APRIL 2011

VA Research Currents

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

Joint venture

New guidebook for researchers will ease VA-DoD collaboration

VA and Defense researchers have produced a new 56-page guidebook to spur more collaboration between the agencies on clinical health research. The attractively designed VA/DoD Collaboration Guidebook for Healthcare Research, online at *www.research.va.gov/va-dod,* is filled with practical tips and information for researchers. It covers topics such as identifying collaborators, submitting research proposals, and understanding the rules for data security and human-subjects protection in each agency.

The guidebook is a key step in ongoing efforts over the past two decades to increase VA-DoD collaboration, particularly in health care. Other initiatives have focused, for example, on sharing electronic medical records or building joint health care facilities.

Partnering with military—VA and Defense researchers aim to increase collaborative projects to help both Veterans and active-duty personnel, such as these 101st Airborne troops.

To date, researchers from VA and DoD have also worked together on studies focused on issues such as posttraumatic stress disorder, traumatic brain injury, burn injuries, amputation and prosthetics, sensory loss, and infectious disease. One prominent example of a joint effort is the high-tech DEKA prosthetic arm, developed through funding from the Defense Advanced Research Projects Agency and now being field tested with

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Science and service

Former bench scientist, now with VA's Office of R&D, cited by Urban League for community role

At his desk in VA's Office of Research and Development on M Street in Washington, DC, Tshaka Cunningham, PhD, keeps a photo showing President Bill Clinton visiting his lab in the Diamond AIDS Research Center at Rockefeller University in New York, where Cunningham completed his doctoral studies in 2005.

The presidential visit was one of many milestones in the young scientist's life. From the football fields of Princeton University, where he played in Ivy League championships as a wide receiver in the mid-1990s, to a yearlong postdoctoral fellowship in Paris, to TV and radio guest spots and speaking engagements in recent

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years as an expert on HIV/AIDS prevention, Cunningham has evolved as a renaissance man who combines his passion for science with a fierce dedication to community service.

The latest highlight in Cunningham's career came earlier this month. He was honored by the Northern Virginia Urban League for his accomplishments in science and his role in the community. *VA Research Currents* spoke about both areas with Cunningham, who today is a scientific program manager with VA's Rehabilitation Research and Development Service, overseeing two research portfolios worth about $25 million.

***VA Research Currents:* Describe your science background in a nutshell.**

Cunningham: I'm a molecular biologist by training, with a bachelor's from Princeton University and a PhD from Rockefeller University. My PhD work focused mostly on virology and immunology, particularly in HIV/AIDS. A major highlight was that I was part of a team that was the first to identify a species-specific host restriction factor that prevents HIV from infecting certain monkey cells. This started a whole field of research that could eventually lead to a therapeutic breakthrough for HIV patients—if the research community can figure out how to safely introduce such host-restriction factors into human stem cells. Since 2008, in addition to my VA role, I've taught microbiology courses at Howard University School of Medicine and supervised graduate research projects in Howard's Cancer Center and the National Human Genome Research Center on the Howard campus.

What is the scope of your work with VA, and what are some examples of the research you oversee?

I oversee the aging and neurodegenerative diseases portfolio for the Rehabilitation Research and Development service within the Office of Research and Development. I also temporarily oversee the sensory systems portfolio, which includes hearing, vision and speech-language research.

One of the projects I find especially exciting is a study on Vitamin D supplementation in aging Veterans. It's led by Dr. Silvina Levis Dusseau at the Miami VA Medical Center. Another is a project led by Drs. Paul Fishman, Cha-Min Tang and Samir Jafri at the Baltimore VA Medical Center. They are looking at guiding gene therapy vectors into the substania nigra [the brain area that releases dopamine and helps control movement] in Parkinson's disease patients. The group is using an ultrasound-like imaging method called optical coherence tomography to help produce new functional neurons to replace those damaged by Parkinson's. Both of these are solid studies that should yield very interesting new data for these conditions.

