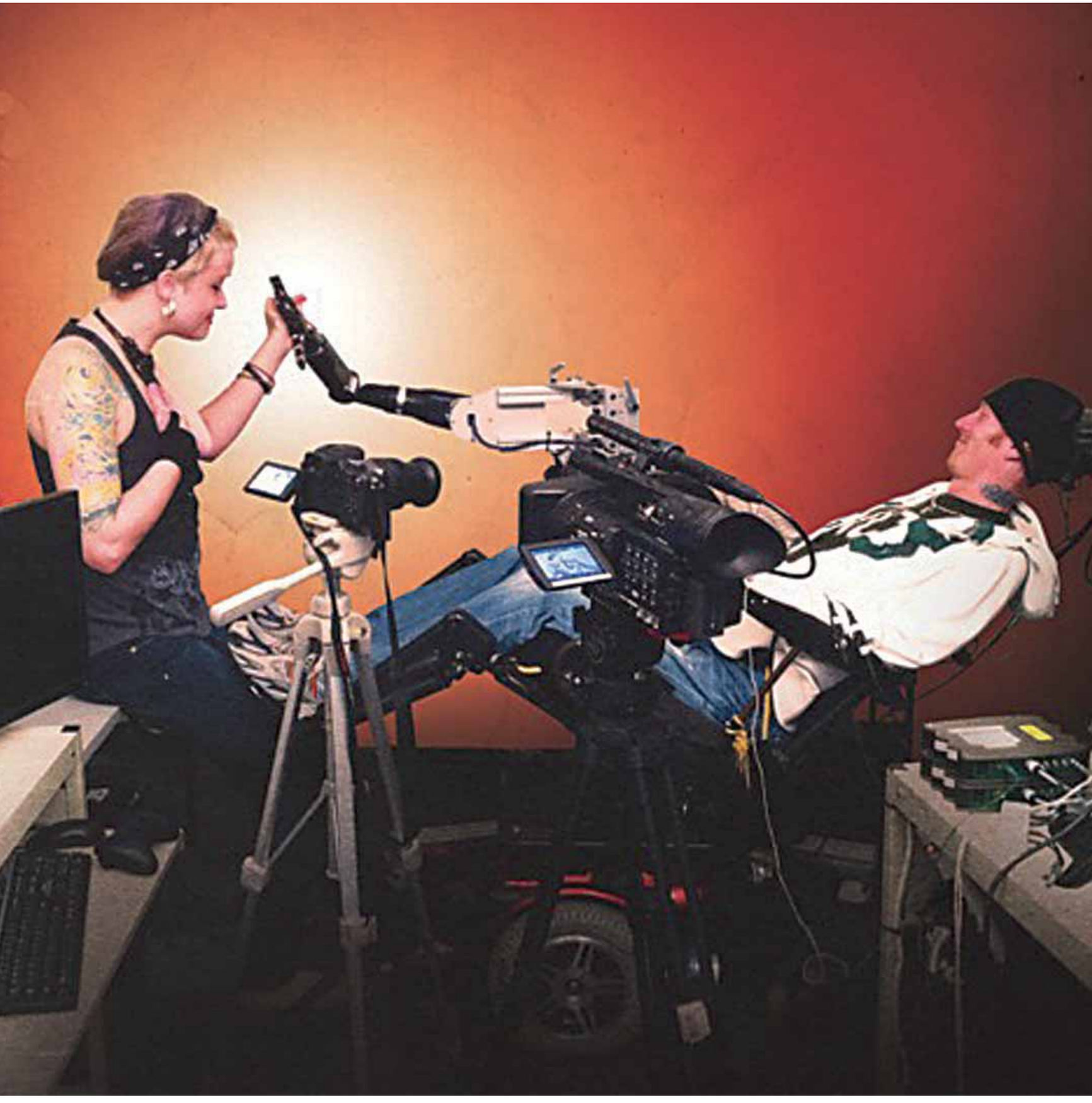
Explorations and revelations taking place in the medical school



For the first time in seven years, Tim Hemmes touches his girlfriend's hand; to do so, Hemmes uses a robotic arm he controls with his thoughts.

MEANINGFUL MOVEMENT

BRAIN INJURY PATIENT ABLE TO MOVE ROBOTIC ARM WITH THOUGHTS

BY ANITA SRIKAMESWARAN

Like a bashful but determined suitor, 30-year-old Tim Hemmes cautiously maneuvered an unsure hand toward his girlfriend. As their palms touched, tears spilled over onto Katie Schaffer's cheeks, while Hemmes' shined with joy and hope.

