VA RESEARCH CURRENTS

NEWS FOR THE RESEARCH COMMUNITY OF THE U.S. DEPARTMENT OF VETERANS AFFAIRS • SEPTEMBER 2006

VA-NYU scientist leads $8.4-million effort toward AIDS vaccine

Susan Zolla-Pazner, PhD, of the VA New York Harbor Healthcare System and New York University, will lead an international team of scientists in a new multimillion-dollar project aimed at developing vaccines against the AIDS virus.

Zolla-Pazner will direct the NYU AIDS Vaccine Discovery Consortium, which has received $8.4 million over three years from the Bill and Melinda Gates Foundation. The project is among others worldwide funded by Gates as part of its Collaboration for AIDS Vaccine Discovery.

The consortium will involve specialists in immunology, virology, crystallography,

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Susan Zolla-Pazner, PhD (third from left), and Phillip Nyambi, PhD (left), of the VA New York Harbor Healthcare System and New York University, meet with collaborators at Alpha Royal Medical Center in Cameroon, in West Africa.

Message from the CRADO

Relating our research to patient care

By Joel Kupersmith, MD, chief research and development officer

In his keynote address at the recent 2006 Senior Management Conference of the Veterans Health Administration, Acting Under Secretary for Health Dr. Michael J. Kussman emphasized the centrality of patient care in VHA's mission. Dr. Kussman said, "We need to provide the best possible care for all our enrollees, one veteran at a time." He referred to patient care as "Job Number One."

Our research enterprise is a vital and valuable part of the VA healthcare system, but it is important to always remember that it exists largely to support patient care. That is why we stress "veteran centricity." Our research must benefit the health of veterans, either in the short or long term. Even the basic science we conduct must relate, in a reasonably clear way, to health issues that affect significant numbers of veterans. Our bench research must be seen as the "preclinical" stage of a translational

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CSR&D seeks to fund studies on diagnostic-treatment combinations

VA's Clinical Science Research and Development Service is seeking Merit Review applications focused on assessing combinations of diagnostic tests and clinical treatments. This medical approach is becoming well-established, in particular, in cancer treatment. An example is the use of the breast-cancer drug Herceptin, a monoclonal antibody, for patients whose DNA microarrays show amplification of the ERBB2 gene.

Successful proposals are expected to result in novel clinical trial designs. Full details can be found in the Solicitations section of the ORD website at www.research.va.gov/funding/solicitations.

Popular herb 'goldenseal' lowers cholesterol in lab tests

Animal and cell-culture tests by a team at the VA Palo Alto Health Care System have shown that goldenseal root, a popular North American herb used mainly to fight upper respiratory infections, may also be an effective cholesterol-lowering agent. The findings appeared online last month in the *Journal of Lipid Research* and are scheduled to appear in print next month.

According to senior investigator Jingwen Liu, PhD, this would be a heretofore unreported application for goldenseal, one of the five top-selling herbs in the U.S. "The cholesterol-lowering effect of goldenseal has never been reported in the literature," said Liu, a molecular biologist.

Previous research by Liu and colleagues found that berberine, an alkaloid found in goldenseal and other herbs, could lower lipids. In a small clinical trial published in 2004 in *Nature Medicine,* a group of Liu's collaborators in China treated 32 hyperlipidemic patients with berberine isolated from the traditional Chinese herb huang lian, or coptis chinensis—used, like goldenseal, mainly as an antimicrobial. On average, the patients' cholesterol and triglyceride levels dropped by about a third.

In the new research, conducted solely in Liu's VA lab, goldenseal root proved more powerful than berberine by itself as an agent against high cholesterol. Based on the evidence from her cell-culture and hamster experiments, Liu believes that other compounds in goldenseal, in addition to berberine, work in concert to keep lipids in check. Her team identified one of these compounds as canadine. They are working to purify and characterize two others.


Photo by Chuck Revell

Jingwen Liu, PhD, of the Palo Alto VA, has been researching the cholesterol-lowering abilities of natural compounds.