I also created the Diversity Working Group for the VA Genomic Medicine Program to advise VA on increasing minority Veteran participation in genomics studies. And I am working with others to create a Historically Black Colleges and Universities research scientist training program to increase the numbers of minority scientists working in VA.

What inspired you toward a career in science?

I was exposed to laboratory science when I was around eight years old by my grandmother, Alfreda Simmons, who was a research technician at the National Cancer Institute for over 30 years. She would take me to the lab with her when I was a little kid. That planted the first seeds in my mind that I might want to be a scientist one day. When one of my favorite uncles died of colon cancer when I was 15, I felt compelled to become a researcher to help in the fight against human disease. After a summer research internship during high school at the Georgetown University Lombardi Cancer Center, I fell in love with molecular science and have been involved with it ever since.

Among other public-service work, you are a mentor at T.C. Williams High School in Alexandria, Va. Tell us about that.

I work with at-risk boys who are part of the dismal statistics for minority male graduation rates in inner-city schools. Currently, only 42 percent of the African-American males at T.C. Williams are graduating on time. We work with the kids on basic life skills issues—for example, resume writing, public speaking, anger management, dressing for success. We hope to get them to take a more active role in their education and aspire toward higher academic achievement.

For more of VA Research Currents' interview with Dr. Tshaka Cunningham, visit www.research.va.gov/currents.

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Editor: Mitch Mirkin

Magnuson Award given to stroke rehab innovator

In the last decade, a paradigm shift in the field of stroke rehabilitation and treatment has occurred, and one of the major forces behind the shift is Richard Macko, MD, director of the Maryland Exercise and Robotics Center of Excellence at the VA Maryland Health Care System and a professor at the University of Maryland School of Medicine. In recognition of his work, the clinician-researcher will receive VA's Magnuson Award for Outstanding Achievement in Rehabilitation Research and Development during National VA Research Week events in Washington, DC, on May 4 *(see below)*.

Dr. Richard Macko

The annual Magnuson Award is named for Paul B. Magnuson, a bone and joint surgeon and chief medical director for VA in the years after World War II. Magnuson Award winners receive a $5,000 cash award and a plaque, along with an additional $50,000 per year for three years to support a currently funded, nationally peer-reviewed research project.

Macko's team has developed structured exercise regimens—some involving treadmills, for example—that have been shown to improve stroke survivors' mobility even years later. The group's clinical and lab studies have also documented how inflammation and metabolic abnormalities in muscles paralyzed by stroke lead to insulin resistance, which boosts the risk of diabetes and cardiovascular disease, including stroke reoccurrences. Their research has shown, however, that the risk can be reversed by the right types of exercise.

"Macko and his team are the premiere muscle, metabolism and exercise physiology investigators for stroke survivors in North America," notes Daniel Hanley, MD, a professor at Johns Hopkins Medicine. "His findings have led to completely new, yet practical, understanding of how to enhance the quality of life of the stroke survivor with simple, generalized treatments."

Says Macko: "When I first started putting chronic stroke survivors who were 20 years past their stroke on treadmills, my colleagues thought I was crazy. Until recently, clinicians thought that stroke treatment and physical therapy had to be 'frontloaded' and that after a certain time, stroke survivors didn't advance. We've shown that stroke survivors, 10 years out from their stroke, can benefit in numerous ways from structured physical exercise. We're seeing improved ambulatory function as far as 20 years after a stroke."

Photos by Mitch Mirkin

On the move—Veterans James McMahon (top, with exercise physiologist Jeff Beans) and Earl Elsey Jr. take part in stroke rehabilitation therapy at the Baltimore VA Medical Center.