The moment was a reminder to the researchers and physicians watching the unfolding drama of why they had been working so hard for so long. Since a motorcycle accident snapped his neck seven years ago, Hemmes hasn't been able to move his body below his shoulders, nor has he had feeling there. Using technology and fundamental understanding of neurobiology advanced by researchers in the University of Pittsburgh School of Medicine, Hemmes guided with his thoughts a robotic arm made by Johns Hopkins University's Applied Physics Laboratory, managing a high five that was a profound illustration of the emotional power, often taken for granted, of touching a loved one.

"We're not just trying to generate movement," says Pitt's Andrew Schwartz, a PhD professor of neurobiology whose experiments in monkeys helped inform the algorithms that were used in this trial of brain-computer interfaces in patients with spinal cord injury.

The ultimate goal is to develop a device that gives paralyzed people the ability to make purposeful movements. The Pitt researchers imagine it would help immobile people perform activities of daily living—like handling a cup and fork or opening doors—and express themselves through gesture—perhaps a welcoming handshake, a jubilant high five, or a tender hug.

Schwartz's monkeys learned to manipulate a robotic arm while their arms were restrained. The monkeys came to see the mechanical arm as their own, licking remaining bits of marshmallow from the grabber after the test tasks were completed, using the grabber to nudge food around in the mouth, and even grooming the metal as they would their own fur.

Schwartz notes that when Hemmes reached out with the prosthetic arm, "you really did start to sense that, for instance, his girlfriend had taken this as an embodied hand of Tim's, and was actually feeling the extension of Tim's body scheme to that hand."

Michael Boninger, an MD professor and chair of Pitt's Department of Physical Medicine and Rehabilitation, describes a brain-computer interface as a device that taps into thoughts so they can be translated into action. The grid being used in the trial grew out of electrocortigraphy (ECoG), a technique in which electrodes are placed directly on the brain to study brain signals (often to help doctors pinpoint cortical areas in the brain that set off seizures). The grid sits on the surface of the brain, gathering neuronal signals from the motor cortex mapped to where Hemmes imagined and observed arm movement. In a Pitt pilot study led by Elizabeth Tyler-Kabara, an MD/PhD assistant professor of neurological surgery, and Wei Wang, MD/PhD assistant professor of physical medicine and rehabilitation, epilepsy patients admitted for seizure-mapping tested the grid. In that study, volunteer patients raised their eyebrows, flexed their elbows, or made other specific movements to send signals through the grid to a computer processor, enabling them to move a cursor on a computer screen or take Super Mario through an adventure. The results of this pilot project paved the way for techniques in patients with spinal cord injury.

Hemmes, the high-fiving patient, was first charged with the task of moving one ball to touch another on a computer screen. Soon, his commitment to the project and his own desire to best his previous "score" had him quickly progressing from two-dimensional movements of up-down and right-left to moving the ball "in and out" on a 3D TV screen. He worked with the arm only a few times during the 28-day study protocol. The high five with Schaffer happened after he'd done the same thing with lead researcher Wang—in part, to celebrate the end of nearly daily data collection.

"When you plan an experiment, you always picture it," Boninger said. "What you can't picture really is the human factor. Seeing [Hemmes'] face light up as well as those of the amazing team of investigators that were working with him was quite a spectacular sight."

This year, more participants will be enrolled in the ECoG-based protocol. In tandem, the team will start a yearlong trial to test another kind of brain-computer interface, a 10-by-10 microelectrode array that barely penetrates the brain to pick up signals from hundreds of neurons in the motor cortex; it's the same type of interface that Schwartz has been using in the monkey experiments. Tyler-Kabara will implant two grids in each participant: one in the area mapped for arm movement and the other for the hand. The higher-signal resolution could allow greater control of the arm, including the fingers, and a full exploration of its potential.

Then, they hope to make the device wireless and add sensors to the arm to deliver signals to the brain and recreate sensation.

Hemmes' achievement has validated conclusions reached after 20 years of studying neural signaling and motion, Schwartz says. And, he notes, now hundreds of people are working toward moving the technology forward from what his small group started.