The study showed that the compounds boost the production of a protein known as LDLR (liver low-density lipoprotein receptor). Anchored to the surface of liver cells, LDLR grabs particles of LDL, or "bad," cholesterol from the blood and draws them inside the cell. This lowers cholesterol in the bloodstream.

Statin drugs—used by millions of Americans to lower cholesterol—accomplish the same job, but they do so by blocking an enzyme that enables natural production of cholesterol in the liver. When the liver is low in cholesterol, this activates LDLR and liver cells take in more harmful lipids from the bloodstream. Statins have been studied for other possible cardiovascular and anti-inflammatory benefits, but their side effects could include liver and muscle damage.

"Because the bioactive components in goldenseal lower cholesterol by a mechanism different from [that of] statins, goldenseal could be used in combination therapy" with statins to improve their efficacy, said Liu. "In addition, for those patients who do not tolerate statins due to muscle pain, gold-

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Study finds racial differences in doctor-patient communication

African Americans typically walk away from doctor appointments having asked fewer questions than whites—and as a result may be making less-informed medical decisions, suggests a study conducted at the Michael E. DeBakey VA Medical Center in Houston. The results are published in the Sept. 15 issue of *Cancer*.

Lead author Howard S. Gordon, MD, formerly at the Houston VA and Baylor College of Medicine and now at Chicago's Jesse Brown VA Medical Center and the University of Illinois, led a team that analyzed audiotapes of doctors' meetings with 137 patients with suspected or confirmed lung cancer. The results showed that African American patients and the family members or friends who accompanied them asked fewer questions, raised fewer concerns, and made fewer assertions during their appointments—an average of about 24 "active participation" utterances per session, versus 37 for whites. African American patients also received less information from doctors—an average of about 49 "information-giving" statements from the doctor per session, compared with 87 given to white patients.

According to a statistical analysis, it was not race but the degree of patients' passivity or engagement that influenced how much information they received. The study also found that when doctors and patients were of the same race, more information was exchanged.

A lack of trust in doctors may be at the core of African Americans' passivity during the medical encounter, say the researchers, citing previous studies. While the new findings don't discount the possibility that racial bias on the part of doctors may be a factor—or that blacks may simply prefer to communicate less with providers—the study does underscore the importance of patients' being actively involved, note the researchers. When patients don't proactively seek information, a negative cycle may result. According to Gordon and his coauthors, "The results indicate a pattern of communication that may perpetuate patient passivity and limited information-exchange where black patients and patients in [racially] discordant interactions do less to prompt doctors for information, and doctors in turn provide less information to these patients."

Howard Gordon, MD, led a study analyzing doctors' interactions with lung-cancer patients.

Gordon's VA coauthors included Richard L. Street JR, PhD, and Julianne Soucheck, PhD. Barbara F. Sharf, PhD, of the department of communication at Texas A&M University, also contributed to the study, which was funded by VA and the Agency for Healthcare Research and Quality. ■

HERB (from pg. 2)

enseal could be an alternative." She emphasized that the herb's safety and efficacy for this purpose would need to be evaluated in clinical testing.

Liu's VA collaborators included Parveen Abidi, PhD; Wei Chen, MD; Fredric B. Kraemer, MD; and Hai Li, PhD. Their work was supported by VA and the National Center for Complementary and Alternative Medicine.

Facing page: Botanical illustration of goldenseal created by Kris Morrow, Medical Media, Palo Alto VA.

CHERP researcher receives Young Investigator award

Kevin Volpp, MD, PhD, a staff physician at the Philadelphia VA Medical Center and investigator at VA's Center for Health Equity Research and Promotion, received the John. D. Thompson Prize for Young Investigators from the Association of University Programs in Health Administration. The award honors faculty from member programs for their contributions to health-services research.