Research Week 2011: 'Discovery and Collaboration for Exceptional Health Care'

The theme of this year's National VA Research Week, to be commemorated May 2 – 6 at VA medical centers nationwide and at VA headquarters in Washington, DC, is "Discovery and Collaboration for Exceptional Health Care." The theme reflects VA's key partnerships with its academic affiliates, other government agencies, and private industry; and the agency's success in translating study findings into better care for Veterans. In particular, this year's celebration marks the 65th anniversary of VA Policy Memorandum Number 2, an historic agreement that allowed VA to affiliate with the nation's medical schools. The arrangement has had a huge impact on research and care. To learn more, visit *www.research.va.gov/researchweek.*

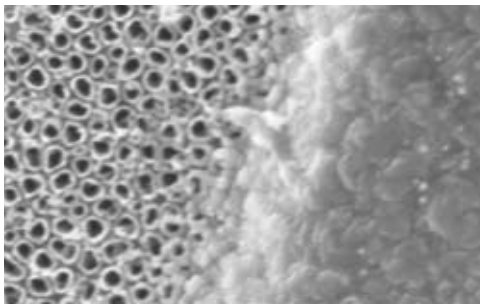
Discovery could speed progress on titanium implants

For years, prosthetics researchers have studied the feasibility of implanting titanium components directly into the residual limb for those who have lost a leg. This avoids the need for a socket, which can bring complications such as pain and sweating. One challenge, though, has been preventing bacteria from entering the body around the implant.

Thomas Webster, PhD, a nanoscientist with the Center for Restorative and Regenerative Medicine at Brown University and the Providence VA Medical Center, believes his team has discovered a way around that obstacle. In lab experiments, the researchers modified the surface of titanium leg implants to promote skin cell growth, thereby creating a natural skin layer and sealing the gap where the device has been implanted into the body. They also figured out how to sprinkle skin-growing proteins on the implant to hasten the sealing process.

In one phase of the research, the scientists fired an electron beam of titanium coating on the part of the implant that is inserted into the bone. This created a "landscape" of microscopic mounds. The mounds mimic the texture of natural skin and trick skin cells into colonizing the surface and multiplying. Next, they dipped the end of the implant into acid and gave it a jolt of electricity. This caused the titanium atoms on the component's surface to scatter and regather as hollow, upright, tubular structures. Here too, skin cells reacted to the change by quickly colonizing and forming a seal around the implant.

To further spur skin growth around the implant, the team used molecular tricks to bind FGF-2, a protein secreted by the skin to help other skin cells grow, to the implant. Petri dish tests showed the greatest density of skin cells on implant surfaces that were "nano-modified" and laced with FGF-2.



Nanotubes on the surface of a titanium implant caused skin cells to colonize more rapidly.

Webster says the techniques are promising, although human trials might be a few years off.

The research was funded by VA and the National Science Foundation. (*Journal of Biomedical Materials Research,* April 2011)

Chronic PTSD linked to smaller hippocampus

In a study by researchers with VA and the University of California, San Francisco, the hippocampus, a brain area involved in memory and stress, was about six percent smaller on average in Veterans with ongoing posttraumatic stress disorder than in those who had recovered from PTSD.

The study of Gulf War Veterans—41 with current PTSD and 41 recovered—was led by Brigitte Apfel, MD, a researcher with the Center for Imaging of Neurodegenerative Diseases at the San Francisco VA Medical Center. The team measured brain volume with magnetic resonance imaging.

Apfel says that there are two ways to interpret the results: Either the hippocampus gets smaller in PTSD and resumes normal size with recovery, or people with smaller hippocampal volumes to begin with are less likely to recover from PTSD. Some evidence supports the first hypothesis, Apfel says. "We know from animal studies that hippocampal volume can change. If some animals are exposed to stress, their hippocampal volume will shrink and then recover later in the absence of stress. This gives hope that, in people, hippocampal

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GUIDEBOOK *(from page 1)*

study participants at several VA sites.

The new guidebook, funded by VA's Health Services Research and Development Service, was created by six lead authors from VA and DoD and more than a dozen advisors and reviewers representing the two agencies.

