



RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs



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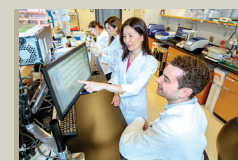
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Cover photo: Dr. Brian Schulz of VA's Office of Research and Development helps demonstrate a system that uses virtual reality in therapy for combat Veterans with PTSD. Researchers at the Providence VA Medical Center are combining the technology with brain stimulation. Their project was among those featured at VA Research Day on the Hill in June (see page 6).

The print edition of
VA Research Currents
 is published quarterly by:
VA Research Communications
U.S. Department of Veterans Affairs
 31 Hopkins Plaza, Ste. 102
 Baltimore, MD 21201
 443-759-3456
 varesearchcurrents@va.gov

Read the expanded online edition of
 VA Research Currents at www.research.va.gov

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VA



U.S. Department
of Veterans Affairs

Gene variants linked to habitual alcohol use

Researchers with the VA Connecticut and Boston health care systems found five new locations on the human genome related to habitual alcohol use. Using VA's Million Veteran Program, the researchers studied the genomes of 126,936 European American Veterans and 17,029 African American Veterans. They found habitual alcohol use—which could lead to alcohol dependence—was linked to gene variants at specific locations on the genome for both groups. One gene, ADH1B, is already known to influence alcohol dependence. Five other gene locations (the most significant of which is called CRHR1) also showed a link to increased habitual alcohol use. These five gene locations have not previously been associated with alcohol use. The results provide new insight into how genetics could underlie harmful alcohol use, say the researchers. (*Biological Psychiatry*, April 8, 2019)



Photo by Mitch Mirkin



Lipid testing boosts statin adherence

Routine lipid testing can lead to Veterans taking their statin medication more regularly, found a study by Michael E. DeBakey VA Medical Center researchers. The study looked at data on patients receiving care through VA for atherosclerotic cardiovascular disease. Researchers looked at medication refill data to see whether patients were taking prescribed statins. Patients with at least one lipid panel over a one-year period had a 66% chance of adhering to their medication, while those without a lipid panel had a 61% chance. Among new statin users, 68% adhered to their medication when they had a lipid panel within 4–12 weeks of beginning treatment. For those without a lipid panel, adherence was 59%. While the difference

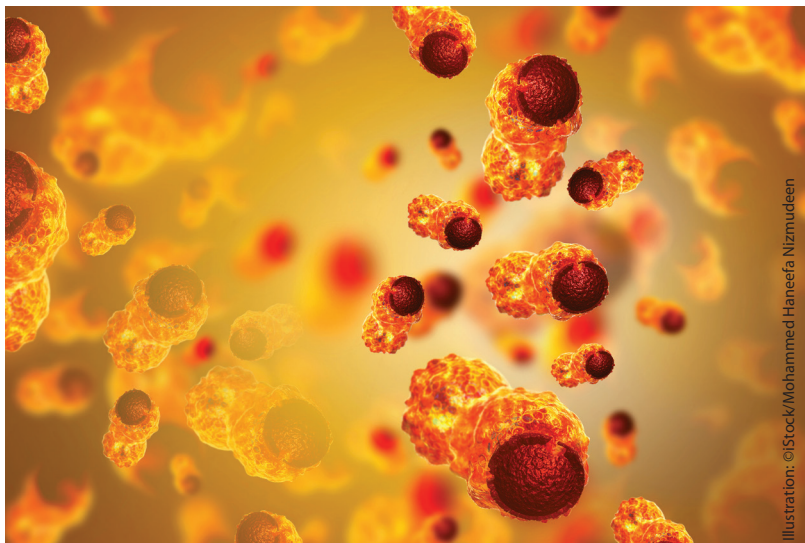
is modest, routine statin testing can significantly increase patient's statin adherence, according to the researchers. (*American Journal of Medicine*, May 16, 2019)



Study: Almost all VA patients would benefit from gene tests to guide drug choice

Almost all Veterans would benefit from genetic testing to see how they would react to various medications, according to a study of data from nearly 8 million Veterans. Specific gene variants affect how people respond to different drugs. The researchers looked at pharmacy and demographic data on 7.7 million Veterans who used VA pharmacies over a six-year period. They projected, based on the Veterans' demographics, that 99% would have at least one gene variant that could affect their response to commonly used drugs. Common prescriptions in VA that could be affected by

gene variation included simvastatin (sold as Zocor) for high cholesterol, tramadol (sold as Ultram) for pain, and warfarin (sold as Coumadin) for high blood pressure. Genetic testing could influence prescribing decisions for many Veterans, concluded the researchers. (*JAMA Network Open*, June 5, 2019)



New insight into how cancer spreads

An international study led by a researcher at the VA San Diego Healthcare System yielded new insight into how cancer spreads. The study focused on a protein known as Caveolin-1, or Cav-1, which scientists have found plays a role in cancer cell migration from a primary tumor into other areas of the body. The new study tested whether a particular part of this protein, called the caveolin scaffolding domain, or CSD, is critical in this process. The team engineered cancer cell lines into three categories. One over-expressed the entire Cav-1 protein. The second over-expressed the protein but without

a working CSD. The third over-expressed green fluorescent protein, as a control. The researchers found that cancer cell migration was inhibited in the first group of cells, but increased in the second group, the cells without the CSD. The finding supports their theory that Cav-1 thwarts cell migration through its CSD. They write, “Modulating the CSD and targeting specific proteins may offer potential new therapies in the treatment of cancer metastasis.” Besides VA and a few other U.S. institutions, the work involved collaborators in Japan, Scotland, and Pakistan. (*Cell Cycle*, online May 22, 2019)



Overuse of antibiotics in dental care

A study led by investigators at VA’s Center of Innovation for Complex Chronic Healthcare found that the great majority of preventive antibiotic prescriptions written by dentists in the U.S. are not in accord with clinical guidelines, and are unnecessary. The team analyzed more than 168,000 dental visits involving more than 91,000 U.S. patients using commercial dental health plans. Per current guidelines, only patients with cardiac conditions who are at high risk for endocarditis, in which germs from other parts of the body, such as the mouth, spread to the heart, should receive prophylactic antibiotic treatment

before invasive dental procedures. The study found that dentists, on the whole, operated well outside the guideline, and that 8 in 10 preventive antibiotic prescriptions were unnecessary. The researchers called the finding “worrisome,” in light of the ongoing crisis stemming from antibiotic overuse and the proliferation of drug-resistant bacteria. Though their data were from 2011–2015, and they note the situation has been “slowly improving,” they still called for better antibiotic stewardship in dentistry. (*JAMA Network Open*, May 3, 2019)



Photo: ©iStock/JTSorrell

Pinpointing genetic targets for meth addiction

Researchers at the Portland VA Medical Center and Oregon Health & Science University are working to understand genetic risk for methamphetamine addiction. In a recent experiment, they used mice that were genetically bred to crave methamphetamine. The researchers first identified two proteins that appear at higher-than-normal levels in the brains of those animals. One is a receptor for glutamate, the most abundant neurotransmitter in the brain, and is known as mGluR5. The other is a scaffolding protein known as Homer2a/b. There are no known drugs that target the latter protein, but there are several

that target mGluR5. The next step was to test drugs known to bind to mGluR5 and make it less active. Those drugs, however, appeared to have little effect on the mice's meth appetite. The researchers concluded that targeting mGluR5 may not be an adequate strategy, and that scientists will need to better understand the role of Homer2a/b in addiction. (*International Behavioural and Neural Genetics Society meeting*, May 2019)

