ORD creating Web-based system to track publications

The Office of Research and Development (ORD) is creating a Web-based system to receive and track notifications from VA investigators about their upcoming scientific articles and meeting presentations. Linda Lutes, director of Communications for ORD, announced the plan on a Nov. 20 field conference call.

According to VHA Handbook 1200.19, VA investigators or their research offices are required to report any upcoming publications or presentations, upon acceptance, to VA Research Communications. Individual ORD services, such as HSR&D and RR&D, have additional reporting requirements. The current email-based reporting procedure is out-

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New program aims to fast-track commercialization, clinical development of VA research

“The valley of death,” says Alex Ommaya, ScD, is how insiders wryly refer to the perilous chasm between academic research and commercial development. In drug development, for instance, fewer than 10 percent of new compounds tested in humans are released to market.

Ommaya was named in October to direct the new Translational Research program of VA’s Office of Research and Development. He wants to boost the odds for VA researchers by finding new ways to propel their innovations forward. He’ll work with VA’s Technology Transfer program in some areas and take advantage of existing mechanisms for partnering with industry, such as Cooperative Research and Development

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Alex Ommaya, ScD, hopes to create new partnerships and collaborations to help speed the path from VA labs and clinical trials to patient care.

Manmade protein could help eye problems, cancer

Potentially blinding blood-vessel growth in the cornea, resulting from eye injury or even surgery, can be reduced by more than 50 percent with a new synthetically engineered protein, according to an animal study by researchers at the Medical College of Georgia and Augusta VA Medical Center. They reported their findings in the November issue of Investigative Ophthalmology and Visual Science.

“We believe eventually we’ll be able to use this protein to help patients in many situations where blood vessel formation is detrimental, including cancer, diabetic retinopathy and macular degeneration,”
PROTEIN (from pg. 1)
said Balamurali K. Ambati, MD, a VA Career Development awardee and corneal specialist at the Augusta VA Medical Center and Medical College of Georgia.

The body can make new blood vessels to promote healing after a corneal transplant, scratch on the cornea, or other traumas. Known as angiogenesis, this natural response becomes harmful when new growth blocks vision, or when a tumor hijacks the process to survive.

Protein affects even well-established blood vessels

The researchers used the protein they developed to reverse obstructive blood-vessel growth in a mouse model, even a month after injury. Ambati said this indicates that even well-established blood vessels are susceptible to the effects of the protein, known as an “intraceptor.”

The intraceptor traps vascular endothelial growth factor, or VEGF, inside the protein-making machinery of a cell. It’s made with a portion of a VEGF receptor called sflt-1, a free-floating receptor recently shown to help keep the cornea clear by taking up and effectively neutralizing VEGF.

“We’ve designed a novel recombinant molecule where we take a subunit of sflt-1 and couple it with a four-amino-acid peptide tail,” explained Ambati. “The tail essentially handcuffs the manmade molecule within the protein-making machinery of the cell so that it stays there and anything that binds with it—namely VEGF—stays there too. So it’s a very specific way of down-regulating a target protein.”

Last year, Ambati and colleagues published a study in which the intraceptor helped reduce blood- vessel development in the test tube and animal models for corneal injury and melanoma. “Now we are talking about making [the blood vessels] go away,” he said.

The intraceptor appears to trigger regression of blood vessels by inducing programmed cell death, or apoptosis, in the vascular endothelial cells that line blood vessels.

Working from inside the cell

Some existing anti-angiogenesis treatments target VEGF outside cells. Ambati points out the advantages of his team’s approach: “It is important to bind it within cells because certain cells, such as cancer and blood vessel cells, have the capability to produce their own VEGF and their own receptors. Imagine trying to block from the outside a factory that has everything it needs inside. You have to throw a monkey wrench inside the factory—and that’s what we managed to do.”

For the study, the manmade protein was injected directly into the cornea with a microneedle, but Ambati said the treatment would ideally be given as a topical eye drop with a long-term delivery system.

His team is also studying the intraceptor’s potential role in destroying blood vessels that help sustain cancers. They also are looking at a biodegradable polymer cage so they can encapsulate the intraceptor, tag it with a homing device for target cells, and deliver it “like a missile carrying a payload” into the desired cells, where it will slowly release the intraceptor.

PUBLICATIONS (from pg. 1)

The new system has been planned based on input from meetings and focus groups with Central Office and field staff—including, for example, the Boston-based Center for Information Dissemination and Education Resources, which already tracks upcoming publications for HSR&D; and VA’s network of Geriatric Research Education and Clinical Centers, which has its own Web-based system for the same purpose.