Volpp studies the impact of organizational and financial changes in the healthcare system on quality of care, and the effects of financial incentives for patients on their use of preventive services. He was lead author on a recent study involving 179 smokers at the Philadelphia VA Medical Center that found that modest financial incentives led to higher rates of enrollment in and completion of a smoking-cessation program, as well as higher 75-day—but not 6-month—quit rates.

The rich history of VA research

Early pioneer in leukemia research: Ludwig Gross, MD, of the Bronx VA

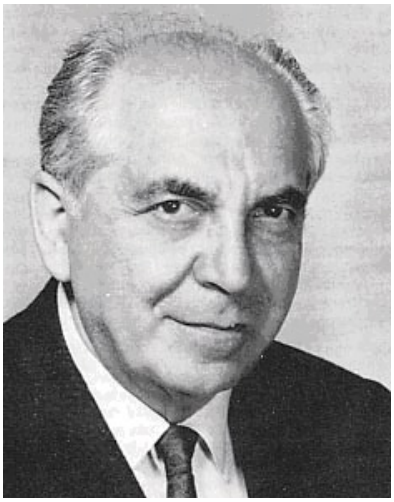
The following account is based on an excerpt from "VA Research, 1925 – 1980," a history compiled by Dr. Marguerite Hays, who directed VA's Medical Research Service from 1974 – 1979 and the overall VA research program from 1979 – 1981. The complete, fully referenced text is expected to be available in print or on CD by early next year. The material below has been edited slightly due to the space constraints of this newsletter.

In the late 1940s, Ludwig Gross, MD, was active in research at the Bronx VA Hospital, where he had transferred while still in uniform. Nobel Prize winner Rosalyn Yalow and her colleagues Bernard Roswit and Solomon Berson were working on research using radioisotopes at the same time at the Bronx VA. During the time he could spare from his clinical duties, Gross bred leukemia-prone mice and tried to prove his theory of the viral cause of mammalian leukemia by transmitting this tendency to develop leukemia to normal mice. In 1949, he finally succeeded.

Escape from Nazi Europe

Gross was a war refugee from Poland. In 1939, he lectured at the National Institutes of Health and speculated that a virus caused leukemia and some day we would have a vaccine for it. He then returned to Europe and was in Poland when the Nazis invaded. He escaped just in front of the Nazi line.

When, after many difficulties, he managed to return to the United States, he applied for a commission in the U.S. Army. At first he was turned down because he was not a citizen. He went to the Polish Ambassador, who introduced him to the Surgeon General, who wrote a letter that supported his entry in the U.S. Army Reserve in Cincinnati.



Ludwig Gross, MD, in 1975.

While he was in Cincinnati, he studied neuroblastoma, a condition that may be found in the grandfather and in the grandson. Gross considered that this might be due to vertical transmission of disease from generation to generation through the genome. …

He wanted to continue his research even after he entered active Army service. He wrote to Bittner, the discoverer of a genetic line of mice that were very prone to breast cancer, and asked Bittner for a breeding pair of his mice. Bittner sent them. …

In 1944, the Army transferred him to North Carolina. While on leave, he went to Philadelphia, where he visited Dr. Baldwin Lucke, who was working on transmission of kidney cancer in frogs. They discussed the problem of viral transmission. Later that year, Gross received transfer orders to the Bronx VA Hospital.

In a makeshift lab, he studied the hemolytic action of mouse mammary carcinoma filtrates and extracts on mouse erythrocytes and a similar effect of human cancer extracts on human erythrocytes. He later continued his interest in breast cancer transmission, studying possibly oncogenic particles in mouse and human breast milk.

But Gross's main interest was leukemia, and all he had when he arrived at the Bronx were his mice with a 90% chance of developing breast cancer. Jacob Furth at Cornell had a strain of leukemia-prone mice, the AK strain. When Gross asked Furth for a breeding pair, he gave him 11 of his AK mice.

Gross bred the mice himself. While there was no specific money for research, the hospital allowed him to spend some of his time conducting his studies. He spent five years, 1944-1949, trying to transmit the tendency to leukemia to non-leukemia-prone mice by injection of filtrates. The hospital was considering taking away his research time and space, as he seemed to be nonproductive.