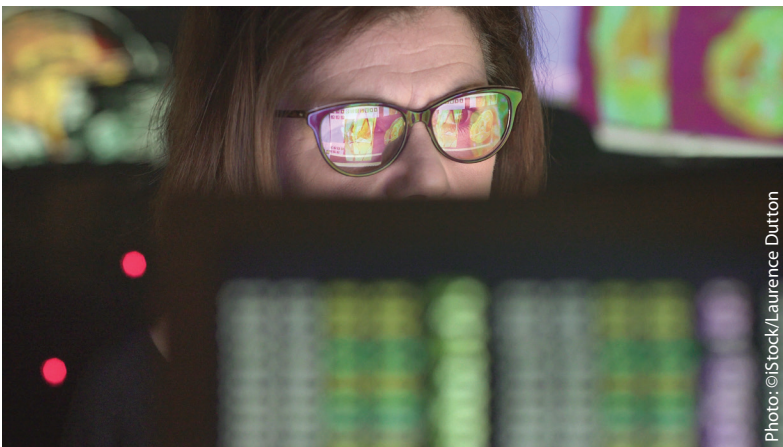


Photo: ©iStock/Laurence Dutton

Algorithm for identifying PTSD in electronic health records

Researchers with VA's Million Veteran Program have designed a computer algorithm to identify PTSD in electronic health records. Although PTSD may be noted in a patient's electronic health record, researchers would need to read individual records to pick out patients with the condition for studies. The algorithm searches records for diagnoses and symptoms to classify patients as likely PTSD, possible PTSD, and likely not PTSD. The algorithm had high

accuracy when compared with manual chart review. The algorithm could be useful for research and quality improvement endeavors within VA, say the researchers. A quick way to identify thousands of cases using electronic health records would help recruiting for large genome-wide association studies of PTSD. (*Journal of Traumatic Stress*, April 2019)



Dr. Brian Schulz of VA's Office of Research and Development (seated) helps demonstrate a system that uses virtual reality to deliver therapy for combat Veterans with PTSD.

VA Research Day on the Hill

VA scientists displayed some of their latest advances at an exhibit in the nation's capital.

Nearly 25 leading VA researchers, some accompanied by Veteran study participants, showcased their latest scientific, medical, and technological advances in Washington, D.C., as part of the second annual “VA Research Day on the Hill” in June 2019.

The advances were on display in the Rayburn House Office Building on Capitol Hill. They focused on topics that are critical to Veterans, including suicide prevention, spinal cord injury, PTSD, prosthetics, pain and opioid research, cardio-pulmonary issues, and female Veterans’ research.

Among the projects and products on display were a comprehensive tele-eye screening program that provides better eye care access for Veterans; a suicide prevention door that improves the lives of Veterans while they are in a VA facility; a form of brain stimulation intended to improve the condition of Veterans with chronic pain and persistent headaches; a 3D technology platform that allows identification of FDA-approved drugs to kill cancer stem cells; and artificial lungs that mimic the circulation of a natural lung.

Congressional staff members and representatives from Veterans’ organizations were on hand to view the display of VA

Photo by Alvin Williams



ingenuity.

Addressing the crowd of nearly 100 people, VA Chief Research and Development Officer Dr. Rachel Ramoni thanked all of the researchers for attending and “making discoveries that improve Veterans’ lives.” She also singled out VA’s top clinical priorities: suicide prevention, PTSD, Gulf War illness, pain management-opioid use, and traumatic brain injury (TBI).

“VA research has been around for almost 95 years,” she said. “From the very beginning, it was meant that our mission should be different, that we should focus on practical outcomes. VA has had a proud tradition of producing innovative and impactful research findings that improve the health of Veterans and the nation. Such efforts would not be possible without the support of VA research, the research scientists and Veteran participants who willingly serve to create innovation and discovery, and ultimately advance health care for our Veterans.”

Dr. Carolyn Clancy, VA’s deputy undersecretary for Discovery, Education, and Affiliate Networks, emphasized that Veterans are the “heart and soul” of the work at VA.

“I can’t overstate the importance of research to the health and well-being of Veterans and other people,” Clancy said. “Just in the last 25 years, we have seen survival rates for many types of cancer increase, better and more varied treatment approaches for PTSD, and greater use of genetic information to tailor drug

regimens to individual patients. I want to express my sincere gratitude for the unwavering support, generosity, and fellowship that we have enjoyed in our mission to improve the lives of Veterans and many others. I look forward to our continued collaboration to make sure that cutting-edge research and cutting-edge care start at VA for the Veterans we serve.”

One of the researchers at the event, Dr. April Maa of the Atlanta VA Health Care System, displayed the tele-eye screening program. It provides better eye care access for Veterans, some of whom are at high risk for potentially blinding diseases.

“I feel honored to be here,” Maa said. “I like to be able to show the good side of VA and highlight all of the research that VA does. This is a great opportunity for me to showcase translational research, which is taking something from science and applying it to the real world.”

Dr. Hardeep Singh of the Michael E. DeBakey VA Medical Center in Texas also attended the event. He displayed a project that involves a collaborative approach to develop and evaluate multifaceted “sociotechnical” tools and strategies to help reduce missed test results in VA. Failure to follow-up on patients’ abnormal test results is a key preventable factor in diagnosis and treatment delays in VA.

“I love this,” Singh said. “It’s a chance to showcase how our research can have an impact on clinical practice, patient care, and policy. We also get exposure to

Photo by Alvin Williams



Photo by Robert Williams



a crowd like this where you can influence someone to make decisions that will eventually improve patient safety.”

Four Veterans who have benefited from the innovations accompanied researchers to the event, including Navy Veteran Abriant Quintana. He suffered a TBI while serving in Afghanistan and is participating in research with Dr. Albert Leung of the VA San Diego Healthcare System. Leung is experimenting with a form of brain stimulation, repetitive transcranial magnetic stimulation (rTMS), as a treatment for Veterans with chronic pain and TBI-related symptoms.

Quintana explained that after the TBI, he took opioids to help ease his symptoms, which included

Photo by Robert Williams



headaches, mood swings, irritability, and weight gain. He built a tolerance for the opioids and increased his consumption, saying they “exacerbated” his symptoms and even led to suicidal thoughts.

But his symptoms have eased in the two years he’s been receiving rTMS, he noted, adding that he’s no longer on opioids.

“My whole outlook on life has changed,” he said. “I went back to college and earned a bachelor’s degree at the University of Redlands. I want to go to law school. I’m learning the piano. I’ve had no negative side effects from the brain stimulation.”

VA’s Office of Research and Development organized the event, which was hosted by Friends of VA Medical Care and Health Research, which helps Veterans receive high-quality health care.

Supporters of the event included the National Association of Veterans’ Research and Education Foundations, which promotes research partnerships to improve Veterans’ health, and Research! America, which advocates for science, innovation, and discovery with the goal of achieving better health for all. ★

Study: Video games can help Veterans recover from mental health challenges

A recent study with a small sample of Veterans trying to recover from mental health issues found that video games can help in overcoming such problems as PTSD and substance abuse disorders.

The researchers concluded that although the impact of video games may vary based on the user, clinicians may wish to discuss video game play with their patients to help them “optimize their use of games to support recovery.”

"Gameplay may promote a mindfulness-like psychological [escape] but can also provide users with benefits of confidence, social connection, personal growth, and opportunities for employment or even leadership," the researchers write. "These benefits are accessible to people with disabilities for whom traditional treatments, leisure activities, or social interactions may be challenged by circumstances or limitations. Games could be implemented in large populations very inexpensively, thus acting as potentially very cost-effective recovery supports or mental health treatments."

Some of the participants, the researchers also note, described using video games to “distract from overwhelming symptoms, including suicidal thoughts and drug or alcohol use.”

