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VA Research Currents

RESEARCH NEWS FROM THE U.S. DEPT. OF VETERANS AFFAIRS

Artificial lung design mimics nature

An artificial-lung prototype built by researchers with Case Western Reserve University and VA's Advanced Platform Technology Center mimics the structure of a natural lung, with a lifelike network of tiny air and blood channels, branching down to artificial capillaries thinner than a human hair. The invention is described in the Sept. 7, 2011, issue of *Lab on a Chip.* Led by engineer Joseph Potkay, PhD, the Cleveland-based researchers call their device "a significant step towards creating the first truly portable and implantable artificial lung systems."

Heart-lung machines that in essence contain artificial lungs have been in use for years. But they are bulky pieces of

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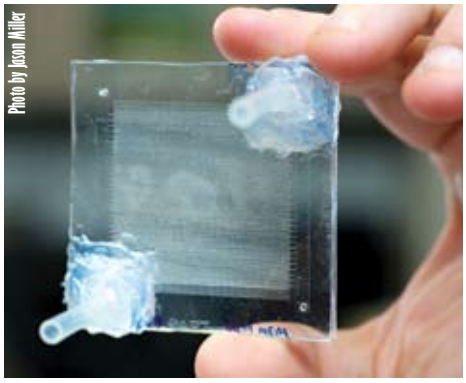

A new artificial lung prototype features micromachined channels for air and blood.

Mind over matter

Mindfulness training helps Veterans cope with potentially debilitating gut disorder

Whack! When George de los Santos thrusts forward a powerful palm strike in the martial arts class he teaches at a Seattle fitness center, there is little hint that he has struggled for decades with a serious health problem.

Irritable bowel syndrome affects 1 in 10 Americans. It can leave patients feeling anxious about routine trips out of the house, concerned they may need a bathroom suddenly and urgently. Many worry about trying new foods because their symptoms may flare up. Dietary changes, drugs, and psychotherapy can help somewhat, but about a third of patients don't get adequate relief, and many seek out complementary and alternative treatments.

De los Santos and other Veterans with IBS have been helped through an eight-week course on Mindfulness-Based Stress Reduction, or MBSR, at the VA Puget Sound Health Care System. The course is available as an adjunct to usual care for Veterans

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Combating IBS—George de los Santos has been able to stay active and enjoy his hobbies—such as martial arts—in part thanks to a VA program that taught him mindfulness skills to cope with irritable bowel syndrome.

Fountain of youth?

Blood exchange between young, old mice rejuvenates the brain

Scientists with VA and Stanford University reported this month in the journal *Nature* on a handful of bloodborne proteins that hinder the brain from making new neurons and whose levels rise with age. If researchers can learn how to block the proteins, they could have a way to thwart the mental effects of aging.

The lab study found factors in the blood that influence the production of new cells in the hippocampus, a brain region crucial for learning and memory. In one phase of the work, researchers joined the circulatory systems of young and old mice: The exchange of blood turned back the clock in the brains of the old mice and had an opposite effect on the young mice.

"We have a model by which we can promote brain aging in young mice by giving them blood from old mice, and rejuvenate old mouse brains by giving old mice blood from young mice," says senior author Tony Wyss-Coray, PhD. Wyss-Coray is the associate director of the Center for Tissue Regeneration, Repair and Restoration at the VA Palo Alto Healthcare System.

Among other memory tests, young mice infused with old blood became less able to recall the location of an underwater platform they could rest on to avoid treading water.

To zero in on the factors in the blood responsible for the effect, the researchers tested scores of proteins linked to the immune system. They found six whose levels were naturally higher in older mice—and artificially elevated in young mice that were exposed to "old" blood.

The single protein that turned out to be the biggest damper on neuron production was CCL11, or eotaxin. The researchers took samples of blood and cerebrospinal fluid from healthy people between ages 20 and 90 and confirmed that CCL11 levels drop with age.

Wyss-Coray says the pharmaceutical industry makes several small molecules that can potentially block the action of CCL11. They were used to develop new drugs for asthma, but the drugs proved ineffective in clinical trials. He says his group is now testing whether the molecules might have a beneficial effect on the brain.

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Memory lane—Dr. Tony Wyss-Coray and colleagues used a radial arm water maze to test the memory of mice, as part of a study on the effects of exchanging blood between young and old mice.