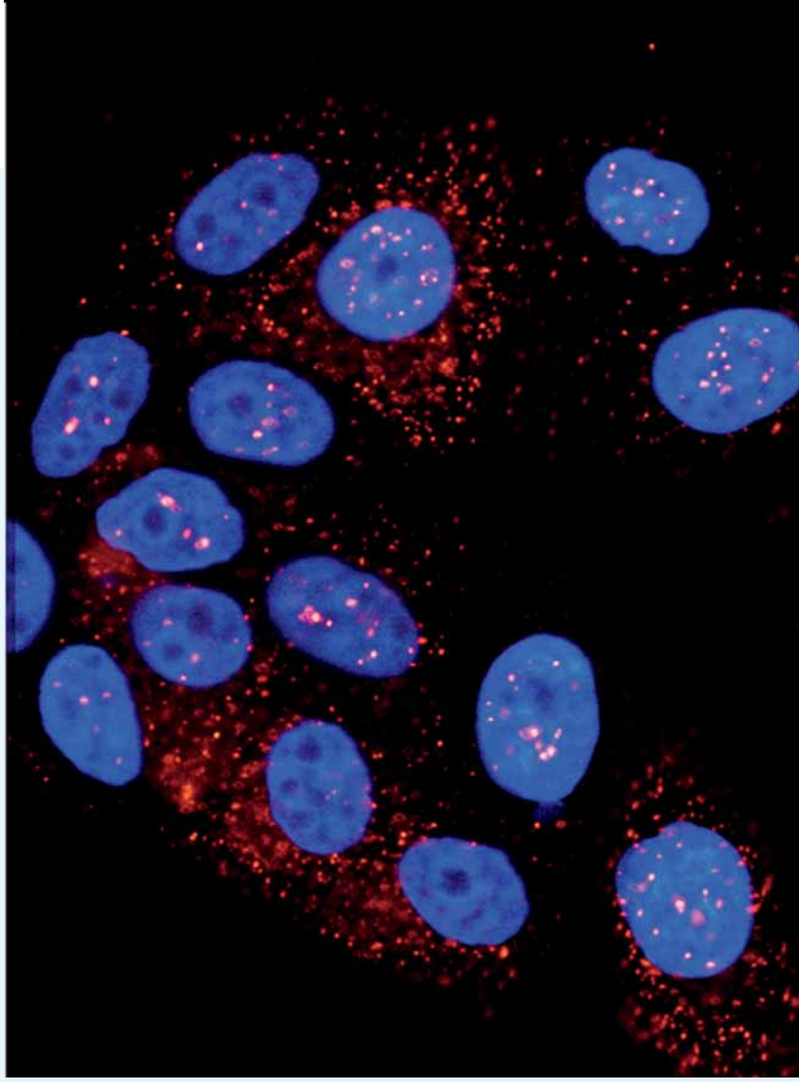
"That's really satisfying," Schwartz adds. ■

ILLUSTRATION: JESSE LENZ (BASED ON PHOTO COURTESY UPMC NEWS BUREAU)

RUNNING A MUC1

ANOTHER REASON TO DETECT CANCER SOONER

BY DANA YATES



The protein MUC1 helps cancer spread. Here, MUC1 within cellular nuclei (magenta dots in the blue) and surrounding the nuclei (red dots) in breast cancer cells.

Within healthy cells, the protein MUC1 (pronounced "muck one") is normally found in low levels, and that's all well and good. But in the cells of adenocarcinomas—epithelial cancers, which include breast, colon, and prostate cancers—MUC1 is found in higher amounts, and its presence has been known to aid the spread of tumors. How and why exactly MUC1 mucks things up, however, has never been clear.

Sandra Cascio, a native of Italy, is a postdoctoral associate who has received a fellowship from the Ri.MED Foundation—a partnership between the Italian government, the Presidency of the Region of Sicily, the Italian National Research Council, the University of Pittsburgh, and UPMC—to conduct biomedical research in Pitt's Department of Immunology. In her work here at Pitt, Cascio may have figured out the mechanisms that send MUC1 running amok, and her paper on the topic was published—without revision—in the December 2011 issue of the *Journal of Biological Chemistry*. The paper was coauthored by Pitt visiting scholar Lixin Zhang and the chair of Pitt's Department of Immunology, Distinguished Professor Olivera Finn, Cascio's mentor. It was selected by Faculty of 1000, a global panel of more than 10,000 expert scientists and clinical researchers, as among the top 2 percent of published articles in the fields of biology and medicine.

"Some inflammatory cells within tumors act to kill [the tumor] while others help it to grow," says Cascio. "One molecule can make a difference."

The molecule the team zeroed in on is a cytokine. In normal cells, cytokines are produced to signal the immune system to fight bacteria, viruses, allergens, and toxins in the body. In response, the immune system battles those harmful agents with inflammation. Within cancer cells, however, there are far more cytokines, and their upsurge promotes inflammation throughout the body—a circumstance that enables the cancer to spread even faster.

The researchers knew that a specific cell-communication pathway known as nuclear factor-κB p65 played a critical role in inflammation. And by using human breast cancer cells that contained abnormal MUC1 proteins, the Pitt team made an important discovery: The MUC1 protein connected with the nuclear factor-κB p65 pathway. Together, the two formed a new and special unit—one that controls cytokine production.