The study included 20 Veterans—15 men and five women—who ranged in age from 25 to 62. Sixteen of the 20 Vets reported they had PTSD or trauma-related symptoms. Most of the participants said they had more than one current mental or behavioral health diagnosis, with PTSD and depression being the most common combination. Three people had more than one type of trauma, such as combat- or training-



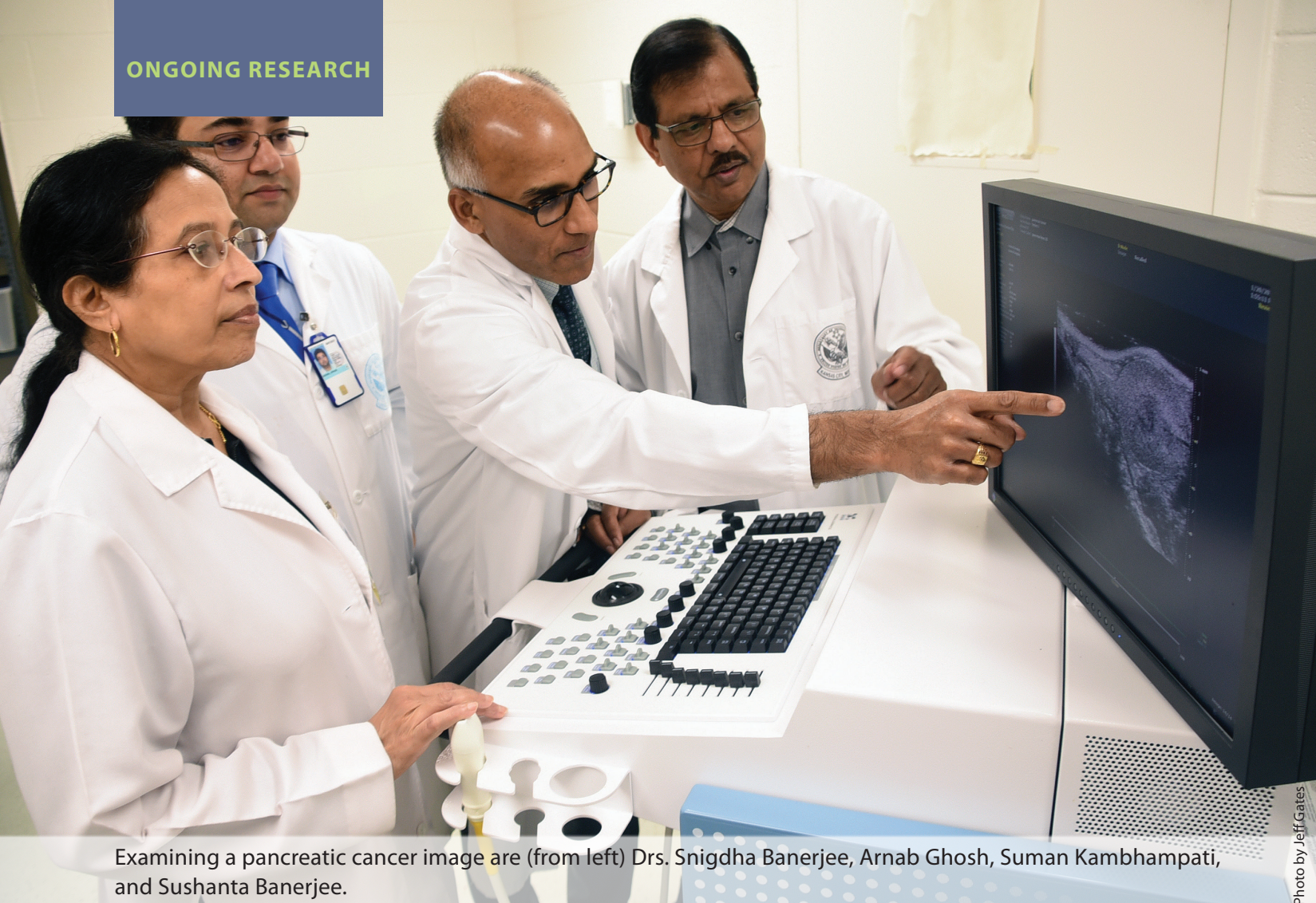
A study with a small sample of Veterans found that video games can help in overcoming such problems as PTSD and substance abuse disorders.

related trauma, military sexual trauma, or childhood sexual abuse.

Dr. Michelle Colder Carras, a public health researcher, led the study, which appeared in November 2018 in the journal *Social Science & Medicine*. With extensive research experience in video game play and in mental health recovery, she interviewed the Veterans on the value of the games. (She's also played video games and has recovered from her own mental health problem.)

In the study, the video game genres included sports, puzzles, gambling, role-player action, fantasy settings, and shooter games. But Colder Carras emphasizes that the genre or specific game isn't what necessarily helped with recovery. The benefits, she says, stemmed more from the connections the Veterans made with other video game players; the distractions they created for themselves by playing the games and removing their focus, for example, from alcohol or drugs; and the meaning they derived from the games.

Read more at www.research.va.gov/currents ★



Examining a pancreatic cancer image are (from left) Drs. Snigdha Banerjee, Arnab Ghosh, Suman Kambhampati, and Sushanta Banerjee.

Photo by Jeff Gates

Kansas City VA lab aims to improve prognosis for pancreatic cancer

A team at the Kansas City VA is working to boost the effectiveness of a drug seen as the best hope for patients with pancreatic cancer. They are also developing a nanomedicine approach for drug delivery they hope will help boost survival rates.

Pancreatic cancer is among the most devastating diagnoses anyone can receive. Only 20% of patients make it past a year, and only 9% can expect to live beyond five years. Those rates are up from a few years ago, in part due to more awareness and better screening, and wider use of aggressive combination therapies. But researchers still have a long road ahead.

The best drug currently available to treat the disease, gemcitabine, offers some benefit, but most pancreatic tumors become resistant to it early on. The drug quickly loses its punch against cancer cells.

That's where Drs. Sushanta and Snigdha Banerjee, a husband and wife team, see an opportunity. Their lab in the Cancer Research Unit at the Kansas City (Missouri) VA Medical Center is intent on figuring out how to make gemcitabine potent over months, instead of just weeks. The group is also partnering with chemical engineers to learn how to deliver another tumor-squashing drug, zoledronic acid, directly to cancer cells via a nanoparticle. That way, it pummels those cells without hurting other tissues.

Both approaches, and especially the latter one, offer hope for the future, says Dr. Suman Kambhampati, an oncologist at the Kansas City VA who has collaborated with the Banerjees on several papers. While he doesn't treat a lot of Veterans with pancreatic cancer—he says his VA hospital, on average, will see 5 to 10 cases a year, which is a small number compared with lung or colon cancer—they account for some of his most trying work as a doctor.

“It's one of the most dreaded diagnoses that we can give to a patient and their family, just given the nature of this cancer and its natural history,” says Kambhampati, who has been a doctor with VA since 1996.

To lay the groundwork for a clinical breakthrough, the Banerjee group has identified key molecular culprits in pancreatic cancer. The gang leader is a protein called CYR61.

Blocking protein may boost effect of drug

Importantly, the protein appears to drive three biochemical processes that make pancreatic cancer tough to treat—and that thwart gemcitabine, in particular.

Sushanta says the main question for the lab has been, “If we block CYR61, can we block all three [processes]?”

One process has to do with cancer stem cells. There is a subset of these cells, mesenchymal cells, whose population explodes early on in pancreatic cancer—thanks in part to CYR61. This pushes the tumor to grow and spread.

The second has to do with how gemcitabine gets activated in the body. Certain enzyme reactions have to take place, or the drug remains inert. “We found that CYR61 plays a vital role in blocking gemcitabine activation,” he says. “[When activation is blocked], you can give a high dose of the drug but it doesn't work, because it's mostly in an inactive form.”

The third has to do with the physical nature of

pancreatic tumors. These masses of cancer cells form a thick fibrous shell, like scar tissue, that acts like a coat of armor to stop drugs from penetrating. The process is known as desmoplasia. “CYR61 promotes this biological barrier,” says Sushanta.

Experiments in their lab, say the Banerjees, have shown clearly that CYR61 is a key player in all three of these pancreatic-cancer hallmarks.

Two mutations trigger pancreatic cancer in genetically engineered mice

The team uses genetically engineered mice that carry two mutations, in genes known as KRAS and p53. KRAS and p53 mutations are common to several cancers, but the specific changes engineered in these rodents lead to pancreatic cancer. The mice develop the disease within three months of birth. Given the rapid lifespan of the mouse, that is the equivalent of a human in his mid-20s.