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Editor: Mitch Mirkin

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equipment that require pure compressed oxygen stored in heavy cylinders. A newer device now in clinical trials outside the U.S. is smaller and more portable, but it still requires pure oxygen.

The new prototype from VA and CWRU is unique in how it copies nature. Because of its intricate silicon tubing and ultra-thin gas diffusion membrane, the device is efficient enough to use air as the ventilating gas—as opposed to pure oxygen stored in a tank. It thus creates new possibilities for portability, and possibly implantation.

Though years away from use in humans, the device could become an option for those with failing lungs due to conditions such as chronic obstructive pulmonary disease or emphysema. It might also be a component in a new generation of lightweight, portable heart-lung units that medics could use on a battlefield. In cases of acute respiratory distress syndrome, the device could be used to help patients breathe while their lungs heal, allowing them to remain mobile.

For the most part, says Potkay, the device would be a temporary measure—a bridge to help patients awaiting a lung transplant, or an aid for those whose lungs are healing.

"In most cases, it would run parallel with the natural lung, so both are operating at the same time, but with the device doing most of the work," says Potkay. "If it were used external to the body, instead of the diaphragm to pull air through the natural lung, we'd have some portable air pump attached to the device to flow air across the artificial lung and allow gas transfer."

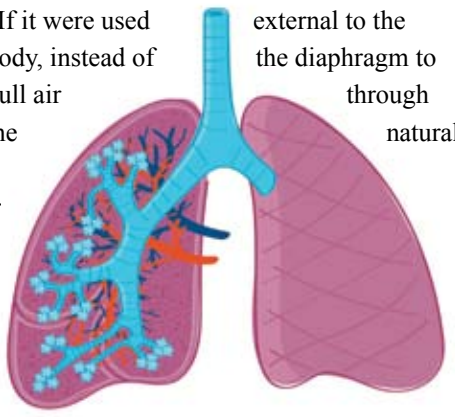

Illustration: iStockphoto

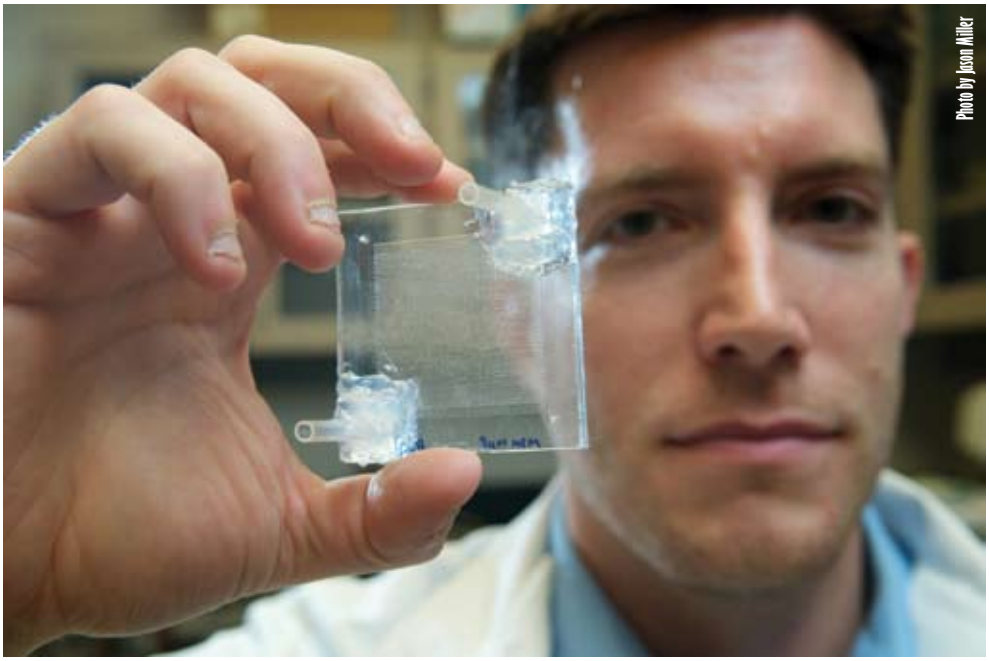

Photo by Jason Miller

Breathe easy—Dr. Joseph Potkay, with VA's Advanced Platform Technology Center and Case Western Reserve University, displays a micromachined artificial lung with tiny air flow and blood channels that mimic the structure of the real organ.