A model of determination

In 1949, Dr. Gilbert Dallborf gave a lecture at the hospital about the Coxsakie virus. He explained that it could be transmitted only in newborns. Before Dallborf even finished the lecture, Gross ran out to his laboratory where he had some newborn normal mice. He injected them with cells from AK mice, and they developed leukemia. Later he found that he could also transmit leukemia with just a filtrate, and that the effect extended into the next

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Recent publications and presentations by VA investigators

Below is a brief sampling of recent publications and presentations by VA investigators, based on notifications received by R&D Communications (see reporting requirements at www.research.va.gov/resources/ policies/pub_notice.cfm.) Every attempt is made to present a cross section of investigators, topics and medical centers. Only VA-affiliated authors are listed here, due to space constraints.

"Adding Injury to Insult: Fracture Risk After Stroke in Veterans." Heather E. Whitson, MD; Ronnie D. Horner, PhD; Pamela W. Duncan, PhD; Kenneth W. Lyles, MD. **Durham, Gainesville.** *Journal of the American Geriatrics Society,* July 2006.

"Borderline Personality Disorder and Traits in Veterans: Psychiatric Comorbidity, Healthcare Utilization, and Quality of Life Along a Continuum of Severity." Valerie L. Forman-Hoffman, PhD, MPH. **Iowa City.** *CNS Spectrums,* Sept. 2006.

"Effect of Using Information From Only One System for Dually Eligible Health Care Users." Mark Kuebeler, MS; Kenneth Pietz, PhD; Laura A. Petersen, MD, MPH. **Houston.** *Medical Care,* Aug. 2006.

"Elevated Hypothalamic Orexin Signaling, Sensitivity to Orexin A, and Spontaneous Physical Activity in Obesity-Resistant Rats." Allen S. Levine, PhD; Michael M. Kuskowski, PhD; Catherine Kotz, PhD. **Minneapolis.** *American Journal of Physiology,* Oct. 2006.

"Human Liver Expresses Ammonia Transporters at Levels Similar to Mouse Liver." I. David Weiner, MD. **Gainesville.** Annual Meeting of the Florida Gastroenterologic Society, Sept. 8, 2006.

"Improving the Bar-Coded Medication Administration System at the Department of Veterans Affairs." Peter D. Mills, PhD, MS; Julia J. Neily, RN, MS, MPH. **White River Junction.** *American Journal of Health System Pharmacy,* Aug. 1, 2006.

"Mental Status After West Nile Virus Infection." Kathleen Y. Haaland, PhD. **Albuquerque.** *Emerging Infectious Disease,* Aug. 2006.

"Racial Disparities in Preferences and Perceptions Regarding Organ Donation." Said A. Ibrahim, MD, MPH. **Pittsburgh.** *Journal of General Internal Medicine,* Sept. 2006.

"Quality of Life and Exercise Performance in Patients in Sinus Rhythm Versus Persistent Atrial Fibrillation: A Veterans Affairs Cooperative Studies Program Substudy." Charlene Tang, PhD, MD; Bramah N. Singh, MD. DSc; Domenic J. Reda, PhD; Crystal L. Harris, PharmD; Ross D. Fletcher, MD; Satish C. Sharma, MD; Alan K. Jacobson, MD; H. Daniel Lewis Jr., MD; Becky Lopez, RN; Dennis W. Raisch, PhD. **Washington, DC; Hines; West Los Angeles; Albuquerque; Providence; Loma Linda; Kansas City.** *Journal of the American College of Cardiology,* Aug. 15, 2006.

"Socioeconomic Determinants of Planned Methadone Treatment." Aram Dobalian, PhD. **Sepulveda.** *American Journal of Health Behavior,* Sept./Oct. 2006.

"Special Report: Brain Gate Trial Update; Spinal Cord Injury, Stroke and ALS." Leigh R. Hochberg, MD, PhD; John Donoghue, PhD. **Providence.** NINDS Neural Interfaces Workshop, Aug. 21-23, 2006.