The team also explored the genetic material that repeats itself in the MUC1 protein. This replicated material, known as tandem repeats, varies in number among individuals. The number of tandem repeats makes no difference in normal cells, but the researchers wondered whether the same was true in cancer cells.

The team developed two MUC1 proteins—one with two tandem repeats and another with 22—and then inserted them into mouse lymphoma cells and human melanoma cells that otherwise lacked any MUC1 protein.

The goal: to determine whether the amount of cytokine produced varied according to the number of tandem repeats.

The researchers discovered that the MUC1 protein with the higher number of tandem repeats stimulated the production of more cytokines. This finding implied that tandem repeats in the MUC1 protein are vital to the formation of the MUC1-p65 complex.

"It's best to nip cancer in the bud. Otherwise we have a harder time controlling its growth," says Finn. "Eighty percent of tumors come from carcinomas. So if all those cancers have the same molecule in common, we can figure out how to target that. And if we can interfere with the formation of the MUC1-p65 complex from the beginning, we can inhibit tumor growth." ■

A LIFE WELL LIVED

ADAPTIVE IMMUNE CELLS KEY TO HEALTHY GOLDEN YEARS | BY DANA YATES

GETTY IMAGES

A new understanding of the immune system of older adults.

The outward signs of healthy aging are easy to see. Consider, for example, an elderly person who is active, independent, and involved in the community. So what, then, is happening inside seniors who age well? At least part of the answer, according to researcher Abbe de Vallejo, is found within the immune system.

An associate professor in the University of Pittsburgh's Departments of Pediatrics and Immunology, de Vallejo is also a member of the Division of Pediatric Rheumatology at Children's Hospital of Pittsburgh of UPMC, the Cancer Immunology Program at the University of Pittsburgh Cancer Institute, and the Pitt-UPMC McGowan Institute for Regenerative Medicine. His research on the immunological side of exceptional aging, funded by the National Institutes of Health, was published in the October 2011 issue of the online journal *PLoS ONE*. The study also involved Anne Newman, professor and chair in the Department of Epidemiology in the University of Pittsburgh Graduate School of Public Health (GSPH) and director of Pitt's Center for Aging and Population Health, as well as others from GSPH and the School of Medicine.

Why would a scientist who is based at a children's hospital study the immunological profile of seniors? "Aging is part of development," says de Vallejo. "It's a process, not a series of stages. And what we learn from older people can help us better understand children."

That said, just as kids aren't miniature grown-ups, it's inaccurate to view seniors as "only defective versions of young or middle-age adults," he notes. There are key differences between the groups, including how their immune systems work.

Until age 50, for instance, the body regularly produces T-cells, the soldiers of the immune system that kill invaders. During the later years, however, the T-cells' ranks are depleted, forcing the body to make do with the limited number that are left. So what does the immune system do to compensate for the decreased supply? It adapts.

With age, T-cells start behaving like natural killer (NK) cells, another component of the immune system that typically attacks tumors and viruses. Normally, a T-cell is sent into battle only when its surface T-cell receptor is activated—or "tickled," as de Vallejo says. Although that trigger can also occur when a T-cell assumes an NK receptor, the Pitt researchers discovered a distinct pattern of T-cell activity among seniors with higher levels of physical and cognitive function compared to those with mild health impairment.

To start, the researchers gathered blood samples from 140 participants whose average age was 86; the research volunteers had been tracked for nearly two decades in the Cardiovascular Health Study (CHS). Funded by the National Heart, Lung, and Blood Institute, the CHS explored the risk factors for cardiovascular disease in adults 65 years or older.

The Pitt team collected additional details about the CHS participants' health, including their hospitalization and medical history. They also used quantitative tests to evaluate participants' physical and cognitive function.

The researchers found the cells of the higher-functioning participants had more stimulatory NK receptors on the surface of their T-cells. In addition, these elders had an ideal balance and quantity of cytokines, which mediate immune responses. Both features suggest an increased ability to fight illness. "[The results] show beneficial adaptation or remodeling in our immune system," says de Vallejo.

On the other hand, the group with mild health impairment had more inhibitory NK receptors and a less-than-ideal arrangement of cytokines. This situation could help disease take hold in the body.

De Vallejo hopes his research will contribute to a philosophical shift in medicine—from replacing deteriorating body parts (e.g., knees) to improving what remains (e.g., immune cells). It's an idea that will take on greater importance in the future. By 2050, in fact, the global population of people 60 or older is expected to reach nearly two billion, according to the United Nations.

"The versatility of T-cells is astounding," says de Vallejo. "We need to find ways to enhance what we have." ■

COURTESY SANDRA CASCIO