The new ORD-wide system, expected to begin pilot testing in early 2007, is being designed as a user-friendly application that will collect information about upcoming presentations or in-press journal articles. User profiles, created when investigators first use the system and updated periodically, will store information on degrees, affiliations and VA funding. Ivette Gosser, ORD’s director of Information Technology, said the system will mesh with other ORD databases—such as RDIS—wherever possible so certain data can be uploaded automatically without requiring duplicate effort.

Investigators—or support staff in local research offices—will be able to upload in- press manuscripts, which will viewable only by the investigators themselves, or their VA coauthors, and by authorized users at investigators’ sites or in Central Office.

The system will allow R&D Communications to track publications that may require actions such as VA news releases or background briefs for ORD or VHA leadership. According to Lutes, eventually the publication-tracking system will also serve as a “library or catalog” of VA research, and will be valuable for a number of purposes.

“The goal is to design a system that can have uses other than to report upcoming
A team at the Tampa VA Medical Center and University of South Florida found that stem cells obtained from human umbilical cord blood could significantly reduce the effects of heart attacks in rats, even when administered up to 24 hours after the onset of the attacks. Moreover, no immune-suppressive therapy was needed to keep the rat hearts from rejecting the human cells.

The scientists reported their findings in the latest issue of the journal Cell Transplantation, and presented a related study on Nov. 12 at the scientific sessions of the American Heart Association.

“These observations suggest that human umbilical cord stem cells can be administered relatively late—that is, at 24 hours—after the onset of an acute heart attack and still produce very beneficial effects,” said lead investigator Robert J. Henning, MD, a staff physician at the James A. Haley VA in Tampa.

If the treatment eventually proves safe and effective for humans, it could “reduce the morbidity associated with heart damage,” said Timothy O’Leary, MD, PhD, VA’s director of Biomedical Laboratory Research and Development. Transplants using human umbilical cord blood (HUCB) stem cells have already been performed in thousands of patients to treat leukemia, neuroblastoma and other diseases.

In 2004, Henning and colleagues published the first study to show that cells from human umbilical cord blood could significantly reduce the size of heart attacks in rats and lead to almost-normal heart function after three or four months. The new study was designed to test the optimal timing for the stem-cell treatment. In humans, therapies such as clot-busting drugs are ideally given within a couple of hours after a heart attack in order to prevent further damage to the heart.

see STEM CELLS on pg. 4

HUCB cells versus other stem cells

The stem cells used in Henning’s lab were donated by cord banks that freeze and store umbilical cords—with consent from the mother prior to delivery—after the cord is separated from the mother and newborn. Some mothers opt to bank umbilical cords for their children’s future medical needs, but there are numerous limitations to the practice—not the least of which is the price—and it is still relatively rare.

Other types of stem cells available for research include those derived from adult bone marrow, and—the subject of much controversy—those obtained from human embryos. As a federal agency, VA does not permit the latter in its research program.

For researchers, stem cells that are more “primitive,” or less developed, have greater potential for medical therapy, in that they can develop into a wider range of cells in the body to restore damaged or diseased tissues or organs.

Said Henning, “We believe that umbilical-cord stem cells are more primitive than the stem cells obtained from human bone marrow, but slightly more mature than the human embryonic stem cells.” He added that the “immature immunogenicity” of the HUCB stem cells reduces the risk that they will be rejected by transplant recipients.

Hold the date for the next VA Research Week:
May 13 – 19, 2007
Study examines trends in VA colorectal cancer screening

The rate of colorectal cancer screening in VA appears to be increasing, although the use of colonoscopy versus other screening methods seems to be decreasing, according to research by a team at VA’s Houston Center for Quality of Care and Utilization Studies.

Their study, published in the Nov. 13 Archives of Internal Medicine, found that the number of colorectal cancer screening tests in VA more than doubled between 1998 and 2003, from 432,778 to 1,179,764. Fecal occult blood testing (FOBT) accounted for the great majority of these screenings, increasing from 81.7 of all tests in 1998 to 90.4 percent in 2003. The use of screening colonoscopy, on the other hand, decreased from 5.7 percent in 1998 to 4.7 percent in 2003. The use of other screening methods—flexible sigmoidoscopy and double-contrast barium enema—also decreased.