Among the topics covered: techniques for finding collaborators with common research interests and goals; administrative and funding mechanisms in VA and DoD; types of formal agreements for collaborative projects; suggestions for developing and submitting proposals; and examples of successful, and unsuccessful, research collaborations.

The guidebook also contains links to additional resources, and a comprehensive list—seven pages' worth—of acronyms commonly used by researchers in both agencies, ranging from AAHRPP (Association for the Accreditation of Human Research Protection) to WRIISC (War Related Illness and Injury Study Center).

According to lead author Linda Resnik, PhD, PT, a research scientist at the Providence VA Medical Center and associate professor at Brown University, "The guidebook is a living document that will need periodic updating so that it contains the most current and relevant content." She says feedback and suggestions can be sent to *vhaprovadodguidebooks@va.gov.*

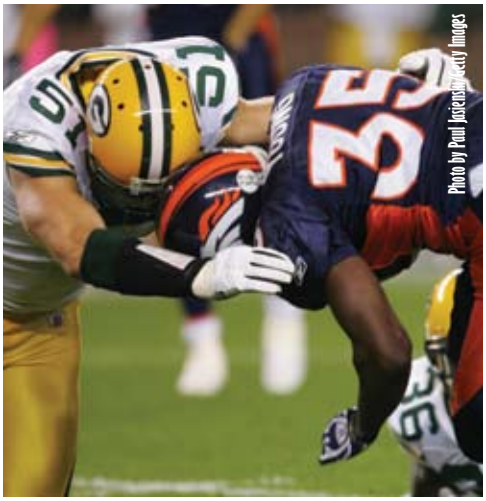
NFL grant expands brain-injury research

The circumstances behind traumatic brain injuries in athletes and combat troops may be light years apart, but in biological terms, they share certain features. So a new grant from the National Football League to scientists with VA and University of California, San Diego, may lead to a better understanding of the injury in both populations.

Research physicist Mingxiong Huang, PhD, and neuroradiologist Roland Lee, MD, have been using two types of brain scans—magnetoencephalography (MEG) and diffusion tensor imaging (DTI)—to study TBI, funded by VA, the Navy and the Brain Trauma Foundation. Now, with a $100,000 grant from NFL Charities, they are expanding the work to look at high school and college football players, as well as students involved in other contact sports.

According to another VA researcher, Ann McKee, MD, who studies brain injury in both athletes and Veterans, "there are clear parallels" between the two types of injuries even if most combat-related TBI involves pressure waves from blasts, as opposed to direct blows to the head. She says both types of injuries can lead to chronic traumatic encephalopathy, a degenerative brain condition in which clumps of tau protein build up in brain cells and disrupt normal function. McKee directs the neuropathology service for the VA New England Healthcare System and oversees brain banks at the Bedford VA Medical Center.

Image savvy—Drs. Roland Lee (foreground) and Mingxiong Huang are using a combination of brain-scanning technologies to detect mild brain injuries that might be missed by conventional scans.



Brain injuries in athletes involve direct blows, whereas combat brain injuries usually stem from exposure to blast waves. Researchers are studying biological factors common to both types.

Injured brains generate abnormal low-frequency brain waves.

The San Diego team's dual-scan method shows subtle injuries that go undetected in conventional CT and MRI scans. According to Lee, injured brains generate abnormal, pathological low-frequency brain waves—like those seen in normal patients during deep, dreamless sleep.

"This is an objective test you can run to show whether the brain function is normal or not," he told the *San Diego Union-Tribune.* He said the work may be especially useful in cases where athletes who have sustained head injuries deny being hurt because they want to keep playing. The same might apply to soldiers and Marines. Said Lee, "You can't fake the results when your brain waves are measured."