One factor that could limit the working life of the device is clotting in the manmade blood vessels. Blood reacts to a foreign body by clotting. The researchers are working on more advanced materials, though, to minimize that risk. Potkay describes efforts at other sites to grow endothelial cells—like those found in the lining of real blood vessels—that could potentially be used on the imitation silicon vessels that snake through his group's device. "This work is still in the early stages of development, but it's intriguing," he says.

His group is also developing a new surface coating that might do a better job of prevent clogging in the artificial capillaries. They are also working on methods to build a durable unit large enough to test in rodent models of lung disease. The team expects to have human-scale artificial lungs ready for clinical trials within a decade.

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The surgical technique used in the study, whereby a young mouse was joined to an old one to merge their blood systems, was pioneered in the early 2000s by VA-Stanford researcher Thomas Rando, MD, PhD, one of the authors on the current study. The method is known as parabiosis.

Meanwhile, the group continues to search for other key proteins, particularly ones that exert effects opposite to those of CCL11. Such proteins, in theory, could serve as anti-aging potions for the brain.

"We hope to find new ones that could be given systemically and affect the brain directly," says Wyss-Coray.

Wyss-Coray and Rando are also with the Geriatric Research, Education and Clinical Center at the Palo Alto VA. Besides VA, funding for the research was provided by the National Institutes of Health and the California Institute for Regenerative Medicine.

Harnessing the power of 'natural language processing'

In a study at six VA medical centers, researchers used Google-like technology called "natural language processing" (NLP) to interpret free text in Veterans' electronic medical records—such as doctors' notes—and identify post-surgery complications. The new method, which outperformed an existing one that relies on administrative codes, could emerge as a powerful tool for quality improvement in VA's nationwide health system.

The findings appeared in the Aug. 24/31 issue of the *Journal of the American Medical Association (JAMA)*.

The study used data on nearly 3,000 VA patients who underwent surgery between 1999 and 2006. Compared with a standard automated method that scans administrative data, NLP was better at picking up adverse post-surgery events such as lung, kidney, or heart problems. To provide a benchmark for both approaches, trained nurses manually reviewed the patient records and carefully looked for any clinical notes indicating complications.

In an accompanying *JAMA* editorial, Dr. Ashish Jha said the researchers, led by Dr. Harvey Murff at the Nashville VA Medical Center and Vanderbilt University, "push beyond the traditional uses of the [electronic health record] by demonstrating that natural language processing, when applied to electronic data, can help clinicians track adverse events after surgery." Jha, a health informatics expert with VA and Boston University, adds that while the study might seem esoteric to some, "its significance should not be underestimated. Instead, these findings suggest that [electronic health records] can transform health care delivery."

A *JAMA* editorial said the study's significance 'should not be underestimated.'

On the record—Dr. Peter Letarte, chief of neurological surgery at the Hines VA Medical Center and a professor at Loyola University, reviews a patient's electronic medical record. In the background is neurosurgery resident Dr. John Braca. Every day, more than 900,000 text-based clinical documents are added to VA's nationwide electronic medical record system.

Usually, VA and other health systems rely on a set of patient safety indicators—developed by the Agency for Health Research and Quality in the early 2000s—to screen for surgery complications and other adverse events on a hospital- or system-wide basis. The indicators automatically scan billing data for diagnostic codes. They are used heavily in surveillance and quality-improvement efforts. The Centers for Medicare and Medicaid Services also use them to rank hospitals.

The new study compared the indicator method against NLP, a burgeoning branch of computer science that teaches machines to make sense of human language. The science is already at work in everyday products such as Internet search engines or translation programs.

Health care researchers have been looking at the technology with a keen eye, especially in VA. The agency's pioneering electronic medical records system stores a wealth of patient data—including free text—that can be mined, with privacy safeguards, to improve patient safety and outcomes.

VA and university investigators in Nashville and several other sites have been conducting additional studies on natural language processing, as part of an overall VA effort known as the Consortium for Healthcare Informatics Research.

The quest for biomarkers

Does genetic material in blood or sputum hold the key to early detection of lung cancer?

"The earlier we can detect the cancer, the better the prognosis," says Feng Jiang, PhD, a researcher at the Baltimore VA Medical Center and the University of Maryland.