According to lead author Hashem El-Serag, MD, VA differs in this trend from other healthcare systems, where colonoscopy use appears to be increasing. He cited, for example, a study of colorectal screening in Washington state that showed no change in the overall use of colorectal screening tests from 1994 to 1998, but a rise in the proportion of these procedures that were colonoscopies, from 36 to 47 percent.

Some clinical practice guidelines, such as those of the American College of Gastroenterology, state a preference for colonoscopy, based on studies showing it as the most effective means of detecting growths in the colon. However, other guidelines are closer to VA’s,

see SCREENING on pg. 7

STEM CELLS (from pg. 3)

In the new research, Henning’s team induced heart attacks in anesthetized rats by tying off a major blood vessel to the heart. The researchers then took tissue samples from the damaged hearts at nine different intervals post-heart attack, ranging from 1 to 96 hours. Next, they exposed each tissue sample to a solution containing 100,000 stem cells and measured how many of the cells successfully migrated to the different damaged tissues. They found that the samples obtained at 2 and 24 hours after an attack attracted the greatest numbers of stem cells—around 76,000 and 70,000 cells, respectively. This held true even after the researchers adjusted the migration results based on the physical size of each heart attack.

Up to 74-percent reduction in infarct size

In the next phase of the experiment, the team injected either an electrolyte solution containing stem cells, or one without stem cells—as a control—into the infarcted hearts of anesthetized rats at 2 or 24 hours after a heart attack had been induced. After a month, the researchers analyzed the heart tissue using a stain that reacts with enzymes found only in healthy heart tissue. The scientists observed that the heart attacks in the stem-cell-treated group were 66 to 74 percent smaller than in the rats treated with only the electrolyte solution. The infarctions occupied 6 and 8 percent of the left ventricular muscle in the 2-hour and 24-hour rats, respectively, compared to infarctions of 25 percent or more in the rats not receiving the stem-cell treatment.

Henning and colleagues also examined the effect of the stem cells on the concentrations of inflammation-causing chemicals that normally flood the site.
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.


“Breast Cancer Cells Secreted Platelet-Derived Growth Factor-Induced Motility of Vascular Smooth Muscle Cells Is Mediated Through Neuropilin-1.” Snigdha Banerjee, PhD; Krishanu Sengupta, PhD; Kakali Dhar, PhD; Smita Mehta, MD; Gopal Dhar, PhD; Sushanta K. Banerjee, PhD. Kansas City. Molecular Carcinogenesis, Nov. 2006.

“Changes in Religiousness and Spirituality Attributed to HIV/AIDS: Are There Sex and Race Differences?” Sian Cotton, PhD; Joel Tsebvat, MD, MPH; Ian Kudel, PhD; Susan N. Sherman, DPA; Anthony C. Leonard, PhD; William C. Holmes, MD, MSCE. Cincinnati, Philadelphia. Journal of General Internal Medicine, Dec. 2006.

“Comparison of Delivery Modes for Online Medical Education.” B. Price Kerfoot, MD; Paul R. Conlin, MD. Brockton. Medical Education, Nov. 2006.


“Dual Use of Medicare and the Veterans Health Administration: Are There Adverse Health Outcomes?” Fredric D. Wolinsky, PhD; Thomas E. Vaughan, PhD; Gary E. Rosenthal, MD. Iowa City. BMC Health Service Research, Oct. 9, 2006.


Ascertaining veterans’ vital status

This bimonthly feature, prepared by VA’s Seattle Epidemiologic Research and Information Center, addresses topics in research methodology that are of broad interest to Research Currents readers. References and links are provided on the Seattle ERIC’s website at: www.eric.seattle.med.va.gov/research_currents.html.

Knowledge of veterans’ vital status is important to VA from both research and policy perspectives. For many years, VA researchers have used the Beneficiary Identification Record Locator Subsystem (BIRLS) death file to determine vital status of veterans. This file can be accessed through the Austin Automation Center, and costs associated with its use have been minimal. However, BIRLS data are not complete for those veterans who do not use VA health care or use it sporadically. The National Death Index (NDI), maintained by the National Center for Health Statistics, has national vital status information that is based on death certificates assembled from state vital statistics records. This file is viewed as the “gold standard” for mortality ascertainment, but using it is more costly and involves a lengthier application process than BIRLS.