Turning findings into action: A snapshot of QUERI

David Atkins, MD, MPH, director of VA's Quality Enhancement Research Initiative, or QUERI *(www.queri.research.va.gov),* was interviewed by the Association of American Medical Colleges (AAMC) about QUERI and its role in improving Veterans' health care. Founded in 1993, QUERI helps translate study findings into everyday clinical practice. The interview with Atkins is reprinted here, with permission, from the March 2011 issue of the *AAMC Reporter,* the organization's flagship newsletter.

Driving better care—E-health and spinal cord injury are among 10 topics that QUERI focuses on. Above, Prescott (Ariz.) VA volunteer James Ellzey (seated) provides information about My HealtheVet to Veteran Richard Imus. Below, Veteran Michael Thomas tries out an innovative prone cart at the Milwaukee VA, under the watchful eyes of cart designer Pascal Malassigne and nurse Margaret Amato.

Reporter: The VA was a very early adopter of implementation science. Why did they initially decide to pursue this field?

Atkins: Back in the 1990s, the VA didn't have a great reputation, and QUERI was part of a wide change in the organization. There was a recognition that, in health care, there was this huge gap between what was known and what was delivered. We realized we needed to devote attention not only to new treatments, but providing the right treatments at the right time. It was a brand new field when the VA started QUERI back then. They had a good team of researchers embedded in their system, and for the most part those scientists had to make it up as they went along. It has been an interesting journey.

How would you say that QUERI has changed the culture of health care at the VA?

The goal has always been to say that there is a science to learning how things change and learning from that process. And where that has worked for us, it has worked because we built successful relationships between researchers and our health care partners. We don't just figure something out and hand it off. We have developed trust and flexibility on both sides, and we recognize that we are focused on the same problem.


Dr. David Atkins

So it is not a research pipeline in the traditional sense. It is more like a bridge that people are crossing back and forth.

What are you working on now?

One we just started up is e-health. Right now, patients in our system can get general health information and renew their meds online, and soon they'll be able to make and view appointments. But moving forward, the vision is that if you go in to have your hip replaced and you have Medicare, you can share your VA records with your private doctor. We are also rolling out the ability for patients to send e-mail to a doctor. What we need to do is figure out how to get patients and doctors to interact differently. Some patients and doctors may jump right in, but others might be slower. How do you speed up that culture change? And how do we generalize this system so that we don't have 500 clinics reinventing the same wheel?

Another one we are looking at started years ago. A while back, we realized we weren't doing well in quality for acute MI

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Beyond randomized clinical trials: 'point of care' studies

For decades, the randomized clinical trial has been the gold standard of medical research. Now, a VA and Stanford University team is exploring an emerging approach to clinical trials that experts say will cost less and be easier to translate into practice.

A paper now online in the journal *Clinical Trials* describes a "point of care" study now under way that will involve more than 3,000 Veterans with diabetes. The trial will compare two treatments—as do many standard randomized clinical trials—but it will be innovative in several ways. In a nutshell, the new approach embeds research into routine clinical care. It compares treatments that doctors are already using, and collects data on which treatments work best within the context of real-world, everyday practice.

"This allows us to make randomized comparisons within the health care system, instead of 'extracting' patients and placing them in a special setting and protocol that are not part of regular everyday care," says Joel Kupersmith, MD, VA's chief research and development officer.

The new approach was developed by a team led by informatics expert Louis Fiore, MD, of the VA Boston Healthcare System and Boston University, and Stanford University biostatistician Philip Lavori, PhD.

Key features of the new model:

• Enrollment of study volunteers occurs during usual care, within the framework of their visits to their regular health care providers.

• Providers draw on data from electronic medical records—or receive electronic alerts, delivered at the point of care—to determine if a patient is right for a study.

• Patients who consent to take part are randomized into one of the study's treatment arms and continue to receive care from their regular providers, with little or no deviation from routine care.

The pilot study now being conducted in VA compares two methods of administering insulin to hospitalized Veterans. VA's electronic medical records system includes ordering and protocols for both methods, and they are used with equal frequency at the Boston-area VA sites where the study has been taking place.