"The Influence of Physician Race and Gender on Obstetrician-Gynecologists' Annual Incomes." William B. Weeks, MD, MBA; Amy E. Wallace, MD, MPH. **White River Junction.** *Obstetrics & Gynecology,* Sept. 2006.

"The Use of Percutaneous Coronary Intervention in Black and White Veterans with Acute Myocardial Infarction." Anne E. Sales, PhD, RN; Stephan D. Fihn, MD, MPH. **Seattle.** *BMC Health Services Research,* Aug. 21, 2006.

"Use of Flexible Sigmoidoscopy to Screen for Colorectal Cancer in HIV-Infected Patients 50 years of Age and Older." Edmund J. Bini, MD, MPH; Fritz F. Francois, MD. **New York.** *Archives of Internal Medicine,* Aug. 14 – 28, 2006.

"WISP-2/CCN5 Is Involved as a Novel Signaling Intermediate in Phorbol Ester-Protein Kinase Calpha-Mediated Breast Tumor Cell Proliferation." Krishanu Sengupta, PhD; Snigdha Banerjee, PhD; Kakali Dhar, PhD; Neela K. Saxena, MS; Smita Mehta, MD; Sushanta K. Banerjee, PhD. **Kansas City.** *Biochemistry,* Sept. 5, 2006.

GROSS (from pg. 4)

generation. He characterized transmission of other viruses as well during this early period and evolved a theory about the viral transmission of malignancies.

After Gross's success in transmitting leukemia through the newborn mice, the Hospital Director, Ralph G. Devoe, a former general, became very supportive and gave him lots of space. …

While extreme, Gross's early experience at the Bronx VA Hospital exemplifies the determination and independence shown by many early VA researchers. They had little guidance and often were not well understood. Little or no research infrastructure was available. But a venturesome spirit that encouraged original thinking and inventiveness permeated the newly "academic" organization. ■

AIDS (from pg. 1)

and structural and computational biology. Zolla-Pazner's team, representing four U.S. sites and four in India and Cameroon, plans to isolate the most powerful antibodies found in patients infected with various HIV strains. They will then identify structures on the virus surface that are targeted by these antibodies, and incorporate them into genetically engineered vaccines that will be tested in rabbits.

One structure to be targeted is the so-called "V3 loop" on HIV's protein coating, which is known as gp120.

"The Gates Foundation grant will enable us to develop candidate vaccines that focus the immune response on the V3 loop of the gp120 protein," said Zolla-Pazner. "This is a proof-of-principle project. If it succeeds, it could be extended to the study of other parts of the HIV virus as well as to other disease-causing organisms."

In the past, many scientists hoped gp120 would provide the basis for successful vaccines because the immune system produces antibodies against it. But a large clinical trial of a vaccine based on this strategy failed, and some researchers lost hope that the antibody approach would work.

Zolla-Pazner, however, has continued since the early 1980s to study pieces of the proteins enveloping the HIV virus, and the antibodies elicited by these foreign strands. She said the V3 loop has remained especially promising. HIV uses this structure to gain a foothold on cells of the immune system. During infection, the V3 loop remains at least partially exposed to the immune system and produces strong antibodies. Unlike others that have proved more problematic, these antibodies don't react with any of the body's own proteins.

"At one time, everybody thought that making antibodies to V3 was the way to prevent HIV infection and that this was going to be a slam dunk," said Zolla-Pazner. But research in mice suggested that anti-V3 antibodies could recognize only a few strains of HIV, and many scientists abandoned this path.

"Our data showed that they weren't as specific as everybody else thought," said the VA researcher. "We had found an antibody to V3 that was really interesting and had the ability to block the infection of lots of HIV strains."