Most pancreatic cancer patients have these same mutations. Rather than being inherited from parents, they are *acquired* mutations triggered by ongoing inflammation in the pancreas. The inflammation could result from lifestyle factors like tobacco and alcohol use, and from conditions such as obesity and diabetes. Certain other toxic exposures—such as from farm chemicals—may play a role as well, suggests some research.

“These [mutations] are the results of chronic inflammation within the cellular milieu of the pancreas,” says Kambhampati.

Knocking down the levels of CYR61, in theory, could make pancreatic tumors far more vulnerable to gemcitabine. Since CYR61 is absent in the normal pancreas, and appears only when the KRAS and p53 mutations work together to exert their sinister effect, the Banerjees are not worried about possible side effects from totally suppressing the protein. They point out it serves no healthy purpose in the body.

How exactly to shut down CYR61 remains to be

"It's one of the most dreaded diagnoses that we can give to a patient and their family, just given the nature of this cancer and its natural history."

Continued on next page

worked out in further experiments. The researchers have to figure out which signaling pathway to disrupt, and with which molecule. In any event, human trials of such an approach are at least a few years off.

Delivering cancer drug in a nanoparticle

Meanwhile, Snigdha is partnering with a team 600 miles away at North Dakota State University that has expertise in nanotechnology. This effort revolves around another drug, zoledronic acid, that mainly boosts bone health—including in cancer patients with bone-related side effects from chemotherapy.

As it turns out, zoledronic acid dials down the expression of CYR61—the pesky protein that promotes pancreatic cancer. The problem is getting the drug into the tumor, or even anywhere near the pancreas.

“Unfortunately, this drug cannot reach the pancreas, because the bones absorb up to 90% of it immediately,” explains Sushanta. “It has high bone absorption.”

Enter the nanoparticle being developed by the Kansas City team and their collaborators to the north. It’s a tiny chemical package that carries zoledronic acid inside, along with a peptide—a chain of amino acids—called iRGD, which has a strong affinity for cancer cells and acts as a homing molecule.

The combination is wrapped in a polymer that opens only under certain conditions—namely, an environment that is very low PH, or very acidic, and hypoxic, meaning there is very little oxygen. Because of desmoplasia, the buildup of scar tissue, that’s precisely what it’s like inside a pancreatic tumor.

“We inject this nanoparticle into mice and it enters only into the tumor cells,” says Sushanta.

“Then it opens up and releases the drug. It will not go anywhere else in the body, only into cancer cells, and it will open only in a hypoxic condition.”

“We found that bone absorption is zero,” he notes.

From a clinical perspective, Kambhampati, the oncologist, says that “zoledronic acid is very relevant because it’s already being used in pancreatic cancer patients, although mostly to address the bone symptoms and high calcium levels.” In other words, doctors already have a good idea of the drug’s overall safety and tolerability in those with cancer.

He likes that the nano approach addresses “the key challenge that remains in pancreatic cancer—tumor impermeability.”

Asked whether he thinks the nanoparticle method using zoledronic acid will be an option for patients in a few years, he says, “It’s very promising.” ★

For an overview of the latest VA research on high-priority topics affecting Veterans’ health, visit www.research.va.gov/topics/default.cfm.

It's more than POSTTRAUMATIC STRESS DISORDER (PTSD)
In earlier years, it was called "soldier's heart," "shell shock," or "combat fatigue." Today, clinicians recognize the issues described by each of these terms as a distinct medical condition called posttraumatic stress disorder, or PTSD.

ABOUT PTSD
-PTSD can occur after a traumatic event like combat, sexual assault, or disaster. While it can be distressing, it's not a sign of weakness or a sign of mental illness. PTSD is a common disorder that affects millions of men and women who have served in the military.

RESEARCH ON PTSD:
-VA has a continuing commitment to fund research on PTSD. In 2011, VA and the Department of Defense (DoD) announced that the two agencies would together invest more than \$100 million to fund PTSD research.

RESEARCH ON TRAUMATIC BRAIN INJURY
VA research related to TBI is wide-ranging. Among the goals of VA researchers working in this field are to shed light on brain changes in TBI, improve diagnostic methods, and refine tools for diagnosing the condition, and develop ways to treat brain injury or limit its severity when it first occurs.

ABOUT TRAUMATIC BRAIN INJURY
-The CDC defines a TBI as "disturbance of the normal function of the brain that can be caused by a bump, blow or jolt to the head, or penetrating head injury."

RESEARCH ON TBI:
-The CDC estimates that 2.2 percent of all combat casualties from Iraq and Afghanistan are brain injuries. TBI is a significant cause of disability among military service members and veterans.

RESEARCH ON TBI:
-VA has a continuing commitment to fund research on TBI. In 2011, VA and the Department of Defense (DoD) announced that the two agencies would together invest more than \$100 million to fund TBI research.

RESEARCH ON MULTIPLE SCLEROSIS
Multiple sclerosis is a complex neurological disease that affects the central nervous system, including the brain, spinal cord, and vision pathways.

ABOUT MULTIPLE SCLEROSIS
-In MS, the immune system attacks the myelin sheath, the fatty tissue that surrounds and protects nerve fibers, as well as the nerve fibers themselves. Damage from these attacks is called demyelination. When any part of the myelin sheath or nerve fiber is damaged or disrupted, nerve impulses traveling to and from the brain and spinal cord are disrupted and interrupted, causing a wide variety of symptoms.

RESEARCH ON MULTIPLE SCLEROSIS:
-VA has also established a national research center at the University of California, San Francisco, to study the underlying biology of MS. The center is focused on understanding the genetic, immunological, and environmental factors that contribute to the development of MS.

Study: Patients with diabetes do as well with physician assistants, nurse practitioners as with physicians

VA patients with diabetes have similar health outcomes regardless of whether their primary provider is a physician, nurse practitioner (NP), or physician assistant (PA), according to a Durham VA Health Care System study.

The results appeared in the June 2019 edition of the *Journal of the American Academy of Physician Assistants*.

“Our study found that there were not clinically important differences in intermediate diabetes outcomes for patients with physicians, NPs, or PAs in both the usual and supplemental provider roles, providing additional evidence for the role of NPs and PAs as primary care providers,” said Dr. George Jackson, senior author on the paper. Jackson is a research health scientist with the Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT) at the Durham VA Medical Center in North Carolina. He is also an associate professor at Duke University.

More demand for primary care providers

Demand for primary care services is growing rapidly. This growth is due mainly to an aging population, who have an increasing number of chronic illnesses. The number of Americans older than 65 is expected to double by 2050, bringing with it increased health care needs. More chronic illnesses means increased complexity of the care needed, making it harder for a single clinician to provide all required care.

In response to this demand, health care systems are exploring new models of care delivery. One approach to address this demand is using teams of multiple clinicians to meet patients’ needs. Several years ago, VA instituted Patient Aligned Care Teams



Within VA, about one-third of primary care visits are with physician assistants or nurse practitioners.

(PACTs) as the model for patient care. PACTs involve a team of care providers working together with Veterans to focus on wellness and disease prevention in addition to treatment.

Each PACT is led by either a physician, nurse practitioner (NP), or physician assistant (PA), and any one of those disciplines can also serve as a supplemental provider, supporting the main provider in the PACT. Within VA, about one-third of primary care visits are with PAs or NPs, rather than with physicians. While care teams led by PAs or NPs are becoming more and more common, questions remain about whether patients do as well with non-physicians leading their care.

While the researchers acknowledge that some patients may still prefer that their care be overseen by a physician, other studies have shown that patients are generally satisfied with care from NPs or PAs. VA has been guided in part by such past findings in expanding the use of PAs and NPs as team leaders. The fact that PAs and NPs had similar results for quality of care without sharing care with a physician suggests that using these providers in primary care may improve the efficiency of health care service, say the researchers.