Recently, VA researchers compared the accuracy of a merged death record file with the NDI. Death information from BIRLS, Social Security Death Master File, Medicare Vital Status File, and Medical SAS Inpatient Files was merged into a single file for 3,000 randomly selected veterans who received VA benefits and were alive as of Jan. 1, 1999. The accuracy of this file was compared to the NDI. The combined file identified 98.3 percent of deaths in the NDI and had 98 percent agreement with the exact date of death as recorded in the NDI. The specificity of the merged file was 99.8 percent, indicating there were very few false positives.

New vital status files available

As a result of these findings and the efforts of the VA Information Resource Center and National Data Systems, three new VA vital status files are now available at the Austin Automation Center. These files include over 12 million living and deceased veterans who currently receive benefits or received them in the past. A significant feature is the inclusion of presumed living status as well as date of death for those who are deceased. There is a mini-file that includes one record per veteran and a master file that includes all possible matches made on the basis of social security number and date of birth. The researcher must then decide which record is the most likely match. A third file is a crosswalk file that links both the scrambled and real social security numbers. The mini and master files include only the scrambled number. Current plans call for these files to be updated several times per year. Documentation, including file names and content, is available at http://vaww.va.gov/nds/AACInfoSystems/VAVitalStatusFile.asp. Procedures for obtaining access to the files can be found at http://www.virec.research.va.gov/Support/Training-NewUsersToolkit/ACRSrequest.htm.

The new vital status files provide VA researchers with complete, timely, and accurate information on mortality. Vital status in these files has high sensitivity and specificity in relation to the NDI, and can be obtained rapidly and at a fraction of the cost.

STEM CELLS (from pg. 4)

of a heart attack, such as tumor necrosis factor, monocyte inflammatory protein, and interferon-gamma. In the rats treated with the electrolyte solution alone, the researchers found a 118- to 644-percent increase in these chemicals in the heart within 12 hours after the onset of the heart attack. The stem-cell-treated rats showed no such elevations.

Henning and colleagues are now studying the exact mechanisms whereby HUCB cells save or restore heart tissue. “We are determining whether the cells act by one or more mechanisms such as transdifferentiating into myocardial heart muscle and blood vessels, modulating the immune response to acute myocardial infarction, or stimulating new blood vessel formation.”

In a separate study they presented at the American Heart Association meeting, Henning’s group showed that injecting the HUCB cells directly into the heart was the most effective delivery method for reducing the size of a heart attack in rats. Injecting them into the coronary artery or intravenously was also effective, said Henning, but required more cells.

The studies were funded by VA and the American Heart Association.

Cyber-security guidance

VA researchers and administrators who need to find the latest policies and procedures regarding cyber security and privacy can visit: www.research.va.gov/resources/policies/cybersecurity.cfm.

This recently updated page on the VA research website contains recent memos from ORD and VHA leadership, as well as many pertinent VA Handbooks and Directives, such as Handbook 1605.1 on the “Privacy and Release of Information” and Directive 2004-002 on using commercial or external Web-hosting services.
PTSD drug fails to show benefit in trial

Guanfacine, a medication commonly prescribed to alleviate symptoms of post-traumatic stress disorder, is no more effective than a placebo, according to a study led by researchers at the San Francisco VA Medical Center.

“There was no benefit at all, and there were several adverse side effects,” said lead author Thomas Neylan, MD, medical director of the PTSD treatment program at the San Francisco VA. “People with symptoms of PTSD should probably stay away from this drug and others of its type.”

The study appeared in the Dec. 1 issue of the American Journal of Psychiatry.

Guanfacine, an alpha-2 agonist, lowers the brain’s supply of the neurotransmitter norepinephrine. “Norepinephrine is released in the brain during states of excited arousal, and PTSD is associated with that state—patients startle easily, have trouble sleeping, and are hypervigilant and anxious,” explained Neylan, who is also an associate professor of psychiatry at the University of California, San Francisco.

Study results surprising

Guanfacine and clonidine, another alpha-2 agonist, are commonly prescribed for PTSD symptoms. “There are at least 20 peer-reviewed articles published in the field of PTSD that recommend drugs which lower norepinephrine,” Neylan said. “However, ours was the first randomized, controlled study of alpha-2 agonists for symptoms of PTSD.”

The VA-funded study compared the effects of guanfacine and an identical placebo pill on 63 male and female veterans at four VA medical centers in California and Hawaii. Twenty-nine participants were randomly assigned to take weekly doses of the drug, and 34 were assigned the placebo, for eight weeks. At the end of the study, the effect of guanfacine on PTSD symptoms was “zero,” according to Neylan, with no differences in men versus women or older versus younger veterans. In addition, the subjects who took guanfacine had significantly more somnolence, light-headedness, and dry mouth than those who took placebo.