The V in V3 stands for variable. The loop is made of sequences of amino acids that vary widely according to the strain of HIV. Only a handful of the sequences are the same in infected individuals, and there are thousands of sequences. Using crystallography and structural biology, Zolla-Pazner and colleagues have begun to understand how the varying V3 loops are recognized by neutralizing antibodies, and how these antibodies prevent HIV from infecting cells.

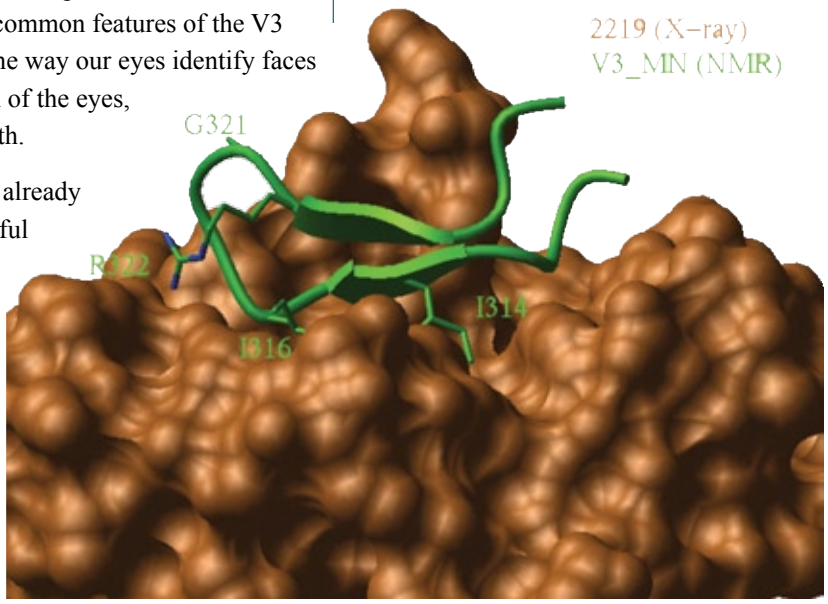
One of the V3's hallmarks is a hair-pin-like turn. Even though the amino acid sequences of the loop vary, its fundamental structure remains the same. "The V3 region in different viruses is indeed always changing but its shape is always similar," said Zolla-Pazner. She explained that antibodies recognize the common features of the V3 loop in the same way our eyes identify faces by the position of the eyes, nose, and mouth.

Her lab has already isolated powerful neutralizing antibodies from the blood of patients infected with HIV subtype B, most common in Europe and the U.S. Her colleagues plan to collect blood from HIV-positive volunteers in Cameroon and India so they can cull additional antibodies from those infected with subtypes A and C, which predominate in those areas. Subtypes A, B, and C account for about 86 percent of all HIV strains.

The antibodies will be tested for neutralizing activity and the most broadly acting will be "crystallized" along with the V3 loops they recognize. The crystals will provide the basis for molecular modeling studies that will analyze the atomic structure of the V3 loop and its associated antibodies. The models will help the researchers identify the features of the V3 loop that are eliciting the antibodies, and help them design vaccines accordingly.

Zolla-Pazner also heads a VA Research Enhancement Award Program (REAP), established in 2002 to spearhead work in designing and developing vaccines for AIDS, tuberculosis and other infectious diseases. ■

The figure below shows the V3 loop (in green), a structure on the outer coating of the AIDS virus, bound to a human neutralizing antibody (in brown). Courtesy of Dr. Timothy Cardozo, NYU School of Medicine.



Christianne Roumie, MD, MPH, checks the blood pressure of Nashville VA patient James Farris.

Patient education adds critical boost to hypertension management

In a study involving 1,341 veterans with hypertension at the Tennessee Valley VA Healthcare System, educational outreach to patients along with provider education was decidedly more effective than provider education alone in helping patients reach their blood pressure goals. The results appeared in the Aug. 1 *Annals of Internal Medicine.*

At the outset of the study, all the veterans were on one antihypertensive drug but still had blood pressure greater than 140/90 mm Hg, which is the target promoted in the 2003 seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7). The patients and their VA physicians were randomly divided into three groups. In the first group, doctors received an email with a link to the JNC 7 guidelines. Doctors in the second group received the guidelines email plus a one-time patient-specific computerized hypertension alert. In the third group, doctors received both interventions, and patients received a letter at home advocating medication adherence, lifestyle modification, and conversations with providers about treatment.