Read more at www.research.va.gov/currents ★

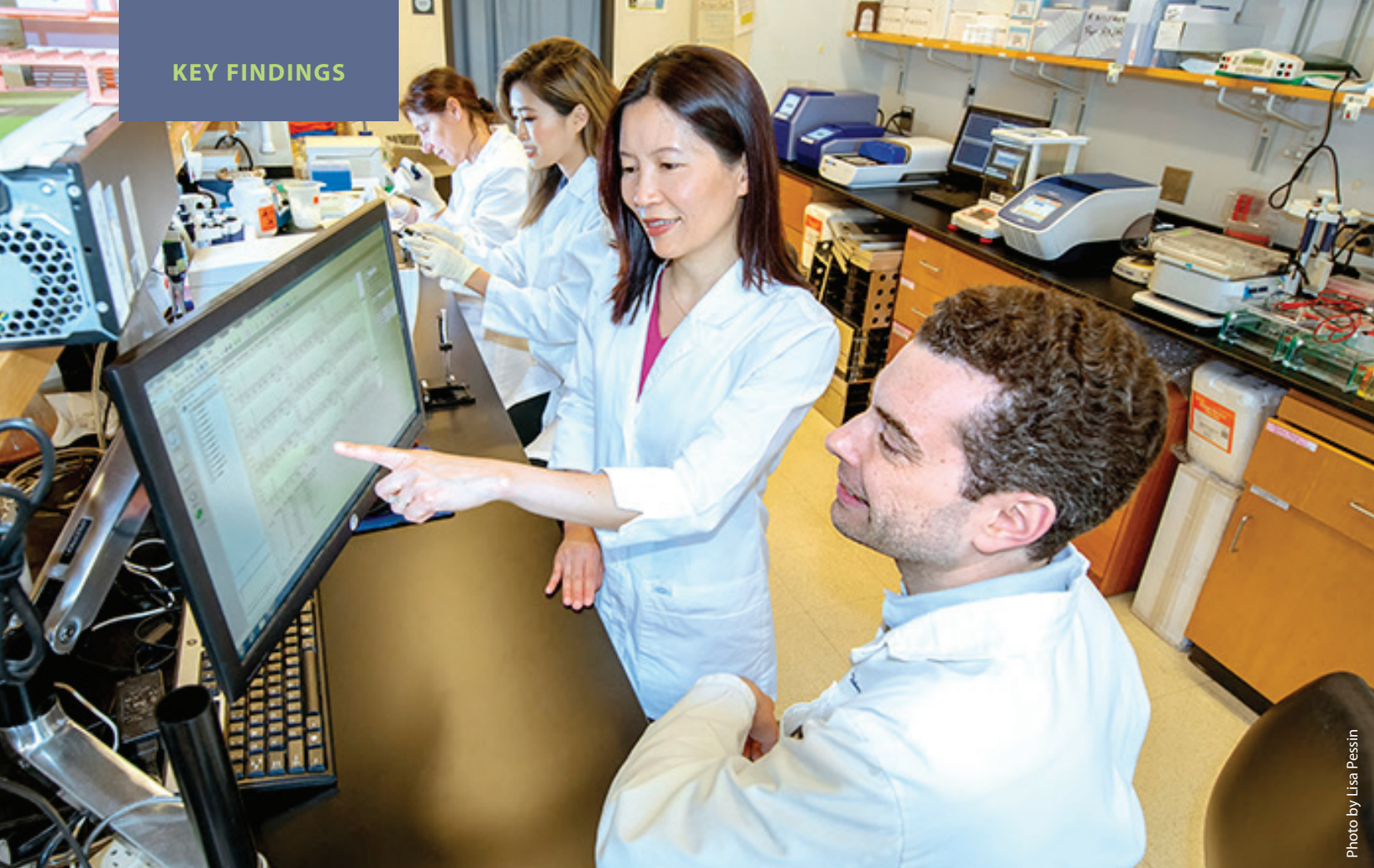


Photo by Lisa Pessin

Dr. Thomas Wingo and Dr. Aliza Wingo (foreground) lead a lab at the Atlanta VA and Emory University dedicated to understanding the genetic basis of Alzheimer's disease and psychological well-being and resilience.

High LDL linked to early-onset Alzheimer's

Researchers at the Atlanta VA found a link between high LDL cholesterol and early-onset Alzheimer's disease. The results could help doctors understand how the disease develops and what the possible causes are, including genetic variation.

Researchers with the Atlanta VA Medical Center and Emory University have found a link between high LDL cholesterol levels and early-onset Alzheimer's disease. The results could help doctors understand how the disease develops and what the possible causes are, including genetic variation.

According to Dr. Thomas Wingo, lead author of the study, the results show that LDL cholesterol levels may play a causal role in the development of Alzheimer's disease.

The results appeared in the May 28, 2019, issue of *JAMA Neurology*.

"The big question is whether there is a causal link between cholesterol levels in the blood and Alzheimer's disease risk," says Wingo. "The existing data have been murky on this point. One interpretation of our current data is that LDL cholesterol does play a causal role. If that is the case, we might need to revise targets for LDC cholesterol to help reduce Alzheimer's risk. Our work now is focused on testing whether there is a causal link."

Wingo is a neurologist and researcher with the Atlanta VA and Emory University.

Elevated cholesterol levels have been linked to increased risk of Alzheimer's later in life. This risk may be due to genetic factors tied to cholesterol. Past research has shown that a major risk factor for Alzheimer's disease is a specific mutation in a gene referred to as APOE. It is the largest known single genetic risk factor for Alzheimer's disease. This APOE variant, called APOE E4, is known to raise levels of circulating cholesterol, particularly low-density lipoprotein (LDL). This type of cholesterol is sometimes referred to as "bad cholesterol" because high LDL levels can lead to a build-up of cholesterol in the arteries. While late-onset Alzheimer's—the common form of the disease—appears to be linked to cholesterol, little research has been done on a possible connection between cholesterol levels and early-onset Alzheimer's risk.

Study involved samples from more than 2,000 people

Early-onset Alzheimer's is a relatively rare form of the condition. The disease is considered "early-onset" when it appears before age 65. About 10% of all Alzheimer's cases are early-onset. Past research has shown that the condition is largely genetics-based, meaning it is likely to be inherited if a parent has it. Three specific gene variants (dubbed APP, PSEN1, and PSEN2) are known to be related to early-onset Alzheimer's disease. APOE E4 is also a risk factor in this form of the disease, as well. These gene variants explain about 10% of early-onset Alzheimer's disease cases, meaning that 90% of cases are unexplained.

To test whether early-onset Alzheimer's disease is linked to cholesterol and identify whether genetic variants underly this possible association, the researchers sequenced specific genomic regions of 2,125 people, 654 of whom had early-onset Alzheimer's and 1,471 of whom were controls. They also tested blood samples of 267 participants to measure the amount of LDL cholesterol.

"The big question is whether there is a causal link between cholesterol levels in the blood and Alzheimer's disease risk."

They found that APOE E4 explained about 10% of early-onset Alzheimer's, which is similar to estimates in late-onset Alzheimer's disease. The researchers also tested for APP, PSEN1, and PSEN2. About 3% of early-onset Alzheimer's cases had at least one of

these known early-onset Alzheimer's risk factors. After testing blood samples, the researchers found that participants with elevated LDL levels were more likely to have early-onset Alzheimer's disease, compared with

patients with lower cholesterol levels. This was true even after the researchers controlled for cases with the APOE mutation, meaning cholesterol could be an independent risk factor for the disease, regardless of whether the problematic APOE gene variant is present. The researchers did not find a link between HDL (high-density lipoprotein) cholesterol levels and early-onset Alzheimer's, and only a very slight association between the disease and triglyceride levels.

