



Study looks at long-term needs of traumatized soldiers

Veterans Returning with Brain Injuries

BY
LOIS
BAKER

TRAUMATIC BRAIN INJURY (TBI) has been identified as the “signature injury” of the wars in Iraq and Afghanistan.

TBI IS KNOWN TO CAUSE deficits in memory, attention and decision-making, and often occurs in conjunction with post-traumatic stress disorder (PTSD), depression, anxiety disorders and substance abuse.

An estimated 150,000 U.S. veterans have been diagnosed with TBI, based on a report issued by U.S. Representative William Pascrell, Jr, co-chair of the Congressional Brain Injury Task Force.

While the numbers are relatively easy to assemble, the long-term cognitive and affective consequences of TBI and the effect on veterans’ quality of life are not well understood, according to the VA, and evidence-based guidelines for diagnosis and treatment are limited.

To be prepared to meet the needs of these veterans over time, the VA’s Health Services Research and Development Unit is funding a \$1.4 million, four-year prospective cohort study of Iraq and Afghanistan-era veterans headed by UB researchers at the Buffalo VA Medical Center. VA medical centers in Albany, Syracuse, Bath and Canandaigua/

Rochester also will participate in the study, the results of which will be used nationwide.

Kerry T. Donnelly, PhD, clinical assistant professor in the Department of Psychiatry in the School of Medicine and Biomedical Sciences, and adjunct assistant professor in the Department of Counseling, School and Educational Psychology, Graduate School of Education, is principal investigator. James Donnelly, PhD, clinical associate professor of counseling, school and educational psychology, is co-investigator.

“This project began here at the Buffalo VA in June 2008,” says Kerry Donnelly. “While the departments of Defense and Veterans Affairs have worked well in concert to address the needs of service members with major injuries, such as limb loss or severe TBI, veterans who might have more subtle cognitive and psychological problems are less likely to be identified in the field or upon returning home.

“Symptoms associated with mild TBI often can be overlooked in deference to more obviously visible injuries,” she continues. “Nonetheless, war-related TBI is a serious

and potentially costly health concern within the VA, and the interplay of TBI and cognitive and affective symptoms in

Iraq War veterans over time has not been adequately explored.

“Further, symptoms similar to those associated with TBI may develop from combat experience alone. We’re interested in studying returning veterans, both with and without TBI, looking at a broader trauma complex.

“Our goal,” she says, “is to provide evidence-based understanding of cognitive and affective correlates of TBI and combat exposure in these veterans, the relationship of symptoms to the use of health care and quality of life, and the evolution of the phenomena over time.”

The study will construct clinical profiles of 500 veterans returning from Iraq and Afghanistan. Profiles will cover cognitive functioning, psychological symptoms, substance use, TBI status, and combat and demographic characteristics, and will examine health-care use among those with different diagnoses, quality of life and community participation.

Veterans will be studied at four time points, six months apart. The investigators also are conducting the first large-scale examination of the reliability and validity of the VA TBI screening tool, a brief survey used nationwide to identify veterans who might have sustained TBI in battle. **BP**

Suicidal Thoughts in Veterans Studied

BY
LOIS
BAKER

JOHN VIOLANTI, PHD ’81, a specialist in suicide among police officers, is preparing to conduct a study on suicide risk among returning veterans. The U.S. Army in February 2009 reported a “stunning spike” in the number of soldiers taking their own lives.

VIOLANTI CURRENTLY is testing a computer-based psychological “task,” which measures how quickly individuals associate feelings of self-harm, as a way of detecting “under-the-radar” suicidal thought.

“I feel that military personnel will not readily admit suicidal thoughts,” Violanti says. “This new test gets to real feelings at a subconscious level. It is called IAT [Implicit Association Testing] and was developed at Harvard University.

“Suicide among returning veterans is a big problem,” he continues. “On their psychological evaluation when they return, there is only one question on suicide: ‘Are You Depressed?’ Who is going to answer that?”

Violanti is a Vietnam veteran and former member of the New York State Police. As a research associate professor in the UB School of Public Health and Health Professions, he has studied suicide among police officers and the effects of policing on officers’ health for 16 years.

According to the Army’s report, the number of soldiers who committed suicide in January 2009 could be as high as 24, which would be the highest monthly total since the Army began collecting data on suicides. **BP**

Numbing without Needles

Nasal Spray May End Dental Injections for Upper Teeth Repair

A NASAL SPRAY shown to numb the upper jaw is set to be tested in an FDA Phase 3 trial that will assess the spray’s effectiveness compared to the current “gold standard” treatment—painful anesthesia injections.