The mean baseline pressure for all three groups was 157/82. After six months, the only veterans who met the JNC7 goal were those who received the letter: Their mean pressure was 138/75, compared to 145/78 for those whose doctors received the guidelines link by email, and 146/76 for those whose doctors received the email plus the alert.

According to lead author Christianne L. Roumie, MD, MPH, and colleagues, the extra reduction in blood pressure among the patient-education group could potentially reduce heart

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CARE (from pg. 1)

process focused on tomorrow's veterans—if not today's—and aimed at improving their healthcare and well-being.

In Dr. Kussman's remarks, we find another important concept: providing the best care "one veteran at a time." How can we apply this mindset to our role as VA researchers? For those of us who work directly with patients in our studies, perhaps the answer is obvious. We must diligently and vigorously protect the rights, privacy and dignity of each and every research participant, in accordance with all VA and other federal regulations. Moreover, we should strive to go beyond the "letter of the law" and relate with compassion, concern and appreciation to every veteran we meet.

Safeguarding veterans' rights includes, of course, being up-to-date on VA policies and procedures in the area of cybersecurity, which has received increasing attention in recent months. If you have not already done so, please visit the following page on the ORD website for a comprehensive overview of these guidelines: www.research.va.gov/resources/policies/cybersecurity.cfm.

Cybersecurity is one of many relevant areas being covered in a series of conferences being held this fall in Baltimore, San Francisco and St. Louis by our Program for Research Integrity Development and Education (PRIDE), under the direction of Dr. Lynn Cates. The focus of these events is "local accountability." Participants are coming away with a firm understanding of the responsibilities of medical centers, institutional review boards, R&D committees, and individual investigators. Caring for "one veteran at a time" requires not only clear and sensible guidance from ORD, but knowledge and commitment on the part of local leadership and every single VA researcher.

I propose that even those of us who do not work directly with veterans can still

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High-tech rehab center dedicates new space

Taking part in a ribbon-cutting ceremony held this spring at VA's Cleveland-based Advanced Platform Technology (APT) Center to mark the opening of its new offices were (from left) Murray Altose, MD, associate chief of staff for research at the Louis Stokes Cleveland VA Medical Center; Ronald Triolo, PhD, executive director of the APT Center; Neal Peachey, PhD, chief of research for the APT Center; and medical center director William Montague. Established last year by VA's Rehabilitation Research and Development Service in partnership with Case Western Reserve University, the APT Center has capabilities in microelectromechanical systems design and fabrication; neural interfacing; polymer and bioactive material development; rapid prototyping; and circuit and software design. Scientists and engineers at the center will design and build prototypes for advanced prosthetics systems, sensory aids, and other clinical applications to help veterans with limb loss, immobility, and sensory deficits.

CARE (from pg. 7)

be guided by the patient-care philosophy espoused by Dr. Kussman. Analyzing data, processing tissue samples, sequencing DNA—these and hundreds of other tasks we do every day as VA researchers are part of a rich mosaic. Our efforts merge to improve the health outlook for tomorrow's veterans, and we all play an essential role in ensuring that VHA delivers the best health-care in the world, "one veteran at a time."

EDUCATION (from pg. 7)

failure by 50 percent, cerebrovascular morbidity and mortality by 42 percent, and coronary heart disease by 14 percent.

"[The trial] shows the effectiveness of adding patient education to provide education in improving blood pressure control among veterans with uncontrolled essential hypertension," wrote the authors.

Roumie and colleagues note, as limitations of the study, that follow-up blood pressure measurements were missing for 27 percent of patients in the study. Furthermore, the study could not detect the mechanism by which patient education improved blood pressure control. ■

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