The researchers also found a new possible genetic risk factor for early-onset Alzheimer's disease. Early-onset Alzheimer's cases were higher in participants with a rare variant of a gene called APOB. This gene encodes a protein that is involved in the metabolism of lipids, or fats, including cholesterol. The finding suggests a direct link between the rare APOB mutation and Alzheimer's disease risk, according to the researchers. However, the link between LDL-C level and

early-onset Alzheimer's was not fully explained by APOE or APOB, suggesting that other genes and mechanisms also increase disease risk.

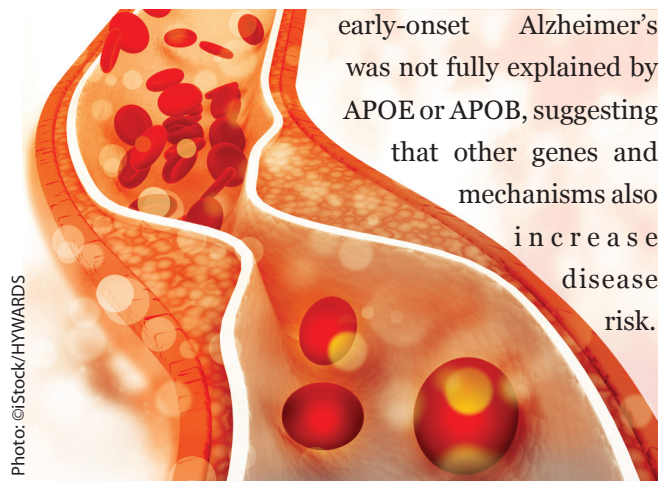


Photo: ©iStock/HYWARDS



Clarence Massey (left) received treatment for his prostate cancer at the Brooklyn campus of the VA NY Harbor Healthcare System. He is seen here with radiation therapist Nader Girgis, who was part of his treatment team.

VA and partners hope APOLLO program will be leap forward for precision oncology

VA and two federal partners want to harness advances in genomic and proteomic medicine to tailor cancer treatment for individual Veterans and service members. The effort is named APOLLO, after the space mission that landed men on the moon.

As an Air Force mechanic in the 1960s, Clarence Massey worked on bombers and fighter jets in Vietnam. More than four decades later, in 2010, he became immersed in another battle. The resident of New York City's historic Harlem neighborhood underwent nine weeks of radiation therapy for prostate cancer.

The treatment itself wasn't too bad, he recalls, but the side effects hit him "like a ton of bricks," says Massey, now 72.

Massey's outcome was a good one. He gives credit to his VA doctors, but, he says, "Mostly I give credit to God. I'm blessed."

In the years since Massey's bout with cancer, biomedicine has come a long way—especially when it comes to analyzing genes and proteins. VA and two federal partners—the Department of Defense and the National Cancer Institute—are looking to harness the power of this science through an effort dubbed APOLLO, in the spirit of the famous space mission

that landed men on the moon. The research program is described in a recent article in the journal *Clinical Pharmacology & Therapeutics*.

The tri-agency project launched in 2016 under the federal Cancer Moonshot, a broader effort likewise inspired by the space theme.

'Each patient is unique, each tumor is unique'

The full title of APOLLO sounds complex: Applied Proteogenomics Organizational Learning and Outcomes. But the overarching goal is simple: individualize cancer treatment. That's what "precision oncology" is all about. It's part of the personalized medicine movement. In cancer, the stakes are perhaps higher than with most other diseases.

The thinking is that lives will be saved—and plenty of nasty side effects spared—if doctors can target and kill tumors like smart bombs destroy enemy bunkers, using very specific information about the patients themselves, and about the cancers growing within them.

"Each patient is unique, and each tumor is unique," explains Dr. Craig Shriver, one of the architects of APOLLO. He directs the Murtha Cancer Center Research Program in the department of surgery at the Uniformed Services University of the Health Sciences, in Bethesda, Maryland.

APOLLO, he says, is a research project aimed at collecting and analyzing a wide array of data from cancer patients, analyzing it all with the help of sophisticated technology and scientists worldwide, and ultimately using the findings to determine the best precision treatment for a given patient. Importantly, the input will also include long-term outcomes of patients, and their responses to surveys as they progress through care.

The main beneficiaries in the short term will be Veterans and active duty troops, as cancer care at VA and military hospitals increasingly incorporates knowledge gained through APOLLO. But the knowledge will eventually filter into medical care at large, so cancer patients everywhere can see better treatment.

Data-sharing resources developed by the National Cancer Institute or its partners will play a key role in that phase. These include the Genomic Data Commons, the Proteomic Data Commons, and The Cancer Imaging Archive.



Photo: ©iStock/HYWARDS

APOLLO is starting operations at 10 military hospitals and one VA site (Palo Alto), with additional VA sites likely to be on board by late 2019. There is also one civilian hospital involved, Anne Arundel Medical Center in Maryland. Cancer patients at these facilities can agree to have their information—including molecular results from their tumors—added to the growing APOLLO research database. All information is coded, so patients are not personally identifiable to researchers. The enrollment target is 8,000 patients over five years.

Effort complemented by VA's Precision Oncology Program

The effort will work hand in hand with VA's Precision Oncology Program. Through POP, increasing numbers of VA patients with cancer are having their tumors genetically analyzed, so their physicians can prescribe more targeted therapies, or so they can be referred to appropriate clinical trials.

POP has its own research arm, called RePOP, supported by the Cooperative Studies Program within the VA Office of Research and Development, and run through the Boston CSP Center.

If there's an explosion right now in precision oncology research, it's inspired in part by the real-world advances that have already taken place. Genetics has a firm foothold in routine cancer care. For instance, a cancer drug called irinotecan is given in lower doses to patients with colorectal cancer who test positive for

a certain gene variant. Their bodies make less of an enzyme that metabolizes the drug. One recent boost to the field came last year when the Centers for Medicare & Medicaid Services approved coverage of a new type of genomic testing for patients with advanced cancer, so they could be matched with targeted therapies based on their genes.

But the ambitious APOLLO project will go far beyond genes. For starters, there are proteins to consider. Hence the “proteogenomics” part of APOLLO’s name.

Shriver, a cancer surgeon and researcher who is also a retired colonel from the Army Medical Corps and decorated combat Veteran, uses a military analogy to explain the link between genes and proteins, and what it means in cancer.

Protein malfunctions as the culprits in cancer

“If you go back to basic high school biology,” says Shriver, “there are three molecular components of life: DNA, RNA, and protein. DNA is the instruction manual. The proteins are the action officers, the troops. They’re out there in the cell doing all the work. And they may or may not listen to the boss [the DNA, or genes].”

“Then you have the RNA—they’re the messengers, the troops sending the message from the DNA to the proteins. But again, the proteins don’t have to listen.”

In other words, cancer involves not only mutations—or abnormal changes—at the gene level, but foul-ups by proteins.

If you imagine genetic analysis being complicated, try adding proteins into the picture. It’s like going from arithmetic to calculus.

There are some 25,000 genes in the human genome, but among them they code for more than 1 million different proteins. Proteins start off as long chains of amino acids. Once they get their marching orders from DNA, via RNA, they need to fold into intricate 3D shapes—unique combinations of coils, fans, zigzags, tubes—that enable them to carry out precise jobs within the cell. All the while, they undergo any number of chemical changes.

The process is delicate and prone to error. “Proteins are finicky,” in Shriver’s words. When things go wrong, cancer, or other diseases, can result.

If APOLLO’s overall design is complex, sorting out what’s going on at the protein level is especially so. The task demands rigorous and consistent methods across all sites, and at all points in a patient’s care. For example, if a Veteran in APOLLO gets a biopsy, there are time constraints that don’t apply in routine cancer care.

“It’s a high-end bio-banking effort because these proteomics platforms require very meticulously acquired samples, beyond standard pathology practice,” says Shriver. “You just can’t walk into a VA which may have a great pathology team and say, hey, start doing this, because now you’ve got to worry about getting these samples within 30 minutes from the OR. They’ve got to be handled differently at the bench. The clinical diagnosis always takes priority and comes first, of course, but then the pathologists have to be comfortable with our expectation that any remaining, unused tissue from consenting patients be processed for research, including APOLLO.”