There's little debate on that point in medical circles, but scientists have been hard-pressed to come up with safe, reliable ways to detect cancers at the very earliest stages, when treatments such as surgery or radiation can have the greatest effect and eliminate a tumor before it has spread.

Jiang and his colleagues are determined to change that, at least for lung cancer. They are working on identifying DNA, RNA, and protein biomarkers—early warning signals of cancer—that are present in specimens that can be obtained noninvasively from patients.

Current diagnostic technology falls short in several ways. CT imaging does a fair job of detecting lung cancer early on, but the scans expose patients to radiation and miss tumors that are still very small. Doctors can also insert a viewing tube down a patient's throat, fitted with tiny clippers to snip up tissue from the airways for a biopsy, but the procedure is highly invasive and uncomfortable for patients, and carries some risk of damage to the airways.

Working with pulmonary doctors in VA and the university, Jiang's team collects patients' blood and sputum samples and genetically analyzes them in the lab. Sputum, or phlegm, is a mix of saliva, mucous, and cells from the lining of the airways that is coughed up by people with respiratory trouble. The cells, when analyzed chemically for their genetic material, are a potential gold mine of information for Jiang's team. Cells from smokers' airways typically reveal some genetic damage; the challenge is homing in on patterns that show up only in cancer.

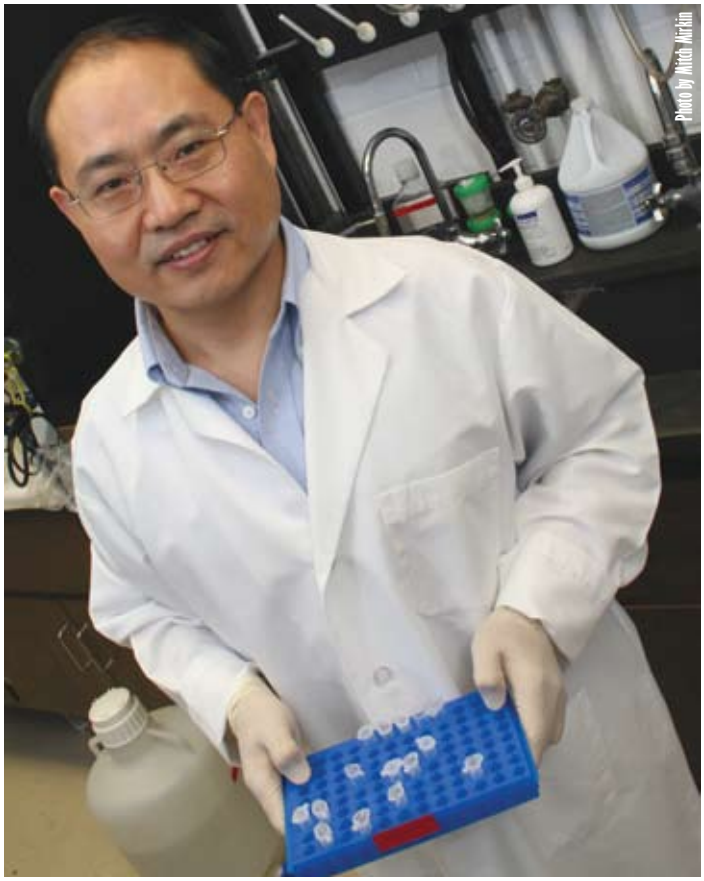
Photo by Mitch Mirkin

Finding cancer earlier—Dr. Feng Jiang, with the Baltimore VA Medical Center and the University of Maryland, is seeking ways to detect cancer sooner than through existing diagnostic methods.

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Photo by Jeff Bowen


Photo by David Sutherland/Getty Images

Coping skills—George de los Santos, who teaches Indonesian and Filipino martial arts, in addition to his career as a business consultant, says mindfulness techniques he learned at the Puget Sound VA Health Care System have enabled him to cope with the stress and anxiety of irritable bowel syndrome.

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with a variety of health conditions. De los Santos and others took part in a formal study of the program's impact on IBS. While the program didn't have a significant effect on their symptoms, it did teach them how to reduce much of the mental stress associated with IBS and boost their quality of life.

De los Santos says he now uses the MBSR techniques almost daily. "I had moderate to severe symptoms. I still have them, but they're now livable."