“A SUCCESSFUL TRIAL of this new dental anesthetic will change dental technology worldwide,” says Sebastian Ciancio, DDS, University at Buffalo SUNY Distinguished Service Professor and chair of the Department of Periodontics and Endodontics.

Ciancio directed the Phase 2 trial and will coordinate the Phase 3 trial. Between 6 and 10 million dental needle injections are given daily, according to Ciancio.

Results of the FDA Phase 2 trial, conducted in 48 subjects at the UB School of Dental Medicine, showed that the spray appears to be safe and effective.

The Phase 3 trial will be carried out later in 2009 at the UB dental school and other clinical sites. Ciancio says that if the Phase 3 trial is successful, it may mean the end of injections for any dental work performed on the upper teeth.

Ciancio and colleagues conducted the initial preliminary dental studies using the nasal spray, which is being developed by St. Renatus, LLC, based in Fort Collins, Colorado.

The nasal spray formula being tested is related to a drug used by ear, nose and throat physicians when they operate on the nose. Patients who received this anesthetic reported that their upper teeth felt numb, sparking interest in using the anesthetic for dental procedures. The spray is effective only on the upper teeth.

Investigators also involved in the Phase 2 and preliminary trials were Eugene A. Pantera, DDS; Carol T. Pantera, DDS; Fadi Ayoub, DDS; Davis Garlapo, DDS; Nina Kim, DDS; and Benita Sobierj, DDS, all of whom are faculty in the UB School of Dental Medicine. **BP**





Statins Improve Heart Function

Pravastatin shown to stimulate cardiac muscle-cell regeneration

STATINS, used widely to treat elevated cholesterol, have been shown to prevent progression of coronary narrowing and to have other beneficial effects on the heart, such as reducing inflammation, that are independent of cholesterol.

NOW, ADDING TO THIS LIST of multiple effects, researchers at UB have shown that the drug pravastatin, one of the oldest statins, may be able to prevent the development of heart disease by regenerating diseased heart muscle.

In a paper published in the January 2009 issue of *Circulation Research*, the investigators report that pravastatin mobilizes bone marrow progenitor cells—blood stem cells that are able to transform into many different types of cells—which infiltrate the heart and develop into cardiac muscle cells, or myocytes, improving cardiac function.

The research was carried out in UB's Center for Research in Cardiovascular

Medicine, using the center's unique swine model of hibernating myocardium—a condition in which myocytes reduce their contraction yet remain viable in areas that have received reduced blood flow over an extended period of time due to narrowed arteries.

“The finding that a drug with an excellent safety profile used widely to lower blood cholesterol is effective in improving cardiac function in hibernating myocardium is a welcome finding,” says Gen Suzuki, MD, PhD, UB research assistant professor of medicine and first author on the study.

“This provides a new strategy for treating patients with ischemic heart failure who are not candidates for coronary

artery bypass graft surgery or coronary balloon angioplasty.”

John M. Canty Jr., MD, Albert and Elizabeth Rekate Professor and chief of the Division of Cardiovascular Medicine in UB's School of Medicine and Biomedical Sciences, and director of the cardiology research center, developed the swine model and is a coauthor on the study.

“Pravastatin increased the number of progenitor cells in bone marrow in proportion to the dose of the drug, which correspondingly increased the number of progenitor cells circulating in the blood stream and ultimately localizing in the heart,” says Suzuki.

“This occurred in as little as five weeks after treatment with pravastatin, using animals that had chronic coronary artery narrowings and dysfunctional hearts, with completely normal cholesterol levels. The number of cardiac myocytes increased in the hibernating hearts after pravastatin, and this ‘new’ population of myocytes was remarkably smaller than the existing myocytes, suggesting they arose from myocyte regeneration.”

By
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THE FINDING THAT A DRUG WITH AN EXCELLENT SAFETY PROFILE USED WIDELY TO LOWER BLOOD CHOLESTEROL IS EFFECTIVE IN IMPROVING CARDIAC FUNCTION IN HIBERNATING MYOCARDIUM IS A WELCOME FINDING.

—GEN SUZUKI, MD, PhD



Suzuki notes that, importantly, animals with normal hearts that received pravastatin showed no increase in new myocytes, even though the drug increased the number of circulating and cardiac progenitor cells.

This finding suggests that the new myocytes formed directly in response to need and to the presence of the heart's diseased state, preventing uncontrolled cardiac muscle growth and proliferation in otherwise normal hearts.

Earlier small clinical studies using a variety of older statins had suggested the possibility that the drugs improved heart function and symptoms in patients with congestive heart failure. Canty notes that this contrasts with randomized clinical trials completed recently to test the effects of the newer and extremely potent drug rosuvastatin, which failed to demonstrate a beneficial effect on survival or symptoms.

“Our current preclinical study now raises the possibility that this difference is associated with age-related changes in progenitor cells in patients, or perhaps

with a proinflammatory state that prevents the beneficial actions of statins,” says Canty. “An alternative possibility could be that the ability of individual statins to mobilize bone marrow stem cells may vary, and may not be a ‘class’ effect, like their actions to lower cholesterol.”

To determine if the latter possibility is at work, researchers at the UB Center for Research in Cardiovascular Medicine now are investigating, as they did with pravastatin, if rosuvastatin (shown to have no major effect in large clinical studies in patients with heart failure) can mobilize bone marrow stem cells and aid cardiac repair in their porcine model of ischemic heart disease.

The research was supported by grants from the Department of Veterans Affairs and the National Heart Lung and Blood Institute. Suzuki is a Buswell Fellow in the School of Medicine and Biomedical Sciences. Vijay Iyer, MD, PhD, and Thomas Cimato, MD, PhD, both assistant professors in the UB Division of Cardiovascular Medicine, also contributed to the study. **BP**

By
KATHLEEN
WEAVER

Prenatal Cocaine Exposure

Study shows infants' response to stress impaired

INFANTS EXPOSED prenatally to cocaine react more emotionally to stress and appear to have fewer stress-reducing coping strategies than infants with no cocaine exposure, according to a study conducted at UB's Research Institute on Addictions (RIA).

The study, carried out with 7-month-old infants, is one of the few conducted to date to examine the effects of prenatal

cocaine exposure on the regulatory system beyond the newborn period.

This research, led by Rina Das Eiden, PhD, a developmental psychologist and RIA senior research scientist, was published in the January/February 2009 issue of *Neurotoxicology and Teratology*.

Eiden also is research associate professor in UB's Department of Pediatrics in the School of Medicine and Biomedical

Sciences, and associate professor in the Department of Psychology in UB's College of Arts and Sciences.

Eiden first examined reactivity, defined as how quickly and intensely the infants responded to stress. Next, she measured regulation, defined as the number of strategies the infants used to cope with stress.

Assessments were conducted in the RIA Infant Lab, a warm, family-room-

like setting. The mother or caregivers was asked to place the infant in a high chair with an attractive toy and stand behind the child. The infant was allowed to play with the toy for 30 seconds, followed by 30 seconds when the mother or caregiver prevented her child from reaching the toy. This sequence then was repeated a second time.

Results showed that compared to cocaine-free infants, babies exposed to the drug prenatally exhibited greater anger and sadness, and reacted more

quickly as stress increased. The non-exposed infants tended to be relatively stable in their reactivity during the assessments.

Cocaine-exposed infants failed to increase the number of strategies to cope with or regulate their emotional reactions, while non-exposed infants used more regulatory behaviors to comfort themselves, results showed.

Regulatory or self-comforting behaviors included repetitive motor actions, sucking and gross motor movements.

Additional attempts by the infants at self-regulation included looking away from the toy, or looking toward the mother or caregiver, the technician or another person to distract attention away from the unavailable toy.

A trained research staff rated the infants' expressions of anger, frustration or sadness using standardized research measures rather than depending on a parent's or caregiver's perceptions. **BP**



All the Wrong Signals

ACS-funded study will examine role of cell signaling in cancer

DURING NORMAL GROWTH and development, cells in the body communicate with each other through protein receptors on the cell surface.

BY LOIS BAKER

AMONG THE PROTEINS used for this communication are receptor tyrosine kinases, or RTKs, which receive signals from outside of the cell and transmit them to the inside of the cell, leading to the turning on or off of specific genes.

RTKs have been shown to play a critical role in the development and progression of many cancers by transmitting too much signal.

Marc S. Halfon, PhD, assistant professor of biochemistry in the School of Medicine and Biomedical Sciences, has received \$720,000 from the American Cancer Society to study how the RTK signaling pathway functions.

Knowledge gained from this study should help guide the future development

Leffler, the American Cancer Society's regional vice president. "It also is a sign of the significant commitment UB has made to fighting cancer, whether it's going smoke free campus-wide or providing cutting-edge cancer research facilities here in Western New York. The University at Buffalo quickly is becoming a national leader in the search for better treatments and a cure."

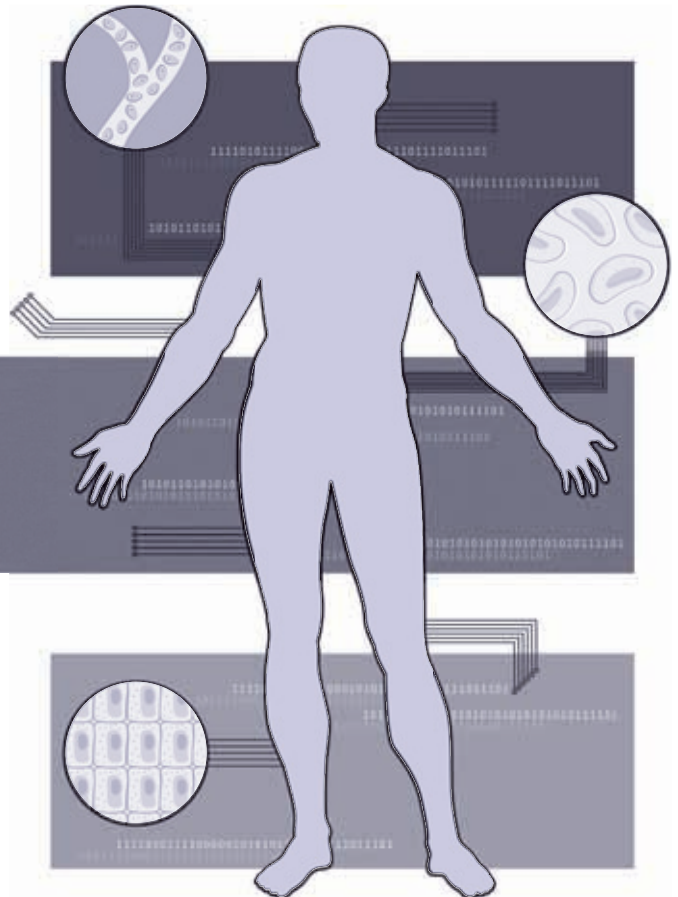
"Altered activity of RTKs and the protein partners of RTKs in cells, termed members of the signaling pathway, have been implicated in many cancers, including leukemia, lymphoma, breast, lung, colon and brain cancer," explains Halfon. "In recent years, a number of drugs blocking RTKs and the RTK signaling pathway members have been approved for the treatment of cancer.

"One poorly understood aspect of RTK signaling," he continues, "is how different members of the RTK family convey different types of information into the cell. In fact, it is not entirely clear whether differences

The researchers work with the fruit fly *Drosophila*, a key model organism that has played an important role in helping to discover crucial aspects of RTK signaling. Their studies are carried out primarily in the New York State Center of Excellence in Bioinformatics and Life Sciences in downtown Buffalo.

"We will use cutting-edge genomic techniques that allow us to investigate all of the genes in the organism in a single experiment," says Halfon. "The work proposed here will make important progress in understanding more clearly how different RTKs carry out their specific roles in both normal and malignant tissue."

The goals of the research are to show definitively that there are intrinsic differences among the RTKs that are responsible for their distinct effects, and to discover genetic mechanisms that cause these intrinsic differences and lead to the activation or repression of specific genes. **BP**



KNOWLEDGE GAINED FROM THIS STUDY SHOULD HELP GUIDE THE FUTURE DEVELOPMENT OF NOVEL RTK-TARGETED DRUGS WITH MINIMAL SIDE EFFECTS TO TREAT AN ARRAY OF CANCER TYPES.

of novel RTK-targeted drugs with minimal side effects to treat an array of cancer types, Halfon says.

"This grant is a testament to the commitment of our volunteers who, in spite of a difficult economy, continue to raise critical funds for research," notes Gretchen

in the RTKs themselves, or differences in other pathway members present in a given cell type, are responsible for the specific effects of signaling seen with one RTK versus another."