Looking at tumor biophysics

Genomic and proteomic findings are among hundreds of data points that will go into the APOLLO information base for each patient. Aside from an array of more conventional data—like patient demographics,

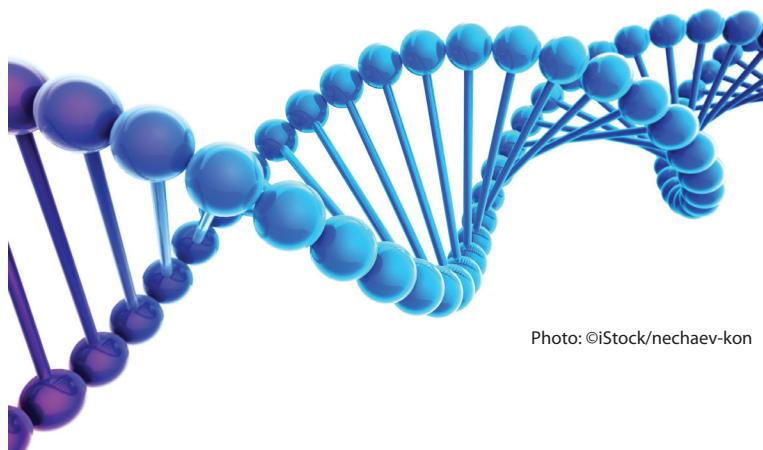


Photo: ©iStock/nechaev-kon

radiology reports, and drug prescriptions—APOLLO will delve into “things that have never been looked at before” on a large scale, says Shriver.

One example is tumor biophysics. How does a tumor—a mass of cancer cells—behave from a biomechanical standpoint? What factors govern how those cells migrate from one body tissue to another—for example, from breast to bone?

That area is of special interest to Dr. Jerry S.H. Lee, one of APOLLO’s leaders and a chemical engineer by training.

He talks about how different body tissues have different “squishiness.” Cancer cells can move about more fluidly in one type versus another. When a cell exits a solid tumor and enters the blood circulation, it’s like “running onto 495 (the Capital Beltway)—although probably not during rush hour,” he says.

“Why and how does it do that? How much of that is a protein, and how much is destined by genes? How does the cell know, hey, this is my stop?”

Lee hopes APOLLO will unearth answers to these

and other questions on the frontiers of cancer science. And he expects that one day, cancers will be classified not by where in the body they take root, but by their unique genetic and overall biochemical signatures. And drugs will be developed and marketed accordingly. “It won’t be, here’s a lung cancer drug, here’s a prostate cancer drug. But rather, here’s a drug that targets this molecular signature,” says Lee.

He points to two recent FDA approvals for drugs targeting genetic biomarkers as evidence of the practicality of this vision. Regarding its 2017 approval for Keytruda, the FDA said it was the first time the agency had “approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.” The second such approval came in 2018, for a drug sold as Vitrakvi. The FDA commented at that time on the emerging trend toward cancer drugs that are “tissue agnostic,” meaning they work regardless of where in the body the cancer exists, as long as a certain biochemical pathway is involved.

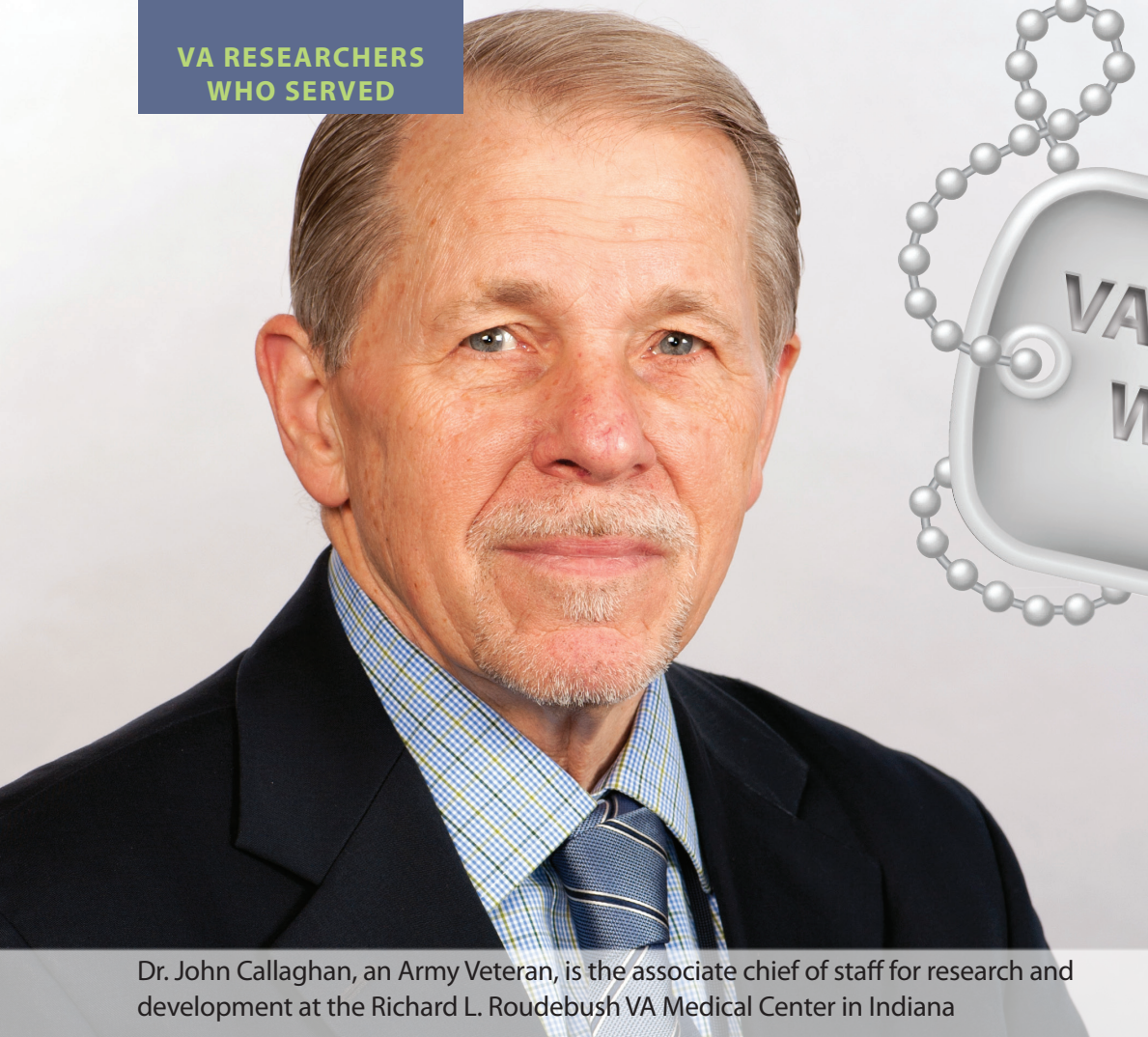
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Dr. John Callaghan, an Army Veteran, is the associate chief of staff for research and development at the Richard L. Roudebush VA Medical Center in Indiana

VA Researchers Who Served: Dr. John Callaghan

Dr. John Callaghan, an Army Veteran, has crafted a career of more than 40 years in internal medicine and clinical pharmacology. Currently, he's the associate chief of staff for research and development at the Richard L. Roudebush VA Medical Center in Indiana. He focuses on personalized, or precision, medicine. The aspect he's most concerned with deals with optimizing drugs for patients based on their individual profiles. He's also an associate professor of medicine and pharmacology-toxicology and the associate dean for VA Research at Indiana University. He held command roles in medical units and military intelligence detachments during his 30-year career in the U.S. Army Reserve and retired as a colonel.

What motivated you to join the military?