It might seem odd that a therapy could improve quality of life without improving symptoms. Welcome to the world of mindfulness, where attitude is everything and physical symptoms are downgraded from their usual dictatorial role.

That might sound like a New Age pitch, but MBSR, first developed by Dr. Jon Kabat-Zinn at the University of Massachusetts in the late 1970s, is highly regarded today in mainstream medicine and is used widely at clinics and hospitals, including some VA sites.

The new VA study has yielded yet more evidence of MBSR's value in patient care. The results of the research, which involved 93 Veterans, appeared in the August 2011 issue of *Alimentary Pharmacology and Therapeutics*.

"We did not find a significant change in symptoms, but quality of life related to bowel symptoms improved significantly and there was a decrease in anxiety related to bowel symptoms," says lead researcher David Kearney, MD, a VA gastroenterologist and associate professor at the University of Washington School of Medicine.

He explains that in mindfulness courses, "Veterans are taught to bring attention to thoughts, physical symptoms, and emotions with curiosity, openness, and non-judgment. They are taught to regard thoughts—for example, about having a serious underlying problem with their body—as ideas that may or may not be true."

For those practicing mindfulness, negative thoughts float away more easily and are less likely to trigger anxiety, stress, and depression. Catastrophizing and rumination decrease. Fear has less of a hold. Practitioners are more likely to "move forward into the feared activity," says Kearney, "and their new way of relating to difficult thoughts and emotions can broaden the range of activities they are willing to engage in, thus improving quality of life."

It's also quite plausible that a drop in stress could physiologically lessen IBS symptoms, although that effect was not evaluated in the VA study.

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Michael Fine, MD, MSc, received the 2011 John M. Eisenberg Award for Career Achievement in Research from the Society of General Internal Medicine. The award recognizes the career achievement of a senior SGIM member whose research has changed the way generalists care for patients, conduct research, or educate students. Fine directs VA's Center for Health Equity Research and Promotion and is a professor at the University of Pittsburgh. His research over the past quarter-century has helped change how internists and pulmonary and infectious-disease specialists manage pneumonia. Fine is also credited with helping to spearhead research on health and health care disparities.

Daniel Anaya, MD, a surgical oncologist and cancer researcher with the Michael E. DeBakey VA Medical Center in Houston, received a 2011 Career Development Award from the Conquer Cancer Foundation, a program of the American Society of Clinical Oncology. The award will support his research on using comprehensive testing to assess the baseline health of older patients with colorectal cancer, with the goal of predicting how surgery and other treatments will impact their quality of life. Anaya is also an assistant professor of surgery at Baylor College of Medicine.

Kathryn Magruder, PhD, MPH, an epidemiologist at the Charleston (S.C.) VA Medical Center, received a Fulbright scholarship to spend this academic year in Turkey as a visiting scholar. She will be studying PTSD among civilians, including displaced Iraqis and possibly Syrian refugees. In addition to conducting new research, Magruder will also give lectures and conduct seminars on her work with U.S. Veterans. With the help of Skype and other technology, she will also continue her role in current VA studies such as two long-term studies on Vietnam Veterans, and a study comparing Web-based versus in-person training for suicide prevention personnel.

Robert Henry, MD, chief of diabetes, endocrinology, and metabolism and director of the Center for Metabolic Research at the VA San Diego Healthcare System, received the 2011 Banting Medal for Service from the American Diabetes Association (ADA). A leading expert on insulin resistance, Henry has received more than 80 grants and awards for diabetes research over the past 25 years, including the ADA's Distinguished Clinical Scientist Award. His most recent studies investigate the metabolic and cardiovascular effects of newer therapies for insulin resistance and diabetes.

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De los Santos, 49, who served in the Air Force, describes one the MBSR techniques he now uses a few times a week. It's called a "body scan," and he does it lying on the floor.

"You assess your present situation in regard to whatever is ailing you. Rather than ignoring it, you acknowledge it. You pay attention to it. I may notice a pain in my abdomen and tell myself, this is nothing new. I've felt this before. It will go away. I accept the pain and move on."

If the discomfort continues to vex him, de los Santos might do a five-minute sitting meditation—another technique he learned in the MBSR course, along with certain yoga postures. In fact, he tries to do a sitting meditation every night before going to bed.