Neylan speculates that instead of lowering the overall level of norepinephrine, a more effective approach might be to inhibit the ability of brain cells to respond to the neurotransmitter. He notes that this is the action of prazosin, a blood-pressure drug that has been found by other researchers to decrease the incidence of nightmares in combat veterans with PTSD.

Neylan’s collaborators included Maryann Lenoci, Kristin Franklin, Thomas Metzler, Clare Henn-Haase, Robert Hierholzer, Steven Lindley, Christian Otte, Frank Schoenfeld, Jerome Yesavage and Charles Marmar.

Screening (from pg. 4)

said El-Serag, in that they “give a menu of choices and don’t specify one as preferred.” However, El-Serag and his coauthors acknowledge the possibility that colonoscopy may be under-used in VA simply because of a lack of resources. Still, they assert that the reliance on FOBT may not necessarily be detrimental to VA patients.

“The predominant use of FOBT for CRC screening in the VA, while strikingly different from other health care systems in the United States, may not necessarily lead to worse outcomes in terms of CRC-related incidence and mortality. It does, however, call for closer examination of the process and outcomes of this process in VA settings.”

Publications (from pg. 2)

publications and presentations,” she said. “The system will be fully searchable—by keywords, article titles, authors, medical centers, funding mechanisms and other parameters—so we expect this will be a useful tool for many folks both in the field and Central Office.”

Gosser added that the system will probably include a feature that links published articles in the database to PubMed citations.

One challenge involved in the project, noted Lutes, is that it will be accessible only through the VA Intranet, and not the Internet. But she and Gosser said ORD is working on ensuring access to that system for VA researchers at all sites.

For more information on the project, or to suggest your site as a possible partner in pilot testing, contact Mitch Mirkin, senior writer and editor for ORD, at mitch.mirkin@va.gov or (410) 962-1800, ext. 252. VA Research Currents will provide an update on the project within a few months.
Agreements. But he’ll also spearhead new efforts to speed the path from VA labs or clinical trials to patient care.

“My goal is to make the process of clinical development easier for our investigators,” said Ommaya, who has a doctorate in health policy and management from Johns Hopkins University and a master’s in biopsychology from Mount Holyoke College. His experience in research and healthcare is surprisingly diverse: He directed “business knowledge management” for Blue Cross/Blue Shield of Florida, and was a senior advisor at the Agency for Healthcare Research and Quality. He’s also been a health policy fellow in the U.S. Senate; a senior analyst for the Defense and Veterans Brain Injury Program; and an intramural researcher at the National Institutes of Health, focusing on areas such as brain injury, malignant glioma, and neuroplasticity. Ommaya also serves on the Medicare Coverage Advisory Committee.

New collaborations on horizon

One major goal for Ommaya in his new post will be forging new collaborations, with both public and private partners.

“I hope to bring new resources to VA investigators. I’m talking with foundations about opportunities for collaborative research training. I also hope to create opportunities for investigators to present research results that are ready for clinical development to private partners.” He says areas of special attention for him will likely include gene-association studies, predictive disease modeling, and the development of adaptive clinical methodology.

Ommaya plans to organize a conference in the coming months to focus on “improving the translational research platform in VA.” Meanwhile, he is encouraging VA researchers to see him as a resource to help identify or remove obstacles in their path toward commercialization or clinical development.

“I look forward to hearing from investigators regarding specific challenges they are facing and their ideas for how we can improve our effectiveness in research translation.”

Ommaya can be reached at alex.ommaya@va.gov or (202) 254-0198.

ORD to fund studies on long-term needs in polytrauma, brain injury

VA is looking to fund up to three research proposals focused on improving long-term care and support for veterans who have experienced traumatic brain injury, polytrauma, or other blast-related injuries. The request for applications (RFA) is open only to investigators at HSR&D, RR&D, QUERI, TREP or REAP centers, and initial concept papers are due Jan. 31, 2007.

New research must be “coordinated with and contribute to the established polytrauma continuum of care,” according to the RFA, and can focus on topics such as factors affecting recovery, or injured veterans’ unmet health, educational or vocational needs. Studies addressing the needs of caregivers are also encouraged. For a copy of the full RFA, contact Dr. Jay Freedman at jay.freedman@va.gov or (202) 254-0267.