I was drafted into the Navy at age 28 in 1971. However, the local draft board in Washington, D.C., rescinded my call-up notice, and the Navy couldn't decide whether or when it might draft me later. To extract myself from this limbo state, I decided to join some medical colleagues at the 88th ARCOM U.S. Army Reserve hospital in Minnesota. Several years later, upon completion of my specialty training in clinical pharmacology and my doctorate in pharmacology, I joined the Indiana University School of Medicine, while working at Eli Lilly and Company, and the 337th Army Reserve general hospital at Fort Benjamin Harrison in Indiana. This was at the height of the Vietnam protests, so I stayed with the 337th and eventually became its commander at the rank of lieutenant colonel. Because of my scientific experience, I was invited to participate in an intelligence role. I served as commander of two military intelligence detachments, until shortly before my retirement from the military.

What inspired your research career?

While I was in medical school at the University of Kentucky, a dynamic professor of pharmacology got me interested in the field pharmacology and drug research. As a physician, I enjoyed the challenges of ethical clinical trial design, collaborations with my basic research colleagues, and caring for volunteers enrolled in clinical drug trials. My experience with these trials convinced me that patients would benefit from biomarkers that could predict and monitor drug response. I also came to recognize the need for pharmacogenetic tools that would identify people who would benefit from the new medication therapies. Drug safety and effective drug treatment are best achieved through personalized medical research and precision health care.

Did you have mentors who inspired you in life, the military, or your research career?

My wife, my daughters, and my parents have been the most influential people in my life. They helped me to become more appreciative of others. My parents sharpened my sense of responsibility and my duty to country, associates, and patients. They helped me frame my life convictions in family and career—both medical and military—and they supported my interest in and dedication to research and education. My father was a role model, especially in his leadership abilities and fairness to others. He was a model of hard work, responsibility, self-motivation, fairness, and support of others. I also had wonderful mentors in medical training, such as the chiefs of pediatric cardiology, pediatric hematologic oncology, and general surgery at the University of Kentucky; in Drs. Robert Wolen and Louis Lemberger during my career with Eli Lilly; and in Drs. Jordan Holtzman and George Sarosi during my VA career. These people motivated me to pursue my interest in clinical pharmacology and drug research.

Describe your military experience.

During the Vietnam War, I was a member of the 88th ARCOM hospital in Minnesota and was a member and later a commander of the 337th general hospital at Fort Benjamin Harrison. I commanded military intelligence detachments during the Gulf War and afterward. My active duty assignments were at Fort

Detrick in Maryland, the National Ground Intelligence Center in Virginia, and at several medical duty stations around the country, such as Fort Benjamin Harrison, Munson Army Health Center in Kansas, Ireland Army Clinic in Kentucky, Womack Army Medical Center in North Carolina, and Brooke Army Medical Center in Texas.

What kinds of research are you involved in? How does it potentially impact Veterans?

I work on genetic studies examining the impact of genes on PTSD and Alzheimer's disease. Because my background is in statistics, my primary focus is on the computation side of things. That means my lab is in an office with a bunch of computers, not a bunch of freezers and test tubes. I write programs and computer scripts to collate and analyze genetic data from hundreds or even thousands of subjects at a time.

Read more at www.research.va.gov/researchers_whoserved ★



Dr. John Callaghan had a 30-year career in the U.S. Army Reserve and retired as a colonel.

Military sexual trauma and chronic pain



Using data on more than 70,000 women Veterans ages 55 and older, VA researchers compared the prevalence of diagnoses related to chronic pain between women who had screened positive for military sexual trauma (MST) and those who had screened negative. Overall, 13.4% had a positive screen.

	With history of MST	Without history of MST
Fibromyalgia	13.3%	7.2%
Headaches or migraine	11.7%	6.0%
Back pain	46.7%	34.7%
Chronic pain syndrome	4.0%	1.9%
Opioid use disorder	1.4%	0.6%

Conclusion: “These findings suggest that MST is a common risk factor among older women Veterans in the VA, contributing to the chronic pain epidemic in this setting.”

Presented by a team from the San Francisco VA Health Care System at the [2018 annual meeting](#) of the International Society for Traumatic Stress Studies. Infographic by VA Research Communications, March 2019. Photo for illustrative purposes only: © iStock/natalie_board.

Complementary and integrative health care: What do Veterans use?

The circles show the percentage of survey respondents who reported using each treatment



Based on survey responses from 1,230 regular users of VA care. From "Complementary and Integrated Health Approaches: What Do Veterans Use and Want," *Journal of General Internal Medicine*, online April 22, 2019. Infographic by VA Research Communications, May 2019. Photos: © iStock.

Check out more VA Research infographics at:

www.research.va.gov/pubs/infographs

The high burden of 'subthreshold' PTSD

- Those with subthreshold PTSD have some PTSD symptoms but not enough to meet the criteria for a PTSD diagnosis.
- The findings below are based on data from the National Health and Resilience in Veterans Study.

Time Period	Subthreshold PTSD	Probable PTSD (meets full diagnostic criteria)
Lifetime (any time during life)	22.3%	8.0%
Past month	13.5%	4.5%

Conclusion: The results of this study suggest that a strikingly high proportion of U.S. veterans—approximately one in five (22.3%)—experience clinically significant PTSD symptoms in their lifetime.

Source: "High burden of subthreshold PTSD among U.S. military veterans." *World Psychiatry*, June 2016. Infographic by VA Research Communications, January 2018. Photo for illustrative purposes only. Photo © iStock/MTNCOM

Individual Placement and Support for Veterans with PTSD

- Individual placement and support helps Veterans with PTSD find employment through job coaching based on their interests and backgrounds, rather than traditional one-size-fits-all vocational rehabilitation and transitional work placements.
- The results below are from the Veterans Individual Placement and Support Towards Advancing Recovery (VIP-STAR) study of 541 Veterans.

	Transitional Work	Individual Placement and Support
Found steady work	23%	39%
Found competitive jobs	57%	69%
Average income for study period	\$10,989	\$14,642

Conclusion: "Individual placement and support" is more successful than transitional work at helping unemployed Veterans with PTSD obtain and sustain competitive employment.

Source: "Effects of Evidence-Based Supported Employment on Achieving Steady Work among Veterans with Posttraumatic Stress Disorder: A Randomized Controlled Trial." *AMA Psychiatry*, Feb. 28, 2018. Infographic by VA Research Communications, February 2018. Photo for illustrative purposes only. © iStock/Sean phillips WILLET

Firearm training among U.S. adults

Findings from a study by VA researchers and colleagues

- The percentage of U.S. firearm owners who reported receiving formal firearm training showed little change between 1994 (56 – 58%) and 2015 (61%).
- The most commonly reported combination of training topics was safe handling, safe storage, and accident prevention.
- Only 15% of owners said their training covered suicide prevention.
- Conclusion: The proportion of U.S. firearm owners with formal fire arm training has not meaningfully changed in two decades. Training programs vary widely. Efforts are needed to standardize and evaluate the effectiveness of training.

Source: "Improvements in Firearm Training among U.S. Adults." *PLoS One*, March 15, 2017. Study by researchers with University of Pittsburgh, University of Colorado, Western Michigan University, and University of North Carolina. Results from 2013 based on nationally representative survey of 8,922 people. (Infographic by VA Research Communications, September 2017. Photo © iStock)



RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs

Oral hygiene to fight pneumonia

VA researchers developed and implemented a program to increase oral hygiene in community living center and hospital patients. This simple initiative has greatly reduced cases of hospital-acquired pneumonia, saving Veterans' lives and increasing their quality of life. Project HAPPEN (Hospital-Acquired Pneumonia Prevention by Engaging Nurses to provide oral care) began in October 2016 at the Salem VA Medical Center's community living center. With the program's success, tooth-brushing has become a priority throughout the medical center, and is now being spread to other hospitals. Many VA medical centers have implemented the program. The VA team has worked with hospitals in all 50 states, Canada, Australia, Brazil, Greenland, and the United Kingdom to spread the word.

For more examples of VA research innovations being translated into everyday care, visit www.research.va.gov/research_in_action.



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