"I go through my day and spend time on things that occurred throughout the day, including the unpleasant things. Often, we as a society tend to not want to address the unpleasant events that occur. But they will creep up on you. You're trying to fight it, not acknowledge it. But it builds up inside you. With the meditation, you learn how to acknowledge, accept, and move on." De los Santos says that if he's upset with himself for eating a slice of pepperoni pizza, which he knows may aggravate his IBS, he accepts the thought and allows it to pass.

Kearney: "As an exercise in paying attention to the present moment, we ask participants to pay attention to the breath as it feels in the present moment in the body and to 'let go' of cycles of thoughts about the future or past."

For an expanded version of this article, visit www.research.va.gov/currents.

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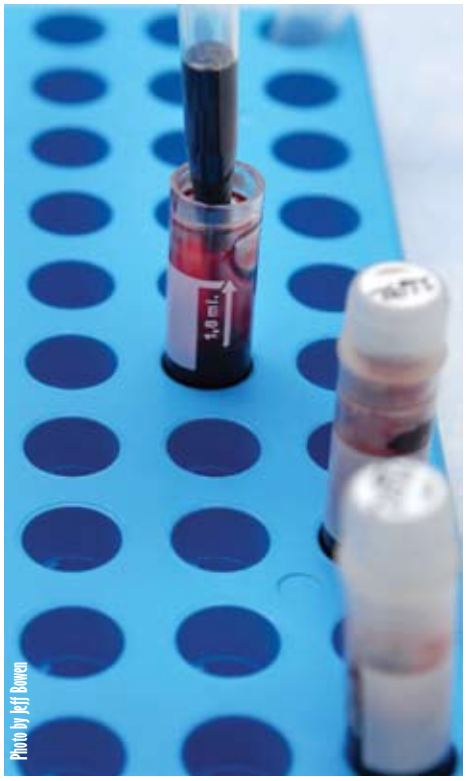
BIOMARKERS *(from page 4)*

The group focuses on non-small cell lung cancer, which accounts for about 80 percent of lung cancers and is the top cancer killer of Americans. Heavy smokers are at nearly twice the risk for the disease. Those with chronic obstructive pulmonary disease —a common lung condition in the VA patient population—can be at four to six times the risk.

Jiang envisions a comprehensive panel of biomarkers, based on blood and sputum, that would leave little doubt about the presence or absence of a tumor. Blood, like sputum, can yield genetic clues as to the presence of cancer, but the signals are less specific. "Sputum tells you the cancer cells came from the lung," he says. "With blood, the cancer cells can be from a tumor elsewhere in the body. Sputum is organ-specific, blood is not."

Methodically, in experiment after experiment, Jiang's team is compiling evidence of promising biomarkers found in both types of specimens.

In 2007, the group reported in *Clinical Cancer Research* that the absence in sputum of two tumor-suppressor genes, HYAL2 and FHIT, could signal cancer. Their fledgling genomic test identified



Chemical clues—RNA in blood could signal lung cancer early on, say researchers with VA and the University of Maryland.

three-quarters of stage 1 lung cancer patients, whereas standard cytology, which uses a microscope to look for changes in cell structure—such as the overall cell size of cells, or the ratio of the nucleus to the cytoplasm that surrounds it—identified fewer than half. In a 2009 report in *Lung Cancer,* Jiang's group showed that the combination of CT scans and genetic analysis of sputum was more accurate than CT scans alone.

More recently, in a 2010 article in *Cancer Prevention Research,* the researchers reported on six genes—the original two identified in their earlier experiments, plus four others—that together packed even greater power for early detection of lung cancer, based on sputum analysis.

And in *Laboratory Investigation* earlier this year, the group published a study involving 58 patients with stage 1 lung cancer and 29 healthy controls. Analyzing blood samples, the scientists identified a panel of microRNAs—tiny non-coding strands of RNA, the chemical cousin of DNA—that had the same altered patterns of expression in blood as in tumor tissue, and could therefore serve as reliable biomarkers.

With his latest funding from VA, Jiang will continue on a similar path and try to find additional RNA markers that can be used with the existing gene probes that have already shown value. Once a full panel of biomarkers is refined and shown effective in clinical use, Jiang believes it can "dramatically reduce mortality for Veterans with lung cancer."