"The idea of embedding research into clinical care has been around for quite a while, but to my knowledge this is the first time that a randomized trial has been fully integrated into a hospital's informatics system," says Fiore. "It demonstrates an effective way to use electronic medical records to improve health care at a local level."

As the study progresses, the health record system is tracking which of the two treatments is associated with better outcomes—in this case, shorter hospital stays. Eventually, the software will begin to preferentially direct more patients to the treatment that has proved more effective. The study continues until the estimated probability that one treatment is better than the other tops 99 percent. The ideal end result, say the researchers, is that evidence from the trial is incorporated relatively quickly and inexpensively into everyday practice, without the usual barriers to implementation.

QUERI *(from previous page)*

[myocardial infarction, or heart attack]. We eventually found that we had no way of knowing the quality of cardiac catheterizations, or even how many cath labs there were. So they built a software system where anyone getting a cardiac cath was entered real time into a database.

You used to write out on a form the information about which arteries were narrowed and what kind of stent you put in, and there was no manner in which we could analyze that data. But now, you can analyze it continuously. Within 72 hours, complicated cases are flagged for review. It's been such a compelling model that we're taking this approach, which we now call transactional quality management, and working to apply it to other cardiac procedures and colonoscopies.

As it is, a lot of the work being done to improve the health care system is like driving while looking in the rear-view mirror. We want something that tells people what to do next.

How does the VA's partnership with medical schools and teaching hospitals help QUERI do its work more effectively?

The VA has always benefitted incredibly from its academic affiliates. It's a very vibrant research community. The VA is a great laboratory, but just working in the VA wouldn't be as attractive if they couldn't work in collaboration with the fellows and trainees in academic facilities. If we didn't have that, we wouldn't have been able to build any of this.

We have 340 different research projects now. This has all grown up in a relatively recent time period. That's been made possible because we started with academic-VA partnerships.

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Inside: **Moving beyond the randomized clinical trial**

Rapid HIV test studied in high-risk Veterans

In a study of 65 Veterans with mental health and substance abuse issues who were living in assisted-living facilities in the community, VA researchers in Philadelphia found that a quick, oral-fluid test for HIV, given by nurses familiar with the patients, was a highly effective screening tool. The results appear in the March/April 2011 issue of the *Journal of the Association of Nurses in AIDS Care.*

All but one of the Veterans in the study agreed to be tested. The HIV prevalence among the group was found to be 3 percent—about six times higher than the rate for the general U.S. population. Positive test results, produced on the spot within 20 minutes, were later confirmed with standard blood tests.

The Veterans in the study ranged in age from 44 to 86. All had at least one mental health diagnosis, most commonly schizophrenia, and many were being treated for addiction to drugs such as heroin or cocaine.

One of the researchers on the study, infectious disease specialist Laurence Buxbaum, MD, PhD, says: "We think the fact that the patients knew the nurses and trusted them allowed for a higher percentage of people agreeing to testing. We had a remarkably high acceptance rate for a group of people who had not been tested and likely refused testing in the past."

Infection detection—Dr. Laurence Buxbaum, with the Philadelphia VA Medical Center and the University of Pennsylvania, contributed to a VA study of a rapid oral test for HIV.

Lead author Pamela Jackson-Malik, PhD, MBA, RN, CNS, says her group is now piloting the rapid test in homeless shelters and VA community-based outpatient clinics. It is already in use, she says, in the Philadelphia VA's addiction recovery unit.

PTSD *(from page 4)*

damage in PTSD is reversible once they have recovered."

Apfel emphasizes that the results are not conclusive. "To begin to do that," she says, "we need a longitudinal study, in which we do brain imaging either before and after trauma or before and after treatment for PTSD. This way, we can follow how symptoms develop and see if hippocampal volume changes over time." (*Biological Psychiatry,* March 